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Review of PHARMACOLOGY

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Latest Exam Pattern Questions and Image Based Questions***

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Goodman Gilman 12th, Harrison 18th and CMDT 2015***

**Gobind Rai Garg
Sparsh Gupta**

Explained Answers
All Recent Questions (2014–2012)
All India (2012–1991)
AIIMS (Nov 2014–1991)
PGI Chandigarh (2014–2000)
DNB (2012–2000) and
Various Solved MCQs of
Other State Exams (2014–1985)



Review of Pharmacology

Ninth Edition

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Dedicated to

My parents, wife Praveen and sweetheart kids Ayush and Samaira

— Gobind Rai Garg

My family members and my teachers (Shri SK Suri and Ms V Gopalan)

— Sparsh Gupta

Preface to the Ninth Edition

We want to thank all the readers for the overwhelming response and great appreciation of the earlier editions of this book. To meet the expectations of students, we have tried to further improve this ninth edition.

Dear friends, the apprehension regarding the 'National Eligibility Cum Entrance Test (NEET)' has now been taken care of as the examination pattern has not been modified drastically. Cracking the NEET and other important PG entrance examinations require a thorough knowledge and understanding of the subject. *Readers of this book have got an edge over others* because of **strong theory** and **conceptual questions**. This along with the **key points** given under the heading of various boxes in the chapters has helped many students to get extremely good ranks in NEET 2012, 2013 and 2014. As one-liner questions are being asked in the NEET, the students need to revise the most important information in the last few days. Keeping this in mind, we have added 'high yield points' separately as boxes on the side of every page. Boxes are labeled as  for Key points,  for mnemonics,  for definition,  for new drugs and  for controversial questions. However, we will recommend students to read the theory of each subject thoroughly, which is must. The questions have been asked as one-liners in last year which may not be the case next year and further in AIIMS and PGI exams you need to be well-versed with the theory. Therefore, we will re-emphasize that there is no substitution of knowledge. If you know the subject thoroughly, you can answer any type of question.

In our constant endeavour to improvise the book, there has been incorporation of important additions in almost all chapters along with the section of 'Recent questions asked by National Board'.

In this ninth edition, we have added a lot of **mnemonics, diagrams and flow charts** to make learning interesting and easier. Another salient feature of this edition is the addition of **DRUG OF CHOICE** in every chapter.

The **question bank** of every chapter has been **divided into subtopics**. It will help students to solve MCQs after reading the theory of a particular topic of a chapter.

For getting a grasp on the NEET questions in a better way, a new chapter 'History of Pharmacology' and a new section 'Image Based Questions' have also been added.

We have **fully revised** the book and *corrected* the typographical and some other errors present in the previous editions. *Further, we have also expanded some of the old topics. As in previous editions, the questions from ten different state PG entrance examinations have also been incorporated at the end of every chapter.*

Questions from latest entrance examinations of AIIMS have been added. Several other questions have been incorporated from PGI, DPG and other state PG entrance examinations.

To make the contents of the book more authentic, we have provided appropriate *references* to all the explanations.

In some topics, there are contradictions between different books. In such a situation, we have quoted the text from Harrison's Principles of Internal Medicine, 18th edition.

To help the students understand the Pharmacology in an easy and interesting way, Dr Gobind Rai Garg has started his own institute named 'Ayush Institute of Medical Sciences'. It is the only institute which is meant for teaching Pharmacology only. Dr Gobind Rai Garg himself conducts separate classes for MBBS students (Jan-Feb) and those preparing for PG entrance examinations (March-April and July-August). For details, you can contact on the E-mail ID provided or at 09990044695.

We must admit hereby that despite keeping an eagle's eye for any inaccuracy regarding factual information or typographical errors, some mistakes must have crept in inadvertently. You are requested to communicate these errors and send your valuable suggestions for the improvement of this book. Your suggestions, appreciation and criticism are most welcome.

April 2015

Gobind Rai Garg
Sparsh Gupta

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Preface to the First Edition



Pharmacology is one of the most difficult and at the same time most important subject in various postgraduate entrance examinations.

As we experienced it ourselves, most of the students preparing for postgraduate entrance examinations are in a dilemma, whether to study antegrade or retrograde. Antegrade study takes a lot of time and due to bulky textbooks, some important questions are likely to be missed. In a retrograde study, the students are likely to answer the frequently asked MCQs but new questions are not covered. We have tried to overcome the shortcomings of both of the methods while keeping the advantages intact.

In this book, we have given a concise and enriched text in each chapter followed by MCQs from various postgraduate entrance examinations and other important questions likely to come. The text provides the advantage of antegrade study in a short span of time.

After going through the book, it will be easier for the student to solve the questions of most recent examinations, which are given at the end of the book.

More and more questions about new drugs are being asked in the entrance examinations nowadays. These NEW DRUGS have been covered along with the text and a separate chapter has been added at the end. Salient features of the new drugs along with the reference in the text have been included in this chapter.

Recently, the questions are being asked from SOME EMERGING TOPICS like anti-obesity drugs, anti-smoking drugs, drugs for erectile dysfunction and nitric oxide. All these topics have been discussed in a separate chapter.

Large number of questions about first choice drugs is being incorporated in the entrance examinations. To cover these questions, a separate chapter entitled "DRUGS OF CHOICE" has been added.

Important ADVERSE EFFECTS caused by drugs have also been included.

It is very difficult and at times very confusing to remember large number of drugs and adverse effects. To make learning easy, several easy to grasp MNEMONICS have been given throughout the text.

Despite our best efforts, some mistakes might have crept in, which we request all our readers to kindly bring to our notice. Your suggestions, appreciation and criticism are most welcome.

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We would also like to acknowledge the encouragement and guidance of **Dr CD Tripathi (Director-Professor and Head, VMMC)**, **Dr SK Bhattacharya (Professor and Head, NDMC Medical College and Hindu Rao Hospital)**, **Dr Uma Tekur (Director-Professor, MAMC)**, **Col Dr AG Mathur (Professor and Head, ACMS)**, **Dr Vandana Roy (Director-Professor and Head MAMC)** and **Dr Shalini Chawla (Professor, MAMC)**, all in the department of Pharmacology, in the completion of this book.

We feel immense pleasure in conveying our sincere thanks to all the residents of department of Pharmacology at MAMC and UCMS for their indispensable help and support.

No words can describe the immense contribution of our parents, Ms Praveen Garg, Ms Ruhee, Ms Anju, Mr Rohit Singla, Mrs Komal Singla, Mr Nitin Misra and Ms Dhvani Gupta, without whose support this book could not have seen the light of the day.

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April 2015

Gobind Rai Garg
Spursh Gupta

From the Publisher's Desk

*We request all the readers to provide us their valuable suggestions/errors (if any)
at: jppgmee@gmail.com
so as to help us in further improvement of this book in the subsequent edition.*

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- **Harrison's** Principles of Internal Medicine, 18th edition
- **Goodman and Gilman's** The Pharmacological Basis of Therapeutics, 12th edition
- **Katzung's** Basic and Clinical Pharmacology, 12th edition
- **HL Sharma and KK Sharma's** Principles of Pharmacology, 2nd edition
- **KD Tripathi's** Essentials of Medical Pharmacology, 7th edition
- **Current Medical Diagnosis and Treatment 2015**

SYMBOLS USED IN BOXES ON 'HIGH YIELD POINTS'

-  Key points
-  Definition
-  Mnemonic
-  New drug
-  Controversial question

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HISTORY OF PHARMACOLOGY

Scientist	Contribution
Oswald Schmiedberg	Father of Pharmacology
Col. Ramnath Chopra	Father of Indian Pharmacology
Sir James Black	Father of Modern Pharmacology
Clark	Gave <i>Theory of drug action</i> based on occupation of receptors by specific drugs.
Otto Loewi	Direct proof of <i>transmission across nerve junctions</i> to be mediated by neurotransmitters.*
Ahlquist	Classified adrenergic receptors into α and β types.
Bergstrom, Samuelsson and Vane	Noble prize for work on PGs and LTs.
Banting and Best	Discovered insulin in 1921
Sanger	Worked out chemical structure of insulin in 1956
Kendall, Reichstein and Hench	Noble Prize for work on corticosteroids in Rheumatoid arthritis.
Lundy	Coined the term balanced anaesthesia
Horace Wells	Used N ₂ O (laughing gas) in 1844 for dental anaesthesia
Guedel	Described 4 stages of anaesthesia with Ether
Serturmer	Isolated active principle of opium and named it morphine after greek God of dreams (Morpheus)
William Withering	Published his work on medicinal uses of Foxglove (digitalis) named 'An account of the Foxglove and some of its medicinal uses: with practical remarks on dropsy and other diseases'.
Vaughan williams and Singh	Classification of anti-arrhythmic drugs
Ehrlich	- Coined the term chemotherapy. - Used the idea that if certain dyes can selectively stain microbes, they can also be toxic to these microbes. - Developed arsenic compounds (Salvarsan) for treatment of syphilis.
Domagk	(a) Ushered the Modern era of chemotherapy (b) Demonstrated therapeutic effect of prontosil (containing sulfonamide) in pyogenic infections.
Fleming	Discovered <i>penicillin</i>
Walksman	Discovered <i>streptomycin</i>

* Previously, it was considered to be electrical. He perfused 2 frog hearts in series. Stimulation of vagus nerve of first heart caused arrest of both. Thus, a chemical must have been released by vagal stimulation of first heart (called *vagusstoff* now known as ACh) which passed in the perfusate and arrested the second heart.

- Essential Drugs:**
 - First Model list by WHO in 1977
 - First National EDL of India in 1996
 - Current edition of India is 17th National list of Essential Medicines. It was modified in 2011. It contains 348 drugs
- Uppsala Monitoring centre (sweden)** is the international collaborating centre for Pharmacovigilance.
In India it is Central Drugs Standard Control Organization (CDSCO)
- Vasomotor reversal of Dale** was first demonstrated with **ergot alkaloids**.
- Centchroman** is a non-steroidal SERM developed at **CDRI India** as an oral contraceptive.
- Synthetic toxin N-methyl-4-phenyl tetrahydropyridine (MPTP) produces nigrostriatal degeneration and manifestations similar to Parkinson's disease.

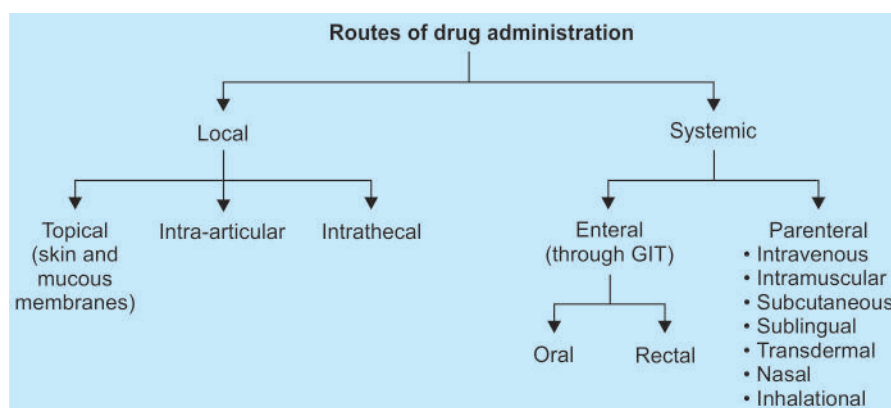
6. **Blaud's pills** (for anemia) consists of FeSO_4 and potassium carbonate.
7. Vitamin B_{12} is also known as **Extrinsic factor of castle**.
8. Vitamin K was isolated from alfa alfa grass.
9. Rat poison contains oral anticoagulants like warfarin.
10. Name of drug warfarin is coined from **Wisconsin Alumni Research Foundation** and its chemical structure being couma **RIN**.
11. New formula WHO-ORS was released in 2002. It contains low Na^+ (75 mM), low glucose (75 mM) and has low osmolarity (245, mOsm/L)
12. 8-Hydroxyquinolines like quiniodochlor and iodoquinol were used in ameobic dysentery but were banned in Japan and few other countries because on long-term use these resulted in epidemics of subacute Myelo-optic Neuropathy (SMON).
13. Thalidomide caused phocomelia in Germany in 1960s when it was used for treatment of vomiting due to morning sickness.

First local anaesthetic	Cocaine (1884) for ocular anaesthesia
First i.v. anaesthetic	Thiopentone
First drug for Schizophrenia	Chlorpromazine
First ACE inhibitor	Teprotide
First oral ACE inhibitor	Captopril
First Fibrinolytic	Streptokinase
First antibiotic	Penicillin
First antitubercular drug	PAS (followed by streptomycin)

Pharmacology is the science dealing with drugs. It is divided into several branches like *pharmacokinetics, pharmacodynamics, pharmacotherapeutics, chemotherapy and toxicology* etc.

When a drug is administered to a person, it will exert some effect on the patient (*Pharmacodynamics*) and the patient's body will have some effect on the drug (*Pharmacokinetics*). These are the two major branches of pharmacology. Before discussing about these branches, we will summarize, how drugs can be administered to a patient (with some important points only).

ROUTES OF DRUG ADMINISTRATION



Local Routes include topical application on the skin and mucous membranes as well as the routes like intra-articular (e.g. hydrocortisone) and intrathecal (e.g. amphotericin B).

Systemic Routes include oral, sublingual, transdermal, nasal, inhalational, rectal and other parenteral routes (intravenous, intramuscular, intradermal and subcutaneous).

- **Oral route** is safer and economical but several drugs are not effective by this route because of *high first pass metabolism* in the liver and intestinal wall (e.g. *nitrates, lignocaine, propranolol, pethidine*).
- **Sublingual route** avoids *first pass metabolism*, can be used in emergencies, can be self-administered and also after getting the desired action, rest of the drug can be spitted. Drugs like *nitroglycerine, isosorbide dinitrate, clonidine, nifedipine* etc. can be administered by sublingual route.
- **Transdermal route** is used only for the drugs which are *highly lipid soluble* and can be absorbed through intact skin. By this route, there is a constant release of the drug (rate of drug delivery to skin is *less than the maximum absorptive capacity of the skin* so that absorption does not become the limiting factor and there is a constant level of the drug in the blood) and it may be administered less frequently. *Nitroglycerine, nicotine, fentanyl and hyoscine* are administered through transdermat patch.
- Drugs administered by **nasal route** are *nafarelin (GnRH agonist), calcitonin and desmopressin*.
- **Inhalational route** is the route by which the rate of drug delivery can be controlled like *i.v.* infusion. The drugs administered by this route include drugs for asthma (e.g., *salbutamol, ipratropium, montelukast and inhalational steroids*) and inhalational anaesthetic agents like *nitrous oxide*.
- **Rectal route** avoids first pass metabolism to 50% extent. *Diazepam* is given by this route in children for febrile seizures.
- Intravenously, drugs can be given as bolus or via infusion. Other parenteral routes include *i.m.* and *s.c.* routes.

DRUGS ADMINISTERED BY VARIOUS ROUTES

Sublingual

- Nitroglycerine
- Isosorbide dinitrate
- Clonidine
- Nifedipine

Transdermal

- Nitroglycerine
- Nicotine
- Fentanyl
- Hyoscine

Nasal

- Nafarelin (GnRH agonist)
- Calcitonin
- Desmopressin

Inhalational route is the route by which the rate of drug delivery can be controlled like *i.v.* infusion.

PHARMACOKINETICS

It is the effect of body on the drug i.e. movement of the drug in, through and out of the body.

1. ABSORPTION

It depends on several factors. Only lipid soluble drugs can cross the biological membranes. So, if a drug is administered by oral route, it has to cross the membranes of GIT and blood vessels to reach the blood. Therefore, it should be in lipid soluble form. If a drug is a weak electrolyte, it is the unionized form which is lipid soluble and the ionized form is water soluble.



Pharmacokinetics is also called **ADME** study as it deals with **A**bsorption, **D**istribution, **M**etabolism and **E**xcretion of a drug.

WHEN MEDIUM IS SAME, DRUGS CAN CROSS THE MEMBRANE

From this statement, we can find that *acidic drugs can cross the membranes in acidic medium* i.e. acidic drugs are lipid soluble in acidic medium (for this acidic drugs must be mainly in the un-ionized form in acidic medium). Opposite is also true for basic drugs. As gastric pH is acidic, therefore acidic drugs are more likely to be absorbed from the stomach, because these will be in unionized (lipid soluble) form here. Thus, aspirin is more likely to be absorbed in the stomach than morphine or atropine (basic drugs).

Note: There is never 100% lipid solubility or water solubility, because ionization of a drug is never 100% or 0%. As we have already discussed, when medium is same the drug is lipid soluble. Suppose, we are talking about an acidic drug having pKa of 5.0 (i.e. at pH = 5.0, it will be 50% ionized and 50% un-ionized). If it is present in a medium with pH = 4.0, it is lipid soluble. But, if the pH of the medium changes to 3.0, what will happen? Obviously, it will become more lipid soluble because more of the drug become un-ionized. We need to remember few concepts:

- If pH of the medium is equal to pKa, then drug is 50% ionized and 50% un-ionized.
- If the pH of the medium is more than pKa (medium becomes alkaline).
 - For acidic drugs, ionized form increases and non-ionized form decreases.
 - For basic drugs, un-ionized form increases and ionized form decreases
- If the pH of the medium is less than pKa, opposite happens, i.e. acidic drugs will be in more un-ionized form and basic drugs be more ionized.
- This ionized or unionized fraction depends on difference (d) between pH and pKa
- When pH = pKa (d=0) Ionization is 50% and un-ionized fraction is also 50%.
- When pH - pKa = 1 (d=1) one form is 90% and other form is 10%
- When d = 2, one form is 99% and other is 1%
- When d = 3, one form is 99.9% and other is 0.1%

Example for a drug with pKa = 5.0

pH of Medium	Nature of drug	(pH-pKa)	Ionized form	Non-ionized form
3.0	Acidic	2	1%	99%
4.0	Acidic	1	10%	90%
5.0	Acidic	0	50%	50%
6.0	Acidic	1	90%	10%
7.0	Acidic	2	99%	1%
8.0	Acidic	3	99.9%	0.1%
3.0	Basic	2	99%	1%
4.0	Basic	1	90%	10%
5.0	Basic	0	50%	50%
6.0	Basic	1	10%	90%
7.0	Basic	2	1%	99%
8.0	Basic	3	0.1%	99.9%

Weak Acids

- Barbiturates
e.g. phenobarbitone
- NSAIDs e.g. aspirin, diclofenac
- Methotrexate
- Sulfonamides
- Penicillins

Weak Bases

- Morphine
- Atropine
- Amphetamines
- Quinine
- Hyoscine

Note: It is simplified form of Henderson-Hasselbach equation:

$$\text{pH} = \text{pK}_a + \log \frac{[\text{A}^-]}{[\text{HA}]}$$



Bioavailability is the fraction of administered drug that reaches the systemic circulation in the unchanged form.

Bioavailability

- It is the fraction of administered drug that reaches the systemic circulation in the unchanged form.
- When we administer a drug orally, first it is absorbed into the portal circulation and reaches the liver. Here, some of the drug may be metabolized (*first pass metabolism* or *pre-systemic metabolism*) and rest of the drug reaches the systemic circulation. Thus absorption and first pass metabolism are two important determinants of bioavailability.
- By i.v. route it is 100%.
- It can be calculated by comparing the AUC (area under plasma concentration time curve) for i.v. route and for that particular route. It can also be calculated by comparing the excretion in the urine.



Absorption and first pass metabolism are two important determinants of bioavailability.

- AUC tells about the **extent of absorption** of the drug.
- **T_{max}** tells about the time to reach maximum concentration, i.e. **rate of absorption**
- **C_{max}** is the **maximum concentration** of a drug that can be obtained

Bioequivalence

Many different pharmaceutical companies can manufacture same compound (with same dose as well as dosage form) e.g. phenytoin is available as tab. Dilantin as well as Tab. Eptoin. If the difference in the bioavailability of these two preparations (same drugs, same dose, same dosage forms) is less than 20%, these are known to be bioequivalent. As the term implies, these are biologically equal i.e. will produce similar plasma concentrations.

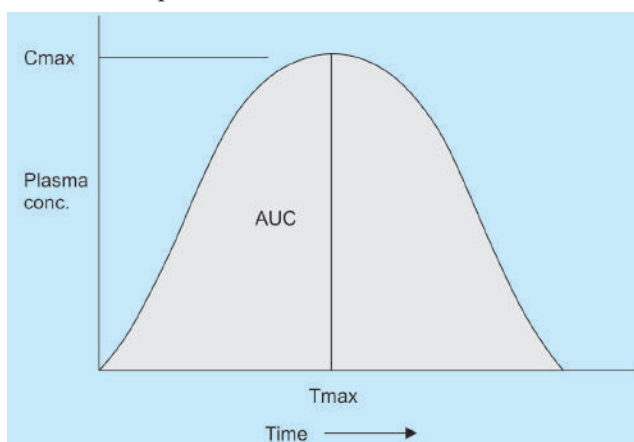


Fig. 2.1: Plot between plasma concentration and time to calculate bioavailability



Drugs with High First pass Metabolism

Nitrates	- Nitrates
Have	- Hydrocortisone
Large	- Lignocaine
Pre	- Propanolol
Systemic	- Salbutamol
Metabolism	- Morphine



AUC Signifies extent of absorption whereas T_{max} tells rate of absorption.

2. DISTRIBUTION

After the drug reaches the blood, it may be distributed to various tissues. This is determined by a hypothetical parameter, **Volume of distribution (V_d)**. It is the volume that would be required to contain the administered dose if that dose was evenly distributed at the concentration measured in plasma. If more amount of drug is entering the tissues, it has a higher volume of distribution and vice-versa. It depends on several factors like lipid solubility and plasma protein binding.

- Drugs which are **lipid soluble** are more likely to cross the blood vessel wall and thus have **high volume of distribution**.

Drugs with high plasma protein binding

- Benzodiazepines
 - Diazepam
 - Chlordiazepoxide
 - Midazolam
- Chlorpropamide
- Tolbutamide
- Cyclosporine
- Fluoxetine
- Imipramine
- Verapamil
- Warfarin

- If a drug is highly **bound to plasma proteins**, (e.g., warfarin, benzodiazepines, furosemide, calcium channel blockers, digitoxin etc.) it will behave like a large molecule and more likely to stay in the plasma. Therefore, less will go to tissues resulting in **reduced volume of distribution**.

It is the free form (which is not bound to plasma proteins of a drug that is responsible for the action as well as the metabolism of a drug. Therefore **plasma protein binding** makes a drug *long acting* by reducing its metabolism. This property can also expose the drug to several drug interactions due to displacement from the binding site by other drugs. The drugs which have low V_d are restricted to the vascular compartment and thus their poisoning can be benefited by dialysis. *Dialysis is not effective in the poisoning due to amphetamines, antidepressants, antipsychotics, benzodiazepines, digoxin, opioids, β -blockers, calcium channel blockers and quinidine.*

Dialysis in Drug Poisoning

Certain drugs can be removed by dialysis. However

- Dialysis does not filter proteins. Therefore, *drugs having high plasma protein binding* (e.g. diazepam) *cannot be removed by dialysis*
- Dialysis removes only those drugs which are present in sufficient free concentration in plasma. Thus, *drugs having high volume of distribution* [More in tissues but less in Plasma] *are difficult to be removed by dialysis* e.g. digoxin, imipramine, propranolol, verapamil etc.
- Thus, drugs having low V_d and low PPB are good candidates of dialysis e.g. salicylates.

Clinical Importance of Plasma Protein Binding

- Duration of action: Drugs with high PPB are usually long acting
- Distribution: High PPB drugs stay in plasma, thus have low V_d .
- Displacement: Highly PPB drug can be displaced by another highly bound drug
- Dialysis: It is not effective for drugs having high PPB

Volume of distribution

It can be calculated by dividing the plasma concentration attained to the dose of a drug administered i.v. Initial plasma concentration (C_0) is calculated by extrapolating the graph of plasma concentration vs time to y-axis.

$$V_d = \frac{\text{Dose administered (i.v)}}{\text{Plasma concentration } (C_0)}$$

It is a measure of the distribution of a drug. If V_d is more, it means more amount of drug is in the tissues and less is in the plasma. Thus, higher dose has to be administered to attain the same plasma concentration for drugs having high V_d than those having low V_d . This high dose is called **loading dose**. Thus, **V_d is the main determinant of loading dose**. Chloroquine is the drug with **highest V_d** (1300 L/Kg).

3. METABOLISM

The primary site of metabolism is liver. Most of the drugs are inactivated by metabolism but some may be activated from the inactive compounds (**Prodrugs**) and others may give rise to active metabolites from the active compound (e.g. diazepam, propranolol).

- Metabolism may occur with the help of **microsomal** (present in smooth endoplasmic reticulum) or **non-microsomal** enzymes. Microsomal enzymes (monooxygenases, cytochrome P450 and glucuronyl transferase) may be **induced** or **inhibited** by other drugs whereas non-microsomal enzymes are not subjected to these interactions.

M

Dialysis is not effective in

A	- Amphetamines
V	- Verapamil
O	- Organophosphates
	- Opioids
I	- Imipramine
D	- Digitalis
Dialysis	- Diazepam

M

PRODRUGS

P	- Prednisone
L	- Levo-dopa
A	- ACE inhibitors (except captopril and lisinopril)
S	- Sulfasalazine
M	- Mercaptopurine
A	- Acyclovir
Makes	- Methyl dopa
Certain	- Cyclophosphamide
	- Clopidogrel
	- Carbimazole
Drugs	- Dipivefrine
Powerful	- Proguanil

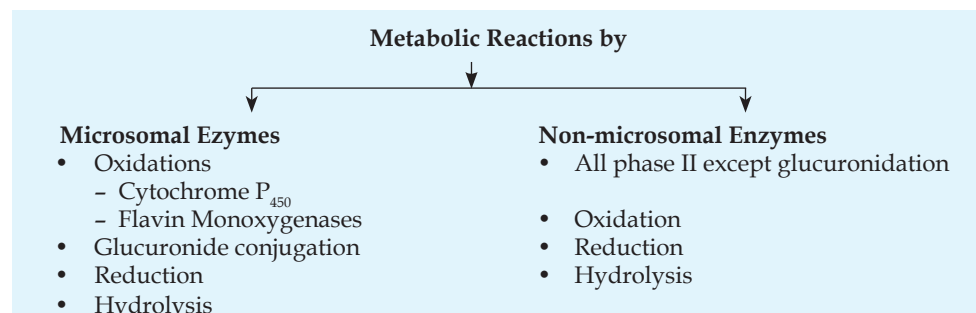
M

Enzyme Inducers

G	- Griseofulvin
P	- Phenytoin
R	- Rifampicin
S	- Smoking
Cell	- Carbamazepine
Phone	- Phenobarbitone

Drug Metabolizing Enzymes

These can be broadly divided into microsomal (present in smooth endoplasmic reticulum) and non-microsomal.



M

Enzyme Inhibitors

Vitamin	- Valproate
K	- Ketoconazole
Cannot	- Cimetidine
Cause	- Ciprofloxacin
Enzyme	- Erythromycin
Inhibition	- INH

G

Glucuronidation is most common phase II metabolic reaction

- The drug which is metabolized by a microsomal enzyme is known as substrate and the chemical increasing or decreasing the number of enzymes is known as inducer or inhibitor respectively.
- Enzyme inducers** will increase the metabolism of other drugs and thus their effect will decrease. Therefore dose of such drugs (which are metabolized by microsomal enzymes) should be increased when administered along with microsomal enzyme inducers. Potent inducers of microsomal enzymes include **rifampicin, phenobarbitone, phenytoin, griseofulvin, phenylbutazone and chloral hydrate**.
- Further, rate-limiting** enzyme of porphyrin synthesis i.e. δ -ALA synthase is a microsomal enzyme. Enzyme inducers like phenytoin and phenobarbitone induce it and increase porphyrin synthesis. Thus, these drugs are contra-indicated in acute intermittent porphyria.
- Enzyme inhibitors** will decrease the metabolism of drugs metabolized by microsomal enzymes, thus predisposes to the toxicity by such agents. Inhibitors include **ketoconazole, cimetidine, erythromycin and metronidazole**.

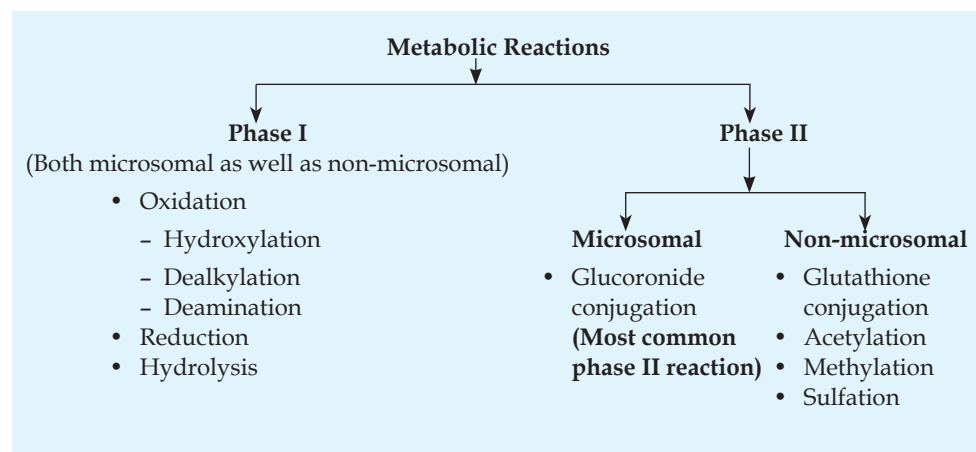
Metabolic reactions may be classified into phase I (non synthetic) and phase II (synthetic) reactions. Function of **phase I reactions** is to attach a **functional group** to the drug molecule whereas **phase II reactions** serve to **attach a conjugate** to the drug molecule. After phase I reaction, drug may be water soluble or lipid soluble whereas **after phase II reaction, all drugs become water soluble** (lipid insoluble). Phase I reactions include oxidation, reduction, hydrolysis, cyclization and decyclization etc. whereas phase II reactions include glucuronidation, acetylation, methylation, sulfation and glycine conjugation etc.

G

Glucuronide conjugation is catalyzed by microsomal enzymes but not by cytochrome p450 enzymes

G

Function of **phase I reactions** is to attach a **functional group** to the drug molecule whereas **phase II reactions** serve to **attach a conjugate** to the drug molecule.



G

Phase I reactions

- Oxidation
- Reduction
- Hydrolysis
- Cyclization
- Decyclization

Phase II reactions

- Glucuronidation
- Acetylation
- Methylation
- Sulfation
- Glycine conjugation

CYP	Substrate	Inducer	Inhibitor
3A4 (Metabolizes 50% of drugs, most common)	• Astemizole • Cisapride • Terfenadine • Cyclosporine • Tacrolimus • Calcium channel blockers • Protease inhibitors • Estrogens	Barbiturates Rifampicin Phenyton Carbamazepine St. John's wort	Erythromycin Ketoconazole Fluconazole Grapefruit juice Ritonavir
2D6 (Metabolizes 20% drugs)	• Most antidepressants – TCA – SSRI – MAO inhibitors • Most beta blockers • Most antiarrhythmics	No known inducer	Quinidine Paroxetine
2 C 19	• Omeprazole • Clopidogrel	Rifampicin Barbiturates	Fluconazole
2 C 9	• Phenyton • Tolbutamide • Warfarin	Rifampicin Barbiturates	Erythromycin Cimetidine
1 A 2	• Theophylline • warfarin	Smoking Rifampicin	Ciprofloxacin
2 E 1	• Acetaminophen • Enflurane • Halothane	Ethanol	Disulfiram

4. EXCRETION

The major route of excretion is kidney. Excretion through kidneys occurs by glomerular filtration, tubular reabsorption and tubular secretion.

Glomerular filtration depends on the *plasma protein binding and renal blood flow*. It **does not depend on the lipid solubility** because all substances (whether water soluble or lipid soluble) can cross the fenestrated glomerular membrane.

Tubular reabsorption depends on the *lipid solubility*. If a drug is lipid soluble, more of it will be reabsorbed and less will be excreted. Opposite is true for lipid insoluble drugs. As lipid solubility depends on ionization, the ionized drug will be excreted by the kidney. Thus, in acidic drug poisoning (*salicylate, barbiturates, chlorpropamide, methotrexate etc.*) urine should be *alkalinized* with sodium bicarbonate because weak acids are in ionized form in alkaline urine and thus are easily excreted. Similarly for basic drug poisoning (e.g. *morphine, amphetamine etc.*), urine should be *acidified* using ammonium chloride.

Tubular secretion does not depend on lipid solubility or plasma protein binding. In the nephron, separate pumps are present for acidic and basic drugs. Drugs utilizing the same transporter may show drug interactions e.g. *probenecid decreases the excretion of penicillin* and increases the excretion of uric acid. Remember, exogenous substances e.g. penicillins are removed whereas endogenous substances like uric acid are retained by these pumps.

Kinetics of Elimination

Rate of Elimination is the *amount of drug eliminated per unit time*. If it is seen as a function of plasma concentration, we derive an important parameter known as **clearance (CL)**

$$CL = \frac{\text{Rate of Elimination}}{\text{Plasma concentration}}$$

Glomerular filtration does not depend on the lipid solubility

Lithium, KI and rifampicin are secreted in saliva

Urine should be *alkalinized* for acidic drug poisoning whereas acidified for basic drug poisoning

ORDER OF KINETICS

Drugs may follow zero order or first order kinetics. It depends on the following formula:

$$\text{Rate of Elimination} \propto \{\text{Plasma Concentration}\}^{\text{order}}$$

- Thus, if a drug follows zero order kinetics, $\{\text{Plasma Concentration}\}^0$ is equal to one, in other words rate of elimination is independent of plasma concentration or rate of elimination is constant.
- From the above formula, rate of elimination is proportional to plasma concentration for the drugs following first order kinetics.

	First Order Kinetics (Linear kinetics)		Zero Order Kinetics (Non linear Kinetics)
1.	Constant fraction of drug is eliminated per unit time.	1.	Constant amount of the drug is eliminated per unit time.
2.	Rate of elimination is proportional to plasma concentration.	2.	Rate of elimination is independent of plasma concentration.
3.	Clearance remains constant.	3.	Clearance is more at low concentrations and less at high concentrations.
4.	Half life remains constant.	4.	Half life is less at low concentrations and more at high concentrations.
5.	Most of the drugs follow first order kinetics.	5.	Very few drugs follow pure zero order kinetics e.g. alcohol
		6.	Any drug at high concentration (when metabolic or elimination pathway is saturated) may show zero order kinetics.

Drugs showing zero/pseudo zero order kinetics

Zero	Zero order kinetics shown by
W	Warfarin
A	Alcohol and Aspirin
T	Theophylline
T	Tolbutamide
Power	Phenytoin

HALF LIFE ($t_{1/2}$)

It is the time required to reduce the plasma concentration to half (50%) of the original value. If metabolism is more, half life is less and vice-versa. It is a *secondary pharmacokinetic parameter derived from two primary parameter; V_d and CL. It determines the dosing interval and time required to reach the steady state* (It does not affect the dose of the drug). Drugs having short half lives are administered more frequently than those having longer half life. It takes 4 to 5 half lives for a drug to reach its steady state.

$$t_{1/2} = \frac{0.693 \times V_d}{CL}$$

Half life is a *secondary pharmacokinetic parameter derived from two primary parameter; V_d and CL*

If a drug follows **first order kinetics**, its **half life is constant**. This is *true both for rising as well as falling plasma concentrations*. When a drug is given by constant i.v. infusion, initially the plasma level rises, it reaches a steady state and when infusion is stopped this level starts declining. Elimination of the drug from plasma is 50% in one half life, 75% (50 + 25) in two half lives, 87.5% (50 + 25 + 12.5) in three half lives and so on. The same is true for rising plasma concentration also i.e. with constant i.v. infusion, in one half life the plasma concentration is half of steady state and in two half lives, it is 75% and so on.

Fig. 2.2: Plasma concentration time curve in first order kinetics when drug administration is stopped at steady state concentration

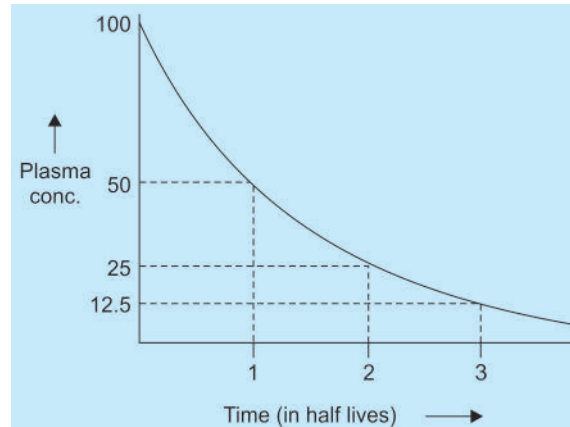
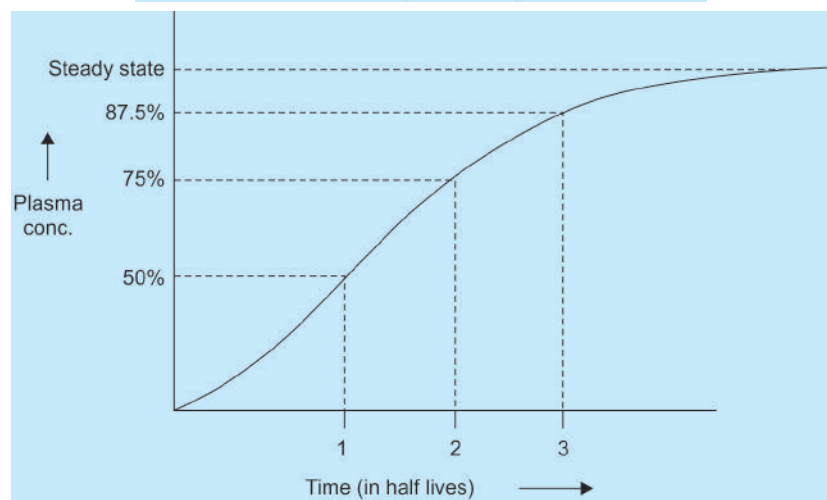


Fig. 2.3: Plasma concentration time curve in first order kinetics with constant i.v. infusion



STEADY STATE

If fixed dose of a drug is administered after regular intervals, its plasma concentration starts increasing. However, as plasma concentration rises, rate of elimination also starts increasing. When rate of administration becomes equal to rate of elimination, plasma concentration stabilizes. This is called steady state.

1. Time to reach steady state depends on $t_{1/2}$. It takes approximately 5 half lives.
2. Steady state plasma concentration achieved depends on dose rate.
3. Variation between peak and trough concentration at steady state depends on dosing interval. However, average steady state plasma concentration remains same irrespective of dosing interval provided dose rate remains same.

Two Dose Strategy

The drugs having high volume of distribution are given by this strategy. First a large dose (loading dose) is administered to attain the steady state quickly and later on, to maintain the plasma concentration smaller dose is given (maintenance dose).

Loading dose: It is mainly used for drugs having long $t_{1/2}$ and large volume of distribution. It is given to load (saturate) the tissue stores. So it is mainly dependent on V_d .

$$\text{Loading dose} = V_d \times \text{Target plasma concentration}$$

Maintenance dose: It is mainly dependent on CL.

$$\text{Maintenance dose} = CL \times \text{Target plasma concentration}$$

THERAPEUTIC DRUG MONITORING (TDM)

- TDM is a process by which the dose of a drug is adjusted according to its plasma concentration.
- It is done for drugs having *known correlation between serum level and drug response or toxicity*.
- It is done for drugs having *wide variation in pharmacokinetics* (absorption, metabolism or excretion), both intra- as well as inter- individual.
- It is done for drugs having *low therapeutic index* like digitalis, aminoglycosides, tricyclic antidepressants, theophylline, lithium, antiepileptics, immuno-modulators and antiarrhythmics etc.
- TDM is done for those drugs whose *effect cannot be easily measured* (like effect of antihypertensive drugs can be easily measured by monitoring BP, so TDM is not used). Due to same reason, TDM is not indicated for anticoagulants (e.g. warfarin) or antidiabetics (e.g. metformin).
- TDM is **not done** for the drugs which are *activated in the body* or produce active metabolites.

TDM is required for

- Digitalis
- Aminoglycosides
e.g. gentamicin
- Lithium
- Antiepileptics
e.g. phenytoin
- Immunomodulators
e.g. Cyclosporine
Tacrolimus

PHARMACODYNAMICS

This is the study dealing with the effect of drugs on the body. It includes actions of drugs as well as their mechanism.

Drugs may act by *physical mechanism* (e.g. osmotic diuretics), *chemical action* (e.g. antacids), stimulation or inhibition of *enzymes* (competitive and non-competitive inhibition) or via *receptors*.

Enzyme Inhibition

Drugs may act by inhibiting the enzymes competitively or non-competitively.

Competitive Inhibition

Important points about this type of enzyme inhibition (e.g. sulfonamides) are:

- Drug should have *similar structure* as that of substrate of the enzyme.
- Inhibitor *binds to the active site* of the enzyme.
- This type of inhibition is *surmountable*, i.e. inhibition can be overcome by increasing the dose of the substrate.
- It results in increase in K_m but does not affect the V_{max} .
- If the drug binds very strongly to the active site, so that it cannot be displaced even by large concentration of substrate, it can result in **irreversible competitive inhibition**. In this type of inhibition, K_m rises and V_{max} decreases.

Noncompetitive Inhibition

Important points about this type of enzyme inhibition (e.g. carbonic anhydrase inhibitors) are:

- Drug *need not have similar structure* as that of substrate of the enzyme.
- It *binds to a different site* of the enzyme, known as *allosteric site*.
- This type of inhibition is *insurmountable*, i.e. inhibition cannot be overcome by increasing the dose of the substrate.
- It results in decrease in V_{max} but does not affect the K_m .

Receptors

These are the binding sites of the drug with functional correlate. Two important terms related to the receptors are affinity and intrinsic activity (IA).

Affinity is the *ability of a drug to combine with the receptor*. If a drug has no affinity, it will not bind to the receptor. So, all type of drugs acting via receptors (agonist, antagonist, inverse agonist and partial agonist) possess some affinity for the receptors. Drugs with high affinity can be used in low concentrations.

M

K_m looks like kilometers, In competition one need to run more kilometers i.e. K_m increases.

D

K_m is Michaelis Menton's constant and is calculated as amount of substrate required to produce half of the maximal velocity whereas V_{max} is maximum reaction velocity.

C

Competitive inhibitors increased K_m and do not alter V_{max} whereas a non-competitive inhibitor result in decrease in V_{max} but does not affect the K_m .

After binding to the receptor, the *ability to activate the receptor* is called its **intrinsic activity**. It *varies from -1 through zero to +1*.

Drugs may be divided into four types *based on their intrinsic activities*.

- **Agonist:** It will bind to the receptor and *activate it maximally*. i.e. **IA is +1**
- **Antagonist:** Binds to the receptor but produces **no effect (IA is 0)**. But now agonist is not able to bind to the receptor because these are already occupied by the antagonist. Thus, it decreases the action of the agonist but itself has no effect.
- **Partial agonist:** It activates the receptor submaximally (**IA between 0 and +1**). It will produce the similar effect in the absence of agonist but it will decrease the effect of a pure agonist. e.g. pindolol has partial agonistic activity at β_1 receptors. In the presence of agonists like adrenaline and nor-adrenaline it will produce antagonistic effect i.e. decrease in heart rate but even in high doses it does not result in severe bradycardia due to some agonistic action.
- **Inverse agonist:** These type of drugs bind to the receptor and produce opposite effect (**IA is negative**) e.g. β carboline is an inverse agonist at BZD receptors.

Antagonist

These may be physical, chemical, physiological or pharmacological.

- **Physical antagonist** binds to the drug and prevents its absorption like charcoal binds to the alkaloids and prevents their absorption.
- **Chemical antagonist** combines with a substance chemically like chelating agents bind with the metals.
- **Physiological antagonist** produces an action opposite to a substance but *by binding to the different receptors* e.g. adrenaline is a physiological antagonist of histamine because adrenaline causes bronchodilation by binding to β_2 receptors, which is opposite to bronchoconstriction caused by histamine through H_1 receptors.
- **Pharmacological antagonists** produce opposite actions by *binding to the same receptor* e.g. beta blockers.

CLASSIFICATION OF RECEPTORS

The receptors are classified into four types based on the signal transduction mechanisms.

G Protein Coupled Receptors (Metabotropic Receptors)

These are heptahelical (serpentine) receptors i.e. have seven transmembrane spanning segments. Drugs bind to the receptor which in turn activates a G protein (GTP activated protein). G-proteins consist of three subunits; α , β and γ . When all three are joined together (along with GDP), G-protein is inactive. When GTP replaces GDP, α -subunit separates from β - γ subunit and become activated. Activated α -subunit may result in one of the 3 actions:

1. **Activation (by Gs) or inhibition (by Gi) of enzyme adenylyl cyclase:** It changes the concentration of cAMP that acts by activating protein kinases (e.g. protein kinase A). Latter produce action by phosphorylation of their substrates. Examples include β -receptors (increase cAMP) and somatostatin (works by decreasing cAMP).
2. **Activation of phospholipase C (by Gq):** This enzyme converts PIP_2 to IP_3 and DAG. Final result is increase in intracellular calcium and thus action e.g. α -receptors, vasopressin V_1 receptors.
3. **Stimulation or inhibition of ion channels** e.g. M_2 receptors of ACh.



Cyclic AMP, IP_3 and DAG act as second messengers

Cyclic AMP, IP_3 and DAG act as second messengers whereas Ca^{2+} is a third messenger. After the action, the intrinsic GTPase activity of alpha subunit result in joining it with β - γ subunits and thus G-protein is available for action again.

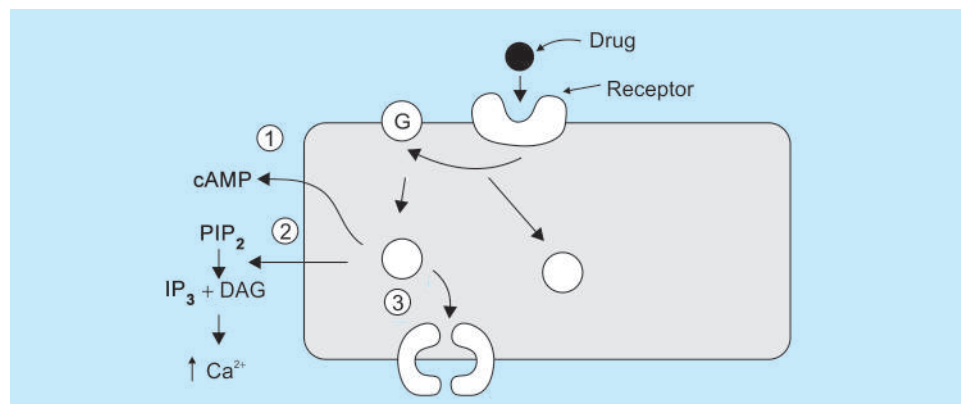


Fig. 2.4: G-protein coupled receptor

Inotropic Receptors

The drug binds directly to the receptor located on an ion channel without mediation by G proteins. These are the **fastest acting receptors**. It includes GABA_A , N_M , N_N , NMDA (receptors of glutamate) and 5-HT_3 receptors.

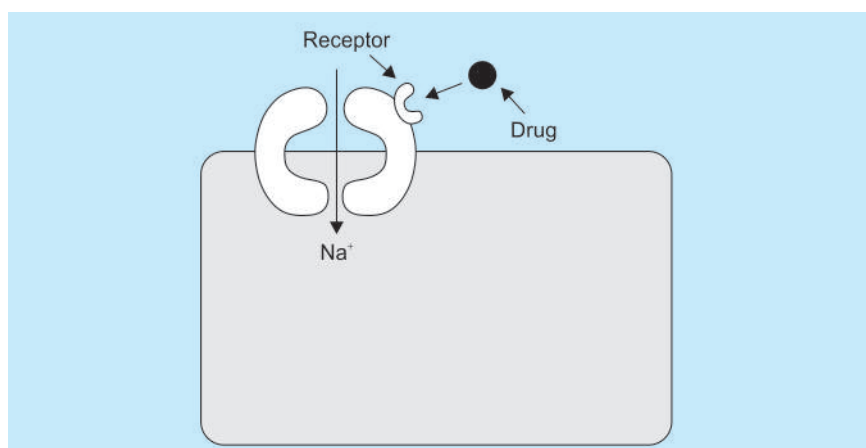


Fig. 2.5: Ionotropic receptors

Inotropic receptors include GABA_A , N_M , N_N , NMDA (receptors of glutamate) and 5-HT_3 receptors.

Enzymatic Receptors

This type of receptor has two sites, the drug binds on the extracellular site and the intracellular site has enzymatic activity (mostly *tyrosine kinase*). This enzyme can be activated via JAK-STAT pathway.

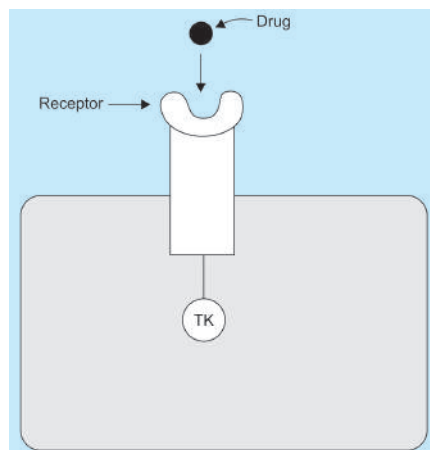


Fig. 2.6: Enzymatic receptors

Insulin, growth hormone, prolactin and cytokines act via enzymatic receptors.

Intracellular Receptors

These types of receptors are **slowest acting**. These may be present in the **cytoplasm** (glucocorticoids, mineralocorticoids, and vit. D) or in the **nucleus** (T₃, T₄, Retinoic acid, PPAR, estrogen, progesterone and testosterone). Both type of receptors finally act by nuclear mechanisms (i.e. by affecting transcription).

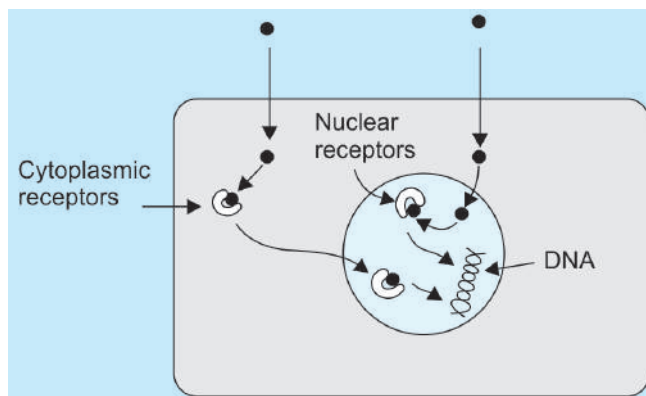


Fig. 2.7: Intracellular receptors

Dose Response Curve (DRC)

It is a graph between the dose of a drug administered (on X-axis) and the effect produced by the drug (on Y-axis). It consists of two components; *dose-plasma concentration curve* and *plasma concentration-response curve*. As plasma concentration is more closely related to response, the graph between plasma concentration and response is usually called **DRC**. Two types of DRC can be described: *Quantal* and *graded*.

QUANTAL DRC

When the response is an 'all or none' phenomenon (e.g. antiemetic drug stopping the vomiting or not), the y-axis (response axis) shows the number of person responding and X-axis shows the plasma concentration. It is used to calculate ED₅₀ and LD₅₀.

Median Effective Dose (ED₅₀): It is the *dose that will produce the half of the maximum (50%) response*. More is ED₅₀, lower is the potency and vice a versa.

Median Lethal Dose (LD₅₀): It is the dose that will result in death of 50% of the animals receiving the drug. More is LD₅₀, safer is the drug.

Therapeutic Index (T.I.): It is a *measure of the safety* of a drug. It is calculated as a ratio of LD₅₀ to ED₅₀. Drugs having high T.I. are safer whereas those having low T.I. are more likely to be toxic.

$$T.I. = \frac{LD_{50}}{ED_{50}}$$

GRADED DRC

When the response can be graded (e.g. reduction in BP), the y-axis shows the magnitude of response.

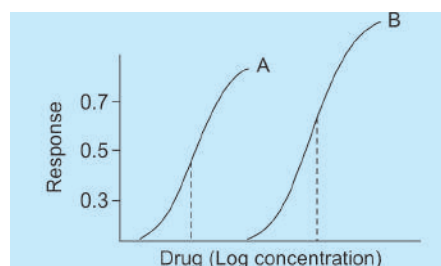


Fig. 2.8: Log DRC of two drugs A and B

DRC is **usually hyperbola** in shape. As curved lines cannot give good mathematical comparisons, so usually the dose is converted to log dose to form **log DRC**, which gives a

sigmoid shaped curve. The middle portion (which is of therapeutic importance) is straight line in the log DRC. Another advantage of converting it into logarithmic form is that large variation in doses can be plotted on the same curve. **Three important parameters** (*potency, efficacy and slope of curve*) can be determined from DRC.

Potency

It is the measure of the amount of a drug needed to produce the response. *Drugs producing the same response at lower dose are more potent* whereas those requiring large dose are less potent. In DRC, more a drug is on left side of the graph, higher is its potency and vice versa. In Fig. 1.8, drug A is more potent than drug B.

Efficacy

It is the maximum effect produced by a drug. *More the peak of the curve greater is the efficacy.* It is clinically more important than potency. In Fig. 1.8, drug B is more efficacious than drug A.

Slope

If the DRC is steeper, that means the response will increase dramatically with slight increase in dose. Thus, *drugs having steeper DRC have narrow therapeutic index* (like barbiturates) than those having less steep curves (e.g. benzodiazepines).

DRC can also be utilized to know whether a drug is competitive or non-competitive inhibitor.

- In case of **competitive inhibitor**, curve will shift to right, i.e. now the same agonist will have less potency in the presence of antagonist. It does not affect the efficacy.
- In case of **non competitive inhibitor**, there will be **flattening of DRC**, i.e. efficacy decreases. It usually does not affect potency. If the antagonist is **irreversible competitive**, then there will be decrease in potency as well as efficacy.

Efficacy is clinically more important than potency.

Drugs having steep DRC have narrow therapeutic index (like barbiturates) than those having less steep curves (e.g. benzodiazepines).

In case of competitive inhibitor, dose response curve will shift to right whereas In case of non competitive inhibitor, there will be flattening of DRC.

Pharmacogenetic Conditions

Due to different genetic make up, some drugs have different effects in different individuals, so these drugs may show either toxicity or lack of effect in certain individuals, if used in conventional dosage. These conditions include:

1. **Acetylator polymorphism:** Some individuals are *slow acetylators* and some are *fast acetylators*. The drugs metabolized by this route may be ineffective in fast acetylators and may show toxicity in slow acetylators.

Important drugs metabolized by acetylation include (remembered as **SHIP**)

- Sulfonamides including dapsone and PAS
- Hydralazine
- Isoniazid
- Procainamide

Note:

- All SHIP drugs can also cause lupus erythematosus.
- Other drugs metabolized by acetylation include acebutolol, amantadine, amrinone, benzocaine, clonazepam, nitrazepam and phenelzine etc.

2. **Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency:** Oxidant drugs may produce *hemolysis* in the patient with deficiency of this enzyme. The important drugs are:

• Primaquine	• Chloroquine	• Menadione
• Sulfonamides including dapsone	• Nitrofurantoin	• Isoniazid
• Quinine	• Nalidixic acid	

3. **Atypical pseudocholinesterase and Succinylcholine:** Succinylcholine is a very short acting drug due to metabolism by pseudocholinesterase. In some individuals, this enzyme is not functioning well (atypical). In such individuals this drug may produce *prolonged apnea*.
4. **Inability to hydroxylate Phenytoin**
5. **Resistance to coumarin anticoagulants**
6. **Malignant hyperthermia by halothane.**

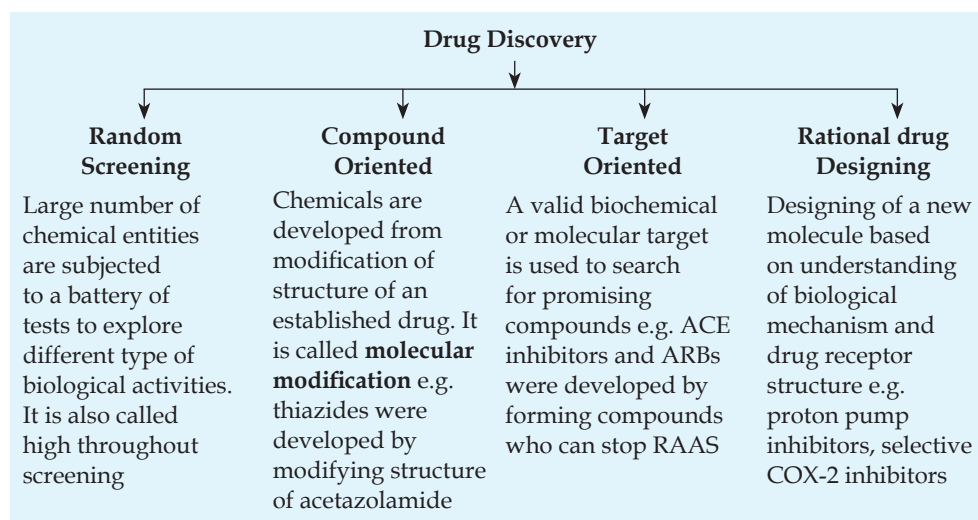
NEW DRUG DEVELOPMENT

Drug development process is broadly divided into

- Drug discovery phase
- Preclinical studies
- Clinical trials

Drug Discovery Phase

Most new drugs are discovered through random screening, compound oriented approach, target oriented approach or rational drug designing.



These all approaches result in selection of several compounds (process called **lead finding**). These are then subjected to various procedures to identify one or two drug candidates (now called **lead compounds**) suitable for further investigations. (This process is called **lead optimization**). These lead compounds are then evaluated in preclinical phase.

Pre-Clinical Studies

The lead compounds are tested on animals to know the whole pharmacological profile. Tests are first performed on small animals (mice, rat, guinea pig etc. and then on large animal (like cat, dog, monkey etc). All studies like pharmacokinetics, pharmacodynamics, toxicology, therapeutic index etc. are performed and promising compounds are selected that can be evaluated in humans.

Clinical Trials

Before a new drug comes to the market, it is extensively tested in animals and in vitro studies for safety and efficacy. If the drug is found to be promising in these studies, an application called **IND (Investigational New Drug)** is filed with the United States Food and Drug Administration (main regulatory authority). If the permission is granted, then drug is tested in humans. This testing is called clinical trials. These are divided into four phases.

In phase 1 clinical trials, The drug is tested in **healthy human volunteers** and we **cannot determine efficacy** in this phase.

Ethical clearance is not necessary in phase 4 clinical trials.

Phase 1: Here, the drug is tested in **normal human volunteers** (extremes of ages ; elderly and children are excluded). As the drug is not tested in the patients, so we **cannot determine efficacy** in this phase. This is mainly for **toxicity** and **pharmacokinetic studies**. This is **first in human study**. The idea of testing the new drug in normal humans is based on the fact that healthy persons are more likely to tolerate the adverse effects of the drug than diseased persons. Because anti-cancer drugs can produce unacceptable toxicity and we cannot expose healthy humans to such a toxicity, the *phase-1 trials for anticancer drugs are done in the patients*.

Phase 2: The drug in this phase is tested in *small number of (20-200) patients*. We can determine *both efficacy and safety* in this phase. This is **first in patient study**.

Phase 3: Here the drug is tested in *large number of patients at several centers* to include patient with different genetic makeup. This is done to generalize the results of the study to variable genetic and ethnic groups.

If the drug is found to be safe and effective in these trials, then another application is filed with FDA (**New Drug Application or NDA**) to market the drug. If approval is granted, the drug is marketed.

Phase 4: This is **post marketing surveillance** of a drug to know the rare adverse effects or those occurring with prolonged use of the drug. In this phase **ethical clearance is not required**.

All phases of clinical trials must follow the ICH-GCP (Good clinical practice guidelines given by International Conference for Harmonization, so that the data generated is credible and interest of the patients/volunteers can be safeguarded.

Recently, Phase O trial has also been added and is known as microdosing studies. This is added to expedite the marketing of the drug.

SUMMARY OF CLINICAL TRIALS

Phase	Name	Conducted on	Blinding and control	Purpose
I	Human Pharmacology and safety	Healthy volunteers (20 – 100)	OPEN LABEL (No blinding)	– To know maximum tolerable dose (MTD) – Safety and tolerability
II	Therapeutic exploratory	100 – 150 Patients (homogenous population)	Single blind Controlled	– To establish therapeutic efficacy – Dose ranging and ceiling effect
III	Therapeutic confirmatory	Upto 5000 patients from several centres (heterogenous population)	Double blind Randomized Controlled	– To confirm therapeutic efficacy – To establish the value of drug in relation to existing therapy
IV	Post marketing surveillance	Large number of patients being treated by practicing physicians	—	– To know rare and long-term adverse effects – Special groups like children, pregnancy etc can be tested
O (Zero)	Microdosing studies	Healthy volunteers (small number)	—	– Very low dose 1/100th of human dose; max 100 µg of drug is administered to know pharmacokinetics. This could avoid costly phase I studies for candidate drugs with unsuitable pharmacokinetics.

Adverse Drug Reactions

These are noxious or unintended effects produced by drugs. These may be classified as

- **Type A:** Augmented pharmacologic effects - Dose dependent and predictable e.g. hypoglycemia caused by anti-hyperglycemic drugs like sulfonylureas
- **Type B:** Bizarre effects (or idiosyncratic) - Dose independent and unpredictable e.g. allergic reactions caused by penicillins
- **Type C:** Chronic effects e.g. peptic ulcer caused by chronic use of NSAIDs
- **Type D:** Delayed effects e.g. teratogenicity caused by thalidomide
- **Type E:** End-of-treatment effects e.g. withdrawal response to morphine
- **Type F:** Failure of therapy

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems



An **orphan drug** is a pharmaceutical agent that has been developed specifically to treat a rare medical condition (affecting fewer than 200,000 people)

Orphan Drugs

An **orphan drug** is a pharmaceutical agent that has been developed specifically *to treat a rare medical condition* (affecting fewer than 200,000 people), the condition itself being referred to as an orphan disease. Examples include *deferipirone* to treat iron overload in thalassemia patients, *N-acetylcysteine* to treat paracetamol poisoning etc. Since the pharmaceutical companies will not like to develop such a drug due to lack of financial benefits, a separate law known as '*The Orphan Drug Act*' was passed in 1983. The intent of the Orphan Drug Act is to stimulate the research, development, and approval of products that treat rare diseases.

Essential drugs

- These are the drugs **that satisfy the priority healthcare needs of a population**. These are selected with regard to
 - Incidence and prevalence of disease (public health relevance)
 - Evidence on safety and efficacy
 - Comparative cost-effectiveness
 - Assurance of quality
- Most essential drugs are formulated as **single compounds**
- WHO brought first essential drug list in 1977. It is updated every 2 years. The current version is 18th WHO essential medicines list and 4th WHO essential medicines list for children updated in April 2013.
- The first national essential medicine list of India was prepared in 1996. It was revised in 2003, 2011 and in 2013. The latest list contains 406 drugs

Schedule of Drugs

'Drugs and cosmetics act 1940' along with 'Drugs and cosmetic rules 1945' and its amendments describe various schedule of drugs. Important schedules are:

Schedule	Deals with
C and C1	Biological and special products
F and F1	Bacterial vaccines
G	Drugs to be labelled with the word "Caution"-It is dangerous to take this preparation except under medical supervision
H	Drugs that must be sold by retail only when a prescription by RMP is produced
M	Good manufacturing practices (GMP)
P	Expiry period of drug formulations
W	Drugs that shall be marketed under generic names only
X	Psychotropic drugs requiring special licence for manufacture and sale
Y	Requirements and guidelines on clinical trials, import and manufacture of new drugs

GOLDEN POINTS

1. Two drugs having opposite response via action on different receptors are called **physiological antagonists**, e.g. adrenaline (causes bronchodilation by action on β_2 receptors) is physiological antagonist of histamine (causes bronchoconstriction by acting on H_1 receptors).
2. Two drugs having opposite response via action on same receptors are called **pharmacological antagonists**, e.g. propranolol (causing bradycardia by acting on β_1 receptors) is pharmacological antagonist of adrenaline (causes tachycardia by acting on β_1 receptors)
3. Alpha 1 (α_1) receptors act by increasing Ca^{2+} whereas β_1 increase cAMP in the cell.
4. Apparent volume of distribution is more than total body fluids (very high), if the drug is sequestered by tissues.

5. Essential medicines are the drugs that cater to priority health-care needs of a population. Most of these are formulated as single compounds.
6. Important drugs causing hemolysis in a patient with G-6-PD deficiency are primaquine, sulfonamides, dapsone and methylene blue.
- 7.

Clinical Trial	Other Name
Phase 0	Microdosing studies
Phase I	Human pharmacology and safety
Phase II	Therapeutic exploratory
Phase III	Therapeutic confirmatory
Phase IV	Post marketing surveillance

8. **Grapefruit juice** acts as inhibitor of CYP3A4 due to its content of **furanocoumarins** and **narigin**.
9. Therapeutic index is a measure of safety of a drug. It is calculated as LD50/ED50.
10. **Schedule H** of drugs and cosmetics act deal with **drugs that must be sold by retail only when a prescription by registered medical practitioner is produced**. Most drugs fall under this schedule.
11. Efficacy refers to maximum response a drug can produce regardless of its dose.
12. Phocomelia is defect in development of long bones. It is caused by thalidomide when given to pregnant females.
13. Drugs metabolized by acetylation and causing SLE like syndrome are:
 - Sulfonamides (including dapsone)
 - Hydralazine
 - Isoniazid
 - Procainamide
14. Rifampicin can result in failure of oral contraceptives due to its enzyme inducing property.
15. Pharmacogenetics refers to study dealing with how variations in human genome affect the response to drugs.
16. Drugs following zero-order kinetics are warfarin, alcohol, high dose aspirin, theophylline, tolbutamide and phenytoin.
17. Most accurate method of calculating drug dosage in children is body surface area.
18. Therapeutic drug monitoring is not required for antihypertensive (e.g. ACE inhibitors), antidiabetic (e.g. metformin) and anticoagulant (e.g. warfarin) drugs.
19. Important microsomal enzyme inhibitors are valproate, ketoconazole, cimetidine, macrolides (except azithromycin), ciprofloxacin and protease inhibitors.
20. Gastric lavage is contra-indicated in corrosive [strong acid or strong base] and kerosene poisoning.
21. Forced alkaline diuresis is effective for management of acidic drug poisoning like phenobarbitone, aspirin and methotrexate, etc.

MULTIPLE CHOICE QUESTIONS

PHARMACOKINETICS (ADME)

- Ritonavir inhibits metabolism of the following drugs except:** (AIIMS May 2013)
 - Amiodarone
 - Phenobarbitone
 - Cisapride
 - Midazolam
- Alkaline diuresis is done for treatment of poisoning due to:** (AI 2012)
 - Morphine
 - Amphetamine
 - Phenobarbitone
 - Atropine
- The mitochondrial enzyme involved in the metabolism of clopidogrel and proton pump inhibitors is:** (AI 2012)
 - CYP 2A
 - CYP 2B
 - CYP 2C10
 - CYP 2C20
- Which of the following is wrongly matched regarding drug elimination?** (AIIMS Nov 2011)
 - Calcium channel blockers: CYP3A4
 - Carvedilol: CYP2D6
 - Digoxin: P-glycoprotein
 - Simvastatin: Glucuronide conjugation
- Which of the following is a prodrug?** (AIIMS May 2008, AIIMS Nov 2006, AIIMS May 2004)
 - Enalapril
 - Clonidine
 - Salmeterol
 - Acetazolamide
- Which of the following drugs is an inhibitor of cytochrome p450 enzymes?** (AIIMS May 2008)
 - Ketoconazole
 - Rifampicin
 - Phenytoin
 - Phenobarbitone
- In metabolism of xenobiotics, all of the following reactions occur in phase one EXCEPT?** (AI 2012, AIIMS Nov 2008)
 - Oxidation
 - Reduction
 - Conjugation
 - Hydrolysis
- Identify the wrong statement:** (DPG 2009)
 - Acidic drugs bind to albumin in plasma
 - Basic drugs bind to alpha-1 acid glycoprotein in plasma
 - Drugs having higher affinity for a plasma protein can displace the other drug from the same protein
 - Sex steroid hormones do not bind to any protein in plasma
- Alkalinization of urine is required for decreasing the poisoning due to:** (AI-2008)
 - Barbiturates
 - Amphetamine
 - Alcohol
 - Morphine
- All of the following results in detoxification of drugs EXCEPT:** (AI-2008)
 - NADPH cytochrome P450 reductase
 - Cytochrome P450
 - Cytochrome oxidase
 - Monooxygenase
- Which of the following antiplatelet drugs is a prodrug?** (AI 2007)
 - Clopidogrel
 - Tirofiban
 - Aspirin
 - Dipyridamole
- A highly ionized drug:** (AI 2005, AI 2004)
 - Is excreted mainly by the kidney
 - Can cross the placental barrier easily
 - Is well absorbed from the intestine
 - Accumulates in the cellular lipids
- The extent to which ionization of a drug takes place is dependent upon pKa of the drug and the pH of the solution in which the drug is dissolved. Which of the following statements is NOT correct?** (AI 2003)
 - pKa of a drug is the pH at which the drug is 50% ionized
 - Small changes of pH near the pKa of a weak acidic drug will not affect its degree of ionization.
 - Knowledge of pKa of a drug is useful in predicting its behaviour in various body fluids.
 - Phenobarbitone with a pKa of 7.2 is largely unionized at acid pH and will be about 40% nonionized in plasma.
- All of the following statements regarding bioavailability of a drug are true except:** (AI 2003)
 - It is a fraction of administered drug that reaches the systemic circulation in unchanged form

- (b) Bioavailability of an orally administered drug can be calculated by comparing the Area Under Curve after oral and intravenous administration
- (c) Low oral availability always and necessarily means poor absorption
- (d) Bioavailability can be determined from plasma concentration or urinary excretion data.
- 15. Which of the following drugs should be removed by dialysis?** (AI 2001)
- (a) Digoxin
- (b) Salicylates
- (c) Benzodiazepines
- (d) Organophosphates
- 16. Which of the following is true?** (AI 2000)
- (a) As the concentration of the drug increases over the therapeutic range, only the bound form of the drug increases
- (b) The bound form is not available for metabolism but is available for excretion
- (c) Acidic drugs binds to beta globulin and basic drugs bind to albumin
- (d) Binding sites are non-specific and one drug can displace the other
- 17. In a patient with nephrotic syndrome and hypoalbuminemia, protein binding of which drug will not be affected:** (AIIMS May, 2002)
- (a) Tolbutamide
- (b) Morphine
- (c) Diazepam
- (d) Valproate
- 18. Drug transport mechanisms include:** (PGI June, 2006)
- (a) Active transport
- (b) Passive transport
- (c) Lipid solubility
- (d) Bioavailability
- (e) Distribution
- 19. Duration of action of i.v. administered drug depends on:** (PGI June, 2006)
- (a) Protein binding
- (b) Clearance
- (c) Distribution volume
- (d) Lipid solubility
- (e) Half life
- 20. Causes for reduced bioavailability include:**
- (a) High first pass metabolism (PGI June, 2006)
- (b) Increased absorption
- (c) IV drug administration
- (d) High lipid solubility
- (e) Non-ionization
- 21. CYP 3A4 enzymes are affected by:** (PGI Dec. 2005)
- (a) Fexofenadine
- (b) Phenytoin
- (c) Carbamazepine
- (d) Azithromycin
- (e) Penicillin
- 22. Which of the following is not true:** (PGI Dec. 2005)
- (a) If a drug is administered rectally it follow 1st order kinetics
- (b) If a drug is administered I.M. it follows zero order kinetics
- (c) If a drug is administered I.V. it follows 1st order kinetics
- (d) Bio availability is usually lower after oral administration than i.v. administration
- 23. CYP-450 inducers are:** (PGI June, 2005)
- (a) Cimetidine
- (b) Ketoconazole
- (c) Phenobarbitone
- (d) DDT
- (e) Theophylline
- 24. Drug distribution is influenced by:** (PGI June, 2005)
- (a) Plasma protein binding
- (b) Lipid solubility
- (c) Degree of blood flow
- (d) Age
- 25. True statement about route of drug administration is:**
- (a) 80% bio-availability by I.V. injection (PGI June, 2004)
- (b) I.M. administration needs sterile technique.
- (c) I.D. injection produces local tissue necrosis and irritation
- (d) Inhalation produces delayed systemic bioavailability
- 26. Volume of distribution of drugs is altered in:** (PGI June, 2004)
- (a) Obesity
- (b) Athletes
- (c) Pregnancy
- (d) Old age
- (e) Neonate
- 27. Which of the following are prodrugs?** (PGI Dec. 2004)
- (a) Mercaptopurine
- (b) Dipivefrine
- (c) Enalapril
- (d) Phenytoin
- (e) Linezolid
- 28. High first pass metabolism is seen in:** (PGI Dec. 2004)
- (a) Lignocaine
- (b) Propanolol
- (c) Salbutamol
- (d) Dipyridamol
- (e) Erythromycin
- 29. In hepatic metabolism, phase II reactions are:** (PGI Dec. 2002)
- (a) Dealkylation
- (b) Sulfation
- (c) Methylation
- (d) Glucuronidation
- (e) Deamination

30. High hepatic extraction ratio is seen in: (PGI June, 2002)
- Propanolol
 - Lidocaine
 - Ampicillin
 - Imipramine
 - Theophylline
31. Regarding termination of drug action:
- Drugs must be excreted from the body to terminate their action
 - Metabolism of drugs always abolishes their pharmacologic activity
 - Hepatic metabolism and renal excretion are the two most important mechanisms involved
 - Distribution of a drug out of blood stream terminates the drug's effects
32. The process by which the amount of a drug in the body decreases after administration but before entering the systemic circulation is called:
- Excretion
 - First pass effect
 - First order elimination
 - Metabolism
33. The most general term for the process by which the amount of active drug in the body is reduced after absorption into the systemic circulation is:
- Excretion
 - Elimination
 - First pass metabolism
 - Distribution
34. Titration of the dose of a drug with the response can be done with which of the following routes of administration:
- Sublingual
 - Transdermal
 - Inhalational
 - Subcutaneous
35. Urinary alkalinizing agents are administered in case of poisoning due to drugs which are:
- Weak bases
 - Weak acids
 - Strong bases
 - Strong acids
36. Which of the following drugs has maximum chances of absorption from gastric mucosa?
- Morphine sulfate
 - Diclofenac sodium
 - Hyoscine hydrobromide
 - Quinine dihydrochloride
37. All of the following factors tend to increase the volume of distribution of a drug EXCEPT:
- High plasma protein binding
 - Low ionization at physiological pH values
 - High lipid solubility
 - High tissue binding
38. Which of the following drugs is commonly administered by intranasal route?
- Adrenaline
 - Desmopressin
 - Ganirelix
 - Insulin
39. Major mechanism of transport of drugs across biological membranes is by:
- Passive diffusion
 - Facilitated diffusion
 - Active transport
 - Endocytosis
40. A drug X is secreted through renal tubules, tubular secretion of this drug can be confirmed if renal clearance of drug X is:
- More than the GFR
 - Equal to the GFR
 - Less than the GFR
 - More than volume of distribution
41. Metabolism of a drug primarily results in:
- Activation of the active drug
 - Conversion of prodrug to active metabolite
 - Conversion of lipid soluble drugs to water soluble metabolites
 - Conversion of water soluble drug to lipid soluble metabolites
42. A new drug is found to be highly lipid soluble. It is metabolized at a slower rate of 10% per hour. On intravenous injection it produces general anaesthesia that lasts only for 15 min. This short duration of anaesthesia is due to:
- Metabolism of the drug in liver
 - High plasma protein binding of the drug
 - Excretion of drug by kidney
 - Redistribution
43. All of the following are advantages of transdermal drug delivery systems EXCEPT:
- They produce high peak plasma concentration of the drug
 - They produce smooth and nonfluctuating plasma concentration of the drug
 - They minimize interindividual variations in the achieved plasma drug concentration
 - They avoid hepatic first pass metabolism of the drug
44. Thiopentone is used for induction of anaesthesia. It shows marked redistribution which is a characteristic of:
- Highly lipid soluble drugs
 - Highly water soluble drugs
 - Weak electrolytes
 - Highly plasma protein bound drugs
45. True statement about weakly basic drugs is:
- These are bound primarily to plasma albumin
 - These are excreted faster in acidic urine

- (c) Are highly ionized in the intestinal juice
(d) These are absorbed mainly from stomach
46. Which of the following statements about a drug having high plasma protein binding is TRUE?
(a) Volume of distribution of the drug is very high
(b) This drug will be filtered quickly by glomerulus
(c) This drug is likely to have minimum chances of drug interactions
(d) High plasma protein binding decreases the volume of distribution
47. Most common phase II drug metabolizing reaction is:
(a) Glucuronidation
(b) Acetylation
(c) Oxidation
(d) Glutathione conjugation
48. All of the following reactions are catalyzed by microsomal enzymes EXCEPT:
(a) Glucuronidation
(b) Acetylation
(c) Oxidation
(d) Reduction
49. Which of the following factors has maximum effect on filtration of a drug by the glomerulus?
(a) Lipid solubility
(b) Plasma protein binding
(c) Degree of ionization
(d) Rate of tubular secretion
50. A factor that is likely to increase the duration of action of a drug D that is partially metabolized by CYP3A4 in the liver is:
(a) Chronic administration of phenobarbital with the drug
(b) Chronic administration of cimetidine with the drug
(c) Displacement from tissues binding sites by another drug
(d) Chronic administration of rifampicin
51. A three year old child is brought to the emergency department having just ingested a large overdose of an antihistaminic drug. This drug is a weak base capable of entering most tissues including the brain. On physical examination the heart rate is 100/ minute, blood pressure is 110/60 mm Hg and the respiratory rate is 20/ minute. In this case of poisoning:
(a) Urinary excretion would be accelerated by administration of NH_4Cl , an acidifying agent
(b) Urinary excretion would be accelerated by administration of NaHCO_3 , an alkalinizing agent
(c) More of the drug would be ionized at blood pH than at stomach pH
(d) Absorption of the drug would be faster from the stomach than from the small intestine.
52. A patient, Rajesh with a history of wheezing, coughing and shortness of breath is being evaluated in the asthma clinic. Several drug treatments with different routes are under consideration. Which of the following statements about routes of administration is most correct?
(a) Administration of a bronchodilator drug by inhaled aerosol is usually associated with more adverse effects than administration of this drug by mouth.
(b) The first pass effect is the result of elimination of a drug after administration and before it enters systemic circulation.
(c) Bioavailability of most drugs is greater with rectal administration than with sublingual administration
(d) Administration of a drug by transdermal patch is often faster but is associated with more first pass metabolism than oral administration
53. Drugs with high plasma protein binding have:
(a) Short duration of action (DPG 2003)
(b) Less drug interactions
(c) Lower volumes of distribution
(d) All of the above
54. Which does not induce microsomal enzymes?
(a) Cimetidine (DPG 2003)
(b) Griseofulvin
(c) Rifampicin
(d) Phenobarbitone
55. Which of the following is a prodrug? (DPG 2002)
(a) Ampicillin
(b) Captopril
(c) Levodopa
(d) Phenytoin
56. Which one of the following drugs does not have active metabolite? (MPPG 2007, MPPG 2004)
(a) Diazepam
(b) Propanolol
(c) Allopurinol
(d) Lisinopril
57. Which one of the following drugs does not undergo hepatic first pass effect? (MPPG 2007)
(a) Propanolol
(b) Lidocaine
(c) Insulin
(d) Morphine
58. Which of the following is a prodrug? (MPPG 2005)
(a) Captopril
(b) Cimetidine
(c) Carbimazole
(d) Carbamazepine
59. High hepatic first pass metabolism is seen in all EXCEPT (MPPG 2004)
(a) Insulin:
(b) Propanolol
(c) Lignocaine
(d) Nitroglycerine

60. Which of the following drugs do not produce active metabolites? (MPPG 2004)
- Enalapril
 - Lisinopril
 - Prednisone
 - Sulfasalazine
61. Apparent volume of distribution (V_d) of a drug exceeds total body fluid volume, if a drug is: (MPPG 2003)
- Sequestered in body tissues
 - Slowly eliminated from body
 - Poorly soluble in plasma
 - Highly bound to plasma proteins
62. Which of the following drug acts as microsomal enzyme inhibitor: (MPPG 2003)
- Rifampicin
 - Cimetidine
 - Phenobarbitone
 - Phenytoin
63. Which of the following is an inducer of microsomal enzymes: (MPPG 2002)
- Phenobarbitone
 - Paracetamol
 - Digoxin
 - Penicillin
64. Removal of acidic drugs from body is done by using: (MPPG 2001)
- Ammonium chloride
 - Sodium bicarbonate
 - Hydrochloric acid
 - Citric acid
65. Very high first pass metabolism is seen in: (DNB 2006, 2004, MH 2000)
- Digoxin
 - Dicoumarol
 - Propranolol
 - Practolol
66. Pharmacokinetics is: (UP 2005)
- Study of absorption, distribution, binding storage/biotransformation and excretion of the drug
 - Study of physiological and biochemical effects of drugs
 - Application of pharmacological information together with knowledge of the disease
 - Scientific study of drugs in humans
67. Which one of the following is a prodrug? (JIPMER 2002) (MP 2005) (UP 2005) (TN 2004)
- Dopamine
 - Epinephrine
 - Levodopa
 - Prednisolone
68. Which one of the following is a prodrug? (TN 2005)
- Dopamine
 - Enalapril
 - Ampicillin
 - Prednisolone
69. 'Bioavailability' is defined as: (TN 2005)
- The volume of plasma completely cleared of a specific compound per unit time and measured as a test of kidney function
 - The percentage of drug that is detected in the systemic circulation after its administration
 - Both
 - None
70. Volume of distribution of drug is given by: (TN 2007)
- $V_d = \frac{\text{Dose administered i.v.}}{\text{Plasma concentration}}$
 - $V_d = \frac{\text{Maximum tolerated dose}}{\text{Dose administered i.v.}}$
 - $V_d = \frac{\text{Dose administered i.v.}}{\text{Total lipid solubility}}$
 - $V_d = \frac{t_{1/2}}{\text{Dose administered i.v.}}$
71. Redistribution phenomenon is seen in: (RJ 2000)
- Halothane
 - Ether
 - Thiopentone
 - All
72. Sulphonamide is conjugated with: (RJ 2001)
- Acetylation
 - Methylation
 - Hydroxylation
 - None
73. Which of the following statements is correct? (RJ 2006)
- Most drugs are absorbed in ionized form
 - Basic drugs are generally bound to plasma albumin
 - Microsomal enzymes are located in the mitochondria of hepatic cells
 - Blood brain barrier is deficient at the chemoreceptor trigger zone
74. Nonsynthetic phase I reaction for drug detoxification is: (Karnataka 1997) (MH 2000)
- Glucuronidation
 - Acetylation
 - Methylation
 - Oxidation
75. Which of the following is NOT a prodrug? (MH 2008)
- Enalapril
 - Imipramine
 - Sulphasalazine
 - Cyclophosphamide
76. Loading dose of a drug is given: (Bihar 2003)
- To achieve steady state concentration in short time
 - For drugs with short $t_{1/2}$
 - To reduce complications
 - All of these
77. Alkalinization of urine is done for: (Bihar 2005)
- Weak acid drugs
 - Weak basic drugs

- (c) Strong acidic drugs
(d) Strong basic drugs
78. **Loading dose depends on the following factors except:** (AP 2006)
(a) Drug concentration to be achieved
(b) Volume of distribution
(c) Clearance of the drug
(d) Bioavailability of drug
79. **Which of the following is NOT an oxidative type of drug metabolism?** (MP 2008)
(a) Deamination
(b) N-oxidation
(c) N-dealkylation
(d) Glucuronidation
80. **Which of the following is a Phase I metabolic reaction?** (Kolkata 2009)
(a) Hydroxylation
(b) Conjugation
(c) Glucuronidation
(d) Sulfation
81. **In drug metabolism, hepatic cytochrome P-450 system is responsible for:** (Karnataka 2003)
(a) Phase I reactions (hydrolysis, oxidation, reduction etc.) only
(b) Phase II reactions (conjugation, synthesis etc.) only
(c) Both phase I and II reactions
(d) Converting hydrophilic metabolites to lipophilic metabolites
82. **Time for peak plasma concentration (T_{max}) indicates:** (Karnataka 2001)
(a) The rate of elimination
(b) The rate of absorption
(c) The duration of effect
(d) The intensity of effect
83. **One of the potential microsomal enzymes inhibitor drug is:** (Karnataka 2001)
(a) Phenobarbitone
(b) Griseofulvin
(c) Sodium valproate
(d) Phenytoin
84. **Which of the following drugs is having the least oral bioavailability?** (Karnataka 2000)
(a) d-tubocurarine
(b) Morphine
(c) Ampicillin
(d) Phenytoin
85. **One of the potent microsomal enzyme inducer drug is:** (Karnataka 2000)
(a) Captopril
(b) Erythromycin
(c) Rifampicin
(d) Cimetidine
86. **Alkalinization of urine is required to treat toxicity of all except:** (MH 2002)
(a) Sulfonamides
(b) Amphetamine
(c) Salicylates
(d) Barbiturates
87. **Cytochrome P450 most commonly involved in drug metabolism:** (Bihar 2005)
(a) CYP 3A4
(b) CYP 1A1
(c) CYP 2E1
(d) CYP 2D6
88. **Which of the following drugs binds to albumin?** (DPG 2006)
(a) Penicillin
(b) Lidocaine
(c) Propranolol
(d) Verapamil
89. **Which of the following is an enzyme inhibitor?** (Jharkhand 2005)
(a) Ketoconazole
(b) Rifampicin
(c) Tolbutamide
(d) Phenobarbitone

■ PHARMACOKINETICS (CALCULATIONS)

90. **Which of the following parameters signifies the effective drug removal from the body?** (AIIMS Nov 2013)
(a) Clearance
(b) Bioavailability
(c) Safety
(d) Volume of distribution
91. **True statement about first order kinetics is**
(a) A constant amount of a drug is eliminated in unit time (AIIMS May 2012)
(b) The half-life increases with an increase in dose
(c) The rate of elimination is constant
(d) The rate of elimination is proportional to the plasma concentration
92. **Loading dose of a drug primarily depends on:**
(a) Volume of distribution (AIIMS May 2008)
(b) Clearance (AIIMS Nov 2006)
(c) Rate of administration
(d) Half life
93. **True statement regarding first order kinetics is:**
(a) Rate of elimination is independent of plasma concentration (AI 2001)
(b) A constant proportion of plasma concentration is eliminated per unit time
(c) Half life increases with dose
(d) Clearance decreases with dose
94. **After I.V. drug administration, elimination of a drug depends on:** (PGI Dec. 2006)
(a) Lipid solubility
(b) Volume of distribution
(c) Clearance
(d) Drug concentration

95. A 70 kg man was given a drug in a dose of 100 mg/kg body weight. Its $t_{1/2}$ is 10 hours, initial plasma concentration is 1.9 mg/ml. True statement is: (PGI Dec. 2006)
- CL is 0.02 litre/hr
 - CL is 20 litre/hr
 - k is 0.0693
 - k is 6.93
 - CL is 0.2 litre/hr
96. Amount of a drug X administered to a patient is 4.0 g and its plasma concentration is found to be 50 mg/ml, what will be the volume of distribution of drug X?
- 100L
 - 80L
 - 60L
 - 50L
97. Maintenance dose rate of a drug depends primarily on:
- Volume of distribution
 - Half life
 - Lipid solubility
 - Total body clearance
98. Rate of elimination of a new drug is 20 mg/hr at a steady state plasma concentration of 10 mg/L, then its renal clearance will be:
- 0.5 L/hr
 - 2.0 L/hr
 - 5.0 L/hr
 - 20 L/hr
99. A drug following first order kinetics is being administered by constant i.v. infusion at a rate of 10 mg/min. Its steady state plasma concentration is 2 mg/min. If the dose rate is increased to 20 mg/dl, what will be the new steady state plasma concentration?
- 6 mg/dl
 - 4 mg/dl
 - 3 mg/dl
 - 1 mg/dl
100. Ram Prashad is admitted to Guru Teg Bahadur Hospital with respiratory infection for which antibiotic tobramycin is ordered. The clearance and Vd of tobramycin in him are 160 ml/min and 40 L, respectively. If you wish to give Ram Prashad an intravenous loading dose to achieve the therapeutic plasma concentration of 4 mg/L rapidly, how much should be given?
- 0.1 mg
 - 10 mg
 - 115.2 mg
 - 160 mg
101. A 30 year old patient on digoxin therapy has developed digitalis toxicity. The plasma digoxin level is 4 ng/ml. Renal function is normal and the plasma $t_{1/2}$ for digoxin in this patient is 1.6 days. How long should you withhold digoxin in order to reach a safer yet probably therapeutic level of 1 ng/ml?
- 1.6 days
 - 2.4 days
 - 3.2 days
 - 4.8 days
102. An old man enters the hospital with myocardial infarction and a severe ventricular arrhythmia. The antiarrhythmic drug chosen has a narrow therapeutic window. The minimum toxic plasma concentration is 1.5 times the minimum therapeutic plasma concentration. The half life is 6 hrs. It is essential to maintain the plasma concentration above the minimum therapeutic level to prevent a possible lethal arrhythmia. Of the following, the most appropriate dosing regimen would be:
- Once a day
 - Twice a day
 - Four times a day
 - Constant intravenous infusion
103. A young male Kallu is brought to the hospital with severe asthma. The pharmacokinetics of theophylline include the following parameters: $V_d = 35$ L; CL = 48 ml/min; half life is 8 hrs. If an intravenous infusion of theophylline is started at a rate of 0.48 mg/min, how long will it take to reach 93.75% of the final steady state?
- Approximately 48 min
 - Approximately 5.8 hrs
 - Approximately 8 hrs
 - Approximately 32 hrs
104. A patient requires an infusion of procainamide. Its half life is 2 hrs. The infusion is begun at 9 AM At 1 PM on the same day, the blood concentration is found to be 3 mg/L. What is the probable steady state concentration after 2 days of infusion?
- 3 mg/L
 - 4 mg/L
 - 6 mg/L
 - 15 mg/L
105. A volunteer Ram will receive a new drug in a phase I clinical trial. The clearance and the volume of distribution of the drug in Ram are 1.386 L/hr and 80 L respectively. The half life of the drug in him would be approximately:
- 83 hr
 - 77 hr
 - 40 hr
 - 0.02 hr
106. Drug X is normally administered to patients at a rate of 50 mg/hour. Elimination of the drug X from body takes place as:
- Hepatic Metabolism 10%
 - Biliary Secretion 10%
 - Renal Excretion 80%
- This drug has to be administered to a 65 years old patient Uttam Singh, with a GFR of 60 ml/min. (assuming normal GFR is 120ml/min). Liver and biliary functions are normal in this patient. What should be the dose rate of drug X in this patient?

- (a) 50 mg/hour
(b) 30 mg/hr
(c) 25 mg/hr
(d) 100 mg/hr.
107. **First order kinetics is characterized by:** (DPG-2008)
(a) Dose dependent elimination
(b) Decreasing clearance as plasma concentration increases
(c) Increasing rate of elimination as plasma concentration increases
(d) No relationship between rate of elimination and plasma concentration
108. **Elimination after 4 half lives in first order kinetic is:** (DPG 2005, MH 2005)
(a) 84%
(b) 93%
(c) 80.5%
(d) 75%
109. **Zero order kinetics is followed by all of the following drugs EXCEPT:** (DPG 2005)
(a) Phenytoin
(b) Barbiturates
(c) Alcohol
(d) Theophylline
110. **At toxic doses, zero order kinetics is seen in:** (DPG 2003)
(a) Penicillin
(b) Phenytoin
(c) Valproate
(d) Carbamazepine
111. **Amount of drug left after four plasma half-lives is:** (DPG 2003)
(a) 6.25%
(b) 12.5%
(c) 25%
(d) 50%
112. **Inter dose interval depends on:** (DPG 2001, MPPG 2002)
(a) Half life of drug
(b) Dose of drug
(c) Age of patient
(d) Bioavailability of drug
113. **Time required to reach the steady state after a dosage regimen depends on:** (MPPG 2003)
(a) Route of administration
(b) Half life of a drug
(c) Dosage interval
(d) Dose of drug
114. **Zero order kinetic is shown by all EXCEPT:**
(a) High dose salicylates (Karnataka 2002, MPPG 2001)
(b) Phenytoin
(c) Ethanol
(d) Methotrexate
115. **The elimination of alcohol follows:** (DNB 2004)
(a) Zero order kinetics
(b) 1st order kinetics
(c) 2nd orders kinetics
(d) 3rd orders kinetics
116. **The clearance of drug means:** (DNB 2005, 2002)
(a) Volume of plasma which is cleared of drug in unit of time
(b) Amount of drug excreted in urine
(c) Amount of drug metabolized in unit of time
(d) All of the above
117. **Zero order kinetics occur in following drug with high dose:** (DNB 2007, 2003, 2006)
(a) Phenytoin and Theophylline
(b) Digoxin and Propranolol
(c) Amiloride and Probenecid
(d) Lithium and Theophylline
118. **Zero order kinetics means:** (MH 2006)
(a) A constant amount of drug is eliminated per unit time
(b) A constant fraction of the drug in the body is eliminated per unit time
(c) The fraction of the administered dose that reaches the systemic circulation
(d) The effect that can be increased by giving a second agent that boosts the effect of the liver's enzyme system
119. **About first order kinetics true statement is:** (Bihar 2005)
(a) Clearance remains constant
(b) Fixed amount of the drug is eliminated
(c) Half life increase with dose
(d) Decreased clearance with increasing dose

PHARMACODYNAMICS AND PHARMACOGENETICS

120. **All of the following can cause SLE-like syndrome except:** (AIIMS May 2013, 2012)
(a) Isoniazid
(b) Penicillin
(c) Hydralazine
(d) Sulphonamide
121. **The neurotransmitters; nor-adrenaline, adrenaline and dopamine act through which of the following receptors?** (AIIMS Nov 2011)
(a) Single pass transmembrane receptors
(b) Four pass transmembrane receptors
(c) Seven pass transmembrane receptors
(d) Ligand gated receptors
122. **If there is a Gs alpha subunit gain-of-function mutation, this results in:** (AI 2011)
(a) Decreased cAMP
(b) Decreased IP₃
(c) Increased GTPase activity
(d) Increased cAMP
123. **Which one of the following statements best describes the mechanism of action of insulin on target cells?** (Delhi PG 2011)
(a) Insulin binds to cytoplasmic receptor molecule and is transferred as a hormone receptor complex to the nucleus where it acts to modulate gene expression.

- (b) Insulin binds to a receptor molecule on the outer surface of the plasma membrane and the hormone receptor complex activates adenylate cyclase through the Gs protein.
- (c) Insulin binds to a transmembrane receptor at the outer surface of the plasma membrane, which activates the tyrosine kinase that is the cytosolic domain of the receptor.
- (d) Insulin enters the cell and causes the release of calcium ions from intracellular stores.

124. True about G protein coupled receptors is:

(AIIMS May 2008)

- (a) G proteins bind to hormones on the cell surface
- (b) All the three subunits alpha, beta and gamma should bind to each other for G proteins to act
- (c) G proteins act as inhibitory and excitatory because of difference in alpha subunit
- (d) G protein is bound to GTP in resting state

125. Which drug is not metabolized by acetylation?

(AIIMS May 2008 AIIMS Nov 2006, AIIMS May 2003)

- (a) Isoniazid
- (b) Dapsone
- (c) Hydralazine
- (d) Metoclopramide

126. Action of alpha subunit of G-protein is:

(AIIMS NOV 2008)

- (a) Binding of agonist
- (b) Conversion of GDP to GTP
- (c) Breakdown of GTP to GDP
- (d) Internalization of receptors

127. All are second messengers except:

(AIIMS NOV 2008, 2012)

- (a) Cyclic AMP
- (b) Guanylyl cyclase
- (c) Diacylglycerol
- (d) Inositol triphosphate

128. A non-competitive inhibitor of an enzyme:

(DPG 2009)

- (a) Increase K_m with no or little change in V_{max}
- (b) Decrease K_m
- (c) Decrease V_{max}
- (d) Increase V_{max}

129. All known effects of cyclic AMP in eukaryotic cells results from:

(DPG 2009)

- (a) Activation of the catalytic unit of adenylate cyclase
- (b) Activation of synthetase
- (c) Activation of protein kinase
- (d) Phosphorylation of G protein

130. All of the following drugs cause hemolysis in patients with G-6-PD deficiency except:

(AI-2008)

- (a) Primaquine
- (b) Chloroquine
- (c) Quinine
- (d) Pyrimethamine

131. All of the following agents act by intracellular receptors EXCEPT:

(AI 2007)

- (a) Thyroid hormones

- (b) Vitamin D
- (c) Insulin
- (d) Steroids

132. Regarding efficacy and potency of a drug, all are true except:

(AI 2002)

- (a) In a clinical setup, efficacy is more important than potency
- (b) In the log dose response curve, the height of the curve corresponds with efficacy
- (c) ED50 of the drug corresponds to the efficacy
- (d) Drugs that produce a similar pharmacological effect can have different levels of efficacy

133. True statement regarding inverse agonist is:

(AI 2001)

- (a) Binds to the receptor and causes intended action
- (b) Binds to the receptor and causes opposite action
- (c) Binds to the receptor and causes no action
- (d) Binds to the receptor and causes submaximal action

134. All are pharmacogenetic conditions except:

(AI 2000)

- (a) Adenosine deaminase deficiency
- (b) Malignant hyperthermia
- (c) Coumarin insensitivity
- (d) G-6-PD deficiency

135. Which of the following property of the drug will enable it to be used in low concentration?

(AIIMS Nov. 2005)

- (a) High affinity
- (b) High specificity
- (c) Low specificity
- (d) High stability

136. All of the following drugs are contraindicated in patients with G-6-PD deficiency, EXCEPT:

(AIIMS May, 2004)

- (a) Cotrimoxazole
- (b) Furazolidone
- (c) Nalidixic acid
- (d) Ceftriaxone

137. K_m of an enzyme is:

(AIIMS May, 2003)

- (a) Dissociation constant
- (b) The normal physiological substrate concentration
- (c) The substrate concentration at half maximal velocity
- (d) Numerically identical for all isozymes that catalyze a given reaction

138. Physiological antagonism is found in:

(PGI Dec. 2007)

- (a) Isoprenaline and salbutamol
- (b) Isoprenaline and adrenaline
- (c) Isoprenaline and propranolol
- (d) Adrenaline and histamine
- (e) Salbutamol and leukotrienes

139. Drugs that should be avoided in G-6-PD deficiency are:

(PGI Dec. 2007)

- (a) Chloroquine
- (b) Quinine
- (c) Sulfamethoxazole
- (d) Nitrofurantoin
- (e) Primaquine

140. Pharmacogenetics is associated with: (PGI Dec. 2005)
- Variability of enzyme action
 - Environmental influence
 - Individual variability in oral absorption
 - Different mechanism of actions in different individuals
 - Different DRC in different individuals
141. Drugs causing SLE are: (PGI June, 2005)
- INH
 - Hydralazine
 - Procainamide
 - Ranitidine
 - Phenytoin
142. Which of the following terms best describes the antagonism of leukotrienes' bronchoconstrictor effect (mediated at the leukotriene receptors) by terbutaline (acting at the adrenoceptors) in a patient with asthma?
- Pharmacologic antagonist
 - Partial agonist
 - Physiologic antagonist
 - Chemical antagonist
143. Which of the following terms best describes a drug that blocks the action of adrenaline at its receptors by occupying those receptors without activating them?
- Pharmacologic antagonist
 - Non competitive antagonist
 - Physiologic antagonist
 - Chemical antagonist
144. Which of the following most accurately describes the transmembrane signaling process involved in the steroid hormone action?
- Action on a membrane spanning tyrosine kinase
 - Action of a G protein, which activates or inhibits adenylyl cyclase
 - Diffusion across the membrane and binding to an intracellular receptor
 - Opening of transmembrane ion channels
145. Which of the following is most likely due to a pharmacogenetic condition?
- Hypoglycemia by insulin
 - Tachycardia by albuterol
 - Metoclopramide induced muscle dystonia
 - Primaquine induced hemolytic anemia
146. Dose response curves of salbutamol for bronchodilation and tachycardia are widely separated on the dose axis. This information suggests that salbutamol is:
- Highly potent cardiac stimulant
 - Highly efficacious bronchodilator
 - Highly toxic drug
 - Highly selective drug
147. Fastest acting receptor/transduction mechanism is:
- Adenylyl cyclase – cyclic AMP pathway
 - Phospholipase C-IP3: DAG pathway
 - Intrinsic ion channel operation
 - Nuclear receptors
148. Which of the following is an inotropic receptor?
- Muscarinic cholinergic receptor
 - Nicotinic cholinergic receptor
 - Glucocorticoid receptor
 - Insulin receptor
149. A partial agonist has:
- High affinity but low intrinsic activity
 - High affinity but no intrinsic activity
 - Low affinity but high intrinsic activity
 - Low affinity and low intrinsic activity
150. Which of the following drugs act through heptahelical (serpentine) receptors?
- Insulin
 - Estrogen
 - Local anaesthetics
 - Salbutamol
151. Which of the following does not act as second messenger?
- Cyclic AMP
 - Inositol trisphosphate
 - Diacylglycerol
 - G proteins
152. 'Drug efficacy' refers to:
- Effectiveness of drug in life threatening conditions
 - The maximal intensity of response that can be produced by the drug
 - The dose of the drug needed to produce half maximal effect
 - The minimum dose of the drug needed to produce toxic effect
153. A 56 yr old man, Surender with heart failure is to be treated with a diuretic drug. Drugs A and B have same mechanism of action. Drug A in dose of 50 mg produces the same magnitude of diuresis as 500 mg of drug B. This suggests that:
- Drug B is less efficacious than drug A
 - Drug A is more potent than drug B
 - Drug A is a safer drug than drug B
 - Drug A will have shorter duration of action than drug
154. Which of the following has cytoplasmic receptor: (DPG 2004)
- Epinephrine
 - Insulin
 - FSH
 - Cortisol
155. Which of the following is true for receptor action of a drug: (MPPG 2002)
- An antagonist has both intrinsic activity and affinity for receptor
 - An antagonist has affinity but no intrinsic activity for receptor
 - A partial antagonist has no intrinsic activity or affinity for receptor
 - Intrinsic activity and affinity are not important for drug action

156. All of the following cross plasma membrane except: (DNB 2006, 2003)
 (a) Epinephrine
 (b) Thyroxine
 (c) Androstenedione
 (d) Estrogen
157. G-coupled protein receptor is: (UP 2006)
 (a) Metabotropic receptors
 (b) Ionic receptors
 (c) Kinase-linked receptors
 (d) Nuclear receptors
158. About inverse agonism, true is: (MH 2006)
 (a) Action on the target receptors is similar to that of agonist
 (b) Binds to the same receptor binding-site as an agonist for that receptor but exerts the opposite pharmacological effect
 (c) Acts on receptors which do not have agonist
 (d) None
159. Antagonism between acetylcholine and atropine: (MH 2006)
 (a) Competitive antagonism
 (b) Physiological antagonism
 (c) Noncompetitive antagonism
 (d) None
160. Michaelis Menton constant is: (AP 2004)
 (a) Concentration of drug at which the reaction velocity is half of maximum
 (b) Concentration of drug at which the reaction velocity is maximum
 (c) Both
 (d) None
161. When two different chemicals act on two different receptors and their response is opposite to each other on the same cell, this is called as: (AP 2006)
 (a) Physiological antagonism
 (b) Chemical antagonism
 (c) Reversible antagonism
 (d) Competitive antagonism
162. Agonist is having: (Bihar 2006)
 (a) Affinity with intrinsic activity is 1
 (b) Affinity with intrinsic activity is 0
 (c) Affinity with intrinsic activity is -1
 (d) None
- whether the drug levels are within the therapeutic range or not. For TDM to be clinically useful the following criteria should be fulfilled: (Delhi PG 2011)
 (a) There should be good relationship between plasma concentration and drug dosage
 (b) The relationship between plasma drug concentration and therapeutic response and/or toxicity should be poor
 (c) When pharmacodynamic tolerance is suspected
 (d) When the clinical response cannot be easily monitored
165. Therapeutic index is a measure of: (AI-2008)
 (a) Safety
 (b) Potency
 (c) Efficacy
 (d) Selectivity
166. Therapeutic drug monitoring is required in all except: (AIIMS Nov., 2007)
 (a) Phenytoin
 (b) Metformin
 (c) Tacrolimus
 (d) Cyclosporin
167. Drugs having narrow therapeutic index are: (PGI Dec. 2002)
 (a) Lithium
 (b) Erythromycin
 (c) Phenytoin
 (d) Propanolol
 (e) Tricyclic antidepressants
168. Therapeutic drug monitoring is required for:
 (a) Prodrugs
 (b) Levodopa
 (c) Lithium carbonate
 (d) MAO inhibitors
169. Therapeutic drug monitoring of plasma concentrations of antihypertensive drugs is NOT practiced because:
 (a) Determination of plasma level of these drugs is quite tedious and long process
 (b) It is easier to measure the effect of these drugs
 (c) Antihypertensive effect do not increase linearly with the dose
 (d) All antihypertensive drugs are prodrugs
170. Drug having very narrow therapeutic range is: (Karnataka 2009)
 (a) Lithium
 (b) Sertraline
 (c) Risperidone
 (d) Dothiepin

■ THERAPEUTIC INDEX AND TDM

163. Therapeutic monitoring of plasma level of drug is done when using all of the following drugs except: (AI 2012)
 (a) Warfarin
 (b) Gentamicin
 (c) Cyclosporine
 (d) Phenytoin
164. Therapeutic Drug Monitoring (TDM) involves measurement of plasma concentrations of drugs to find
 171. Which of the following drug needs serum level monitoring? (Karnataka 2009, MPPG 2002)
 (a) Lorazepam
 (b) Lithium
 (c) Amitriptyline
 (d) Haloperidol
172. Which one of the following drugs has narrow therapeutic range? (MPPG 2007 MPPG 2004)
 (a) Propanolol
 (b) Phenytoin

- (c) Piroxicam
- (d) Prazosin

173. Therapeutic index is an assessment of:

- (a) Potency of a drug
- (b) Onset of action
- (c) Duration of action
- (d) Margin of safety

(MPPG 2005)

174. Therapeutic Index is:

(UP 2007)

- (a) $\frac{ED_{50}}{LD_{50}}$
- (b) $\frac{LD_{50}}{ED_{50}}$
- (c) $ED_{50} - LD_{50}$
- (d) $ED_{50} \times LD_{50}$

175. The ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population of individual is known as:

(UP 2008)

- (a) Efficacy
- (b) Potency
- (c) Therapeutic index
- (d) Partial agonist

176. Plasma drug monitoring is done for:

(Jharkhand 2006)

- (a) Drug with high safety margin
- (b) Drug with low safety margin
- (c) Drug with high therapeutic index
- (d) None

177. ED₅₀ is used for determining:

(Kolkata 2009)

- (a) Potency
- (b) Efficacy
- (c) Safety
- (d) Toxicity

CLINICAL PHARMACOLOGY

178. Design of the study aimed to assess the maximum tolerable dose of a new drug is best described as:

- (a) Case control study
- (b) Phase II Randomized control trial (RCT)
- (c) Phase I trial
- (d) Phase III Randomized control trial (RCT)

(AIIMS May 2013)

179. Comparison of efficacy of a new drug B with an existing drug A is done in which phase of clinical trials?

- (a) Phase I
- (b) Phase II
- (c) Phase III
- (d) Phase IV

(AI 2012)

180. Pharmacovigilance means:

(AIIMS May 2004, 2010)

- (a) Monitoring of drug safety
- (b) Monitoring of unethical trade of drugs
- (c) Monitoring pharma students
- (d) Monitoring drug efficacy

181. True about orphan drug is:

(AIIMS May 2013)

- (a) Developed for orphans
- (b) Drugs used very rarely
- (c) Drugs used for rare diseases
- (d) Rare drug for common diseases

182. True statement about phase 2 clinical trials is:

- (a) Large number of healthy volunteers are studied
- (b) Used to determine maximum tolerated dose
- (c) Used to determine efficacy
- (d) Used to determine toxicity

(AIIMS 2012)

183. When a drug is evaluated for its usefulness in controlled conditions, it is termed as a trial signifying:

(AI 2006)

- (a) Efficacy
- (b) Effectiveness
- (c) Efficiency
- (d) Effect modification

184. In which of the following phases of clinical trial of drugs, ethical clearance is not required?

(AI 2004)

- (a) Phase I
- (b) Phase II
- (c) Phase III
- (d) Phase IV

185. Good clinical practice (GCP) is not required in:

- (a) Preclinical phase
- (b) Phase I trial
- (c) Phase II studies
- (d) Phase IV studies

(AIIMS Nov., 2007)

186. Which of the following is true of 'placebo'?

- (a) Placebo is a dummy medication
- (b) Placebo is the inert material added to the drug for making tablets
- (c) Placebos do not produce any effect
- (d) All patients respond to placebo

187. Which of the following statements best describes an 'orphan drug'?

- (a) It is a drug which acts on orphanin receptors
- (b) It is a very cheap drug
- (c) It is a drug which has no therapeutic use
- (d) It is a drug required for treatment or prevention of a rare disease

188. With respect to clinical trials of new drugs, which of the following is most CORRECT?

- (a) Phase I involves the study of a small number of normal volunteers by highly trained clinical pharmacologists
- (b) Phase II involves the use of the new drug in a large number of patients (1000-5000) who have the disease to be treated
- (c) Phase III involves the determination of the drug's therapeutic index by the cautious induction of toxicity
- (d) Phase IV involves the detailed study of toxic effects that have been discovered in phase III.

189. In which of the following phases of clinical trials, healthy normal human volunteers participate:

- (a) Phase-I (MPPG 2003)
- (b) Phase-II
- (c) Phase-III
- (d) Phase-IV

190. There are some undesirable but unavoidable pharmacodynamic effects of a drug, which are known as:

- (a) Toxic effects (MPPG 2002)
- (b) Idiosyncrasy
- (c) Side effects
- (d) Intolerance

191. The aim of post-marketing studies is: (UP 2005)

- (a) Efficacy of the drug
- (b) Dosage of the drug
- (c) Deals with alteration of the drug includes absorption, distribution, binding/storage
- (d) Safety and comparisons with other medicines

192. In which phase of clinical trials, post-marketing surveillance of a drug is carried out: (MP 2008)

- (a) Phase I
- (b) Phase II
- (c) Phase III
- (d) Phase IV

MISCELLANEOUS

193. Type A (augmented) adverse drug reactions are characterized by all EXCEPT: (Karnataka 2007)

- (a) Qualitatively abnormal responses to the drug
- (b) Predictable from the drug's known pharmacological or toxicological effects
- (c) Generally dose-dependent
- (d) Usually common

194. In pregnancy, all of the following drugs are contraindicated except: (AIIMS May 2011)

- (a) ACE Inhibitors
- (b) Angiotensin Receptor Blockers
- (c) Propylthiouracil
- (d) Thalidomide

195. A newborn baby was born with phocomelia. It results due to which drug taken by mother during pregnancy? (AIIMS Nov 2010)

- (a) Tetracycline
- (b) Thalidomide
- (c) Warfarin
- (d) Alcohol

196. Which of the following drugs can be given safely in pregnancy: (AI 2009)

- (a) Propylthiouracil
- (b) Methotrexate
- (c) Warfarin
- (d) Tetracycline

197. All of the following drugs undergo hepatic metabolism before excretion EXCEPT: (AI 2002)

- (a) Phenytoin
- (b) Diazepam
- (c) Penicillin G
- (d) Cimetidine

198. All the following drugs can cross placenta EXCEPT: (AI 2002)

- (a) Phenytoin
- (b) Diazepam
- (c) Morphine
- (d) Heparin

199. All are reasons for alteration of drug dosage in the elderly except: (AI 2001, AIIMS May 2002)

- (a) They have decreasing renal function with age
- (b) They are lean and their body mass is less
- (c) Have increased baroreceptor sensitivity
- (d) Body water is decreased

200. True about the teratogenicity of a drug is all except:

- (a) Characteristic set of malformations indicating selectivity for certain target organs is seen (AI 2000)
- (b) Heparin is highly teratogenic drug
- (c) Related to the dose of the teratogenic drug
- (d) Affects specifically at a particular phase of development of the fetus

201. Side effects of a drug arise due to interactions of the drug to molecules other than the target. These effects of the drug can be minimized by its high:

- (a) Specificity (AIIMS Nov., 2005)
- (b) Solubility
- (c) Affinity
- (d) Hydrophobicity

202. Receptor mediated action is not seen in: (PGI June, 2004)

- (a) Alcohol
- (b) Antipsychotic
- (c) Antacids
- (d) Benzodiazepines
- (e) Propofol

203. Blood brain barrier is crossed by: (PGI Dec. 2002)

- (a) Dopamine
- (b) Propanolol
- (c) Glycopyrrolate
- (d) Physostigmine
- (e) Streptomycin

204. Drugs that can be safely given in pregnancy are:

- (a) Antifolate (PGI Dec. 2002)
- (b) Quinine
- (c) Chloroquine
- (d) Primaquine
- (e) Tetracycline

205. Which of the following drugs are secreted in breast milk? (PGI June, 2001)

- (a) Antihistaminics
- (b) Antithyroid drugs
- (c) Penicillins
- (d) Diazepam
- (e) Antiepileptics

206. Which of the following drugs should be given in sustained release oral dosage form?
- An anti-arrhythmic drug with a plasma half life of 10 seconds used for acute treatment of PSVT
 - An anti-inflammatory drug with a plasma half life of 24 hr
 - A hypnotic drug with a plasma half life of 2 hours
 - An antihypertensive with a plasma half life of 3 hours
207. Which of the following statements regarding transfer of drugs across placenta is FALSE? (DPG-2007)
- Transfer across placenta is lesser in early pregnancy
 - All drugs to some extent can cross the placenta except heparin and insulin
 - Ion trapping of acidic drugs occur in the placenta
 - P-glycoprotein is present in placenta
208. Which of the following is excreted in saliva? (UP 2005)
- Tetracyclines
 - Ampicillin
 - Lithium
 - Chloramphenicol
209. The pharmacokinetics change occurring in geriatric patients is decline in:
- Gastric absorption
 - Liver metabolism
 - Renal clearance
 - Hypersensitivity
210. Drugs used for rare disease are known as: (TN 2007)
- Orphan drugs
 - Rare drugs
 - Over the counter drugs
 - Emergency drugs
211. All these drugs EXCEPT one cross the blood-brain barrier: (Karnataka 2007)
- Morphine
 - Dopamine
 - Propranolol
 - Ether
212. The term physical half-life is applicable to:
- Repository preparations
 - Prodrugs
 - Radioactive isotopes
 - Alkylating agents
213. Which of the following does not cross blood brain barrier? (Karnataka 2003)
- Glycopyrrolate
 - Atropine
 - Scopolamine
 - Promethazine
214. The following are given intradermally EXCEPT: (DPG 2008)
- Test dose of drugs
 - Insulin
 - BCG vaccine
 - Mantoux test

RECENT QUESTIONS ASKED BY NATIONAL BOARD

- Type B adverse drug reaction is ?
 - Augmented effect of the drug
 - Allergic effect of the drug
 - Effect seen on chronic use of the drug
 - Delayed effect of the drug
- All of the following drugs can cause SLE like syndrome except ?
 - Isoniazid
 - Penicillin
 - Hydralazine
 - Sulphonamide
- All of the following antiepileptics are microsomal enzyme inducers except
 - Valproate
 - Phenobarbitone
 - Phenytoin
 - Rifampicin
- Which of the following drug is contraindicated in pregnancy?
 - Enalapril
 - Amlodipine
 - β -blockers
 - Propylthiouracil
- Two drugs having opposite action on different receptors is which type of antagonism?
 - Physical antagonism
 - Competitive antagonism
 - Non competitive antagonism
 - Physiological antagonism
- Increase in cAMP is caused by:
 - Somatostatin
 - β (Beta) receptor
 - α (Alpha) receptor
 - Acetylcholine
- Apparent volume of distribution (aVd) is more than total body fluid if drug is:
 - Poorly soluble
 - Sequestered in tissues
 - Slow elimination
 - Poorly plasma protein bound
- Most essential medicines should be formulated as:
 - No compound
 - Single compound
 - Multiple compounds
 - Fixed dose combinations
- Drug which does not cause hemolysis in G6PD deficiency is?
 - Primaquine
 - Dapsone
 - Corticosteroids
 - Methylene Blue

10. **Phase 4 clinical trial also called as?**
 - (a) Human pharmacology and safety
 - (b) Post marketing surveillance
 - (c) Therapeutic exploration and dose ranging
 - (d) Therapeutic confirmation
11. **Which of the following is an effect of grapefruit juice on drug metabolism?**
 - (a) Enzyme inducer
 - (b) Enzyme inhibitor
 - (c) Inhibits tubular secretion
 - (d) Inhibits tubular reabsorption
12. **Which of the following is an example of physiological antagonism?**
 - (a) Heparin-Protamine
 - (b) Prostacycline-Thromboxane
 - (c) Adrenaline-Phenoxybenzamine
 - (d) Physostigmine-Acetylcholine
13. **Which is not an alkaloid?**
 - (a) Morphine
 - (b) Neostigmine
 - (c) Emetine
 - (d) Atropine
14. **Therapeutic index is a measure of:**
 - (a) Efficacy
 - (b) Adverse effects
 - (c) Safety
 - (d) Potency
15. **As per "Drugs and cosmetic act" prescription drugs are included in:**
 - (a) Schedule C
 - (b) Schedule H
 - (c) Schedule P
 - (d) Schedule X
16. **All the following drugs are teratogenic except:**
 - (a) Alcohol
 - (b) Phenytoin
 - (c) Warfarin
 - (d) Metoclopramide
17. **All the following drugs act on ionic channels except:**
 - (a) Nicotine
 - (b) Insulin
 - (c) Glibenclamide
 - (d) Diazepam
18. **Efficacy of a drug refers to:**
 - (a) Affinity of drug to bind to receptors
 - (b) Affinity of drug that binds to receptors and activates it
 - (c) Dose that requires to produce response
 - (d) Maximum response a drug can produce
19. **Phocomelia is best described as:**
 - (a) Defect in development of long bones
 - (b) Defect in development of flat bones
 - (c) Defect in intramembranous ossification
 - (d) Defect in cartilage replacement by bones
20. **Phase IV of clinical trials collect information specially about:**
 - (a) Drug efficacy
 - (b) Drug potency
 - (c) Drug toxicity
 - (d) Pharmacokinetics of the drug
21. **SLE like reaction is caused by:**
 - (a) Hydralazine
 - (b) Rifampicin
 - (c) Paracetamol
 - (d) Furosemide
22. **Which of the following can result in oral contraceptive failure?**
 - (a) Valproate
 - (b) Rifampicin
 - (c) NSAIDs
 - (d) Ethambutol
23. **When a drug binds to the receptor and causes action opposite to that of agonist this is called as?**
 - (a) Complete Agonist
 - (b) Partial Agonist
 - (c) Inverse agonist
 - (d) Neutral antagonist
24. **The study of how variation in the human genome affect the response to medications is known as?**
 - (a) Pharmacogenomics
 - (b) Pharmacokinetics
 - (c) Pharmacotherapeutics
 - (d) Pharmacovigilance
25. **Zero order kinetics occur in following drug with high dose:**
 - (a) Phenytoin and propranolol
 - (b) Digoxin and propranolol
 - (c) Amiloride and prebenecid
 - (d) Alcohol and theophylline
26. **Which of the following is the most accurate method for calculating drug dosage in children:**
 - (a) Weight of the child
 - (b) Weight of the child and adult dose
 - (c) Age of the child
 - (d) Body surface area
27. **Therapeutic drug monitoring is done for all the following except:**
 - (a) Phenytoin
 - (b) Metformin
 - (c) Tacrolimus
 - (d) Cyclosporin
28. **The drug which may inhibit P450 for warfarin is which one of the following:**
 - (a) Cimetidine
 - (b) Ethanol
 - (c) Rifampicin
 - (d) Procainamide

29. In which type of poisonings is gastric lavage contraindicated?
 - (a) Organophosphorus poisoning
 - (b) Sedative drug poisoning
 - (c) Corrosive acid poisoning
 - (d) Barium carbonate poisoning
30. All of the following are examples of time dependent late adverse drug reactions except:
 - (a) Glucocorticoid induced osteoporosis
 - (b) Nitrate induced headache
 - (c) Chloroquine induced retinopathy
 - (d) Amiodarone induced tissue phospholipid deposition
31. Phase 4 clinical trial is carried out:
 - (a) Before the marketing approval of a drug
 - (b) After a drug is marketed
 - (c) For drugs used in rare diseases
 - (d) For drugs used in pediatric patients
32. Forced alkaline diuresis is effective in management of poisoning by which of the following agents:
 - (a) Phenobarbitone
 - (b) Lead
 - (c) Iron
 - (d) Organophosphates
33. Which of the following drugs can be given safely in pregnancy:
 - (a) Propylthiouracil
 - (b) Sodium valproate
 - (c) Warfarin
 - (d) Tetracycline
34. Which ONE of the following is TRUE about a competitive antagonism?
 - (a) Antagonism cannot be completely reversed by increased dose of the agonist
 - (b) An agonist cannot displace an antagonists from the receptor
 - (c) Agonists and antagonists bind to the same receptor
 - (d) Dose-response curve of an agonists shifts to the left in the presence of an antagonist
35. Which route of drug administration avoids first pass hepatic metabolism and is used with drug preparation that slowly releases drugs for periods as long as seven days?
 - (a) Topical
 - (b) Transdermal
 - (c) Sublingual
 - (d) Oral
36. Essential medicines are those medicines:
 - (a) That are needed to treat emergency conditions
 - (b) That are needed to treat serious diseases
 - (c) That satisfy the priority health care needs of the population
 - (d) That are introduced recently into the market
37. A drug that compete for active binding site is called:
 - (a) Competitive inhibitor
 - (b) Non-competitive inhibitor
 - (c) Covalent inhibitor
 - (d) Any of these
38. Usually healthy human volunteers are taken in:
 - (a) Phase I of clinical trial
 - (b) Phase II of clinical trial
 - (c) Phase III of clinical trial
 - (d) Phase IV of clinical trial
39. Orphan drugs are:
 - (a) Drugs with high therapeutic failure
 - (b) Drugs with high toxicity
 - (c) Drugs having low therapeutic margin
 - (d) Drugs for rare disease
40. Hemodialysis is useful in all of the following except:
 - (a) Barbiturate poisoning
 - (b) Methanol poisoning
 - (c) Salicylate poisoning
 - (d) Digoxin poisoning
41. Elimination after 3 half lives in first order kinetics is:
 - (a) 12.5%
 - (b) 75%
 - (c) 87.5%
 - (d) 94%
42. Drug remaining in the body after 3 half lives is:
 - (a) 12.5%
 - (b) 75%
 - (c) 87.5%
 - (d) 94%
43. The bioavailability of the drug depends upon:
 - (a) First pass metabolism
 - (b) Second pass metabolism
 - (c) Volume of distribution
 - (d) Excretion
44. Bioavailability is:
 - (a) Amount of drug that reach the systemic circulation
 - (b) Drug metabolized in liver before the drug reaches the systemic circulation
 - (c) Drug metabolized in liver after the drug reaches the systemic circulation
 - (d) Maximum by rectal route
45. Therapeutic index is a measure of:
 - (a) Drug safety
 - (b) Bioavailability
 - (c) Potency
 - (d) Efficacy
46. Partial agonist possess
 - (a) Max. intrinsic activity and low affinity
 - (b) High intrinsic activity and no affinity
 - (c) Low intrinsic activity and high affinity
 - (d) Low intrinsic activity and low affinity
47. About biotransformation untrue is:
 - (a) Inactive metabolites are formed
 - (b) Active metabolites are formed
 - (c) More fat soluble metabolites are formed
 - (d) More H₂O soluble metabolites are formed

48. Which of the following is not a pro-drug?

- (a) Levodopa
- (b) Enalapril
- (c) Dipivefrine
- (d) Amoxicillin

49. Which of the following is a prodrug?

- (a) Lisinopril
- (b) Enalapril

- (c) Chlorpromazine
- (d) Dopamine

50. Pharmacodynamics includes:

- (a) Drug elimination
- (b) Drug excretion
- (c) Drug absorption
- (d) Mechanism of action

EXPLANATIONS

1. Ans. (b) Phenobarbitone (Ref: *Katzung 12/e p58*)

Ritonavir is a powerful inhibitor of CYP3A4, thus the metabolism of substrates of this enzyme will be inhibited by ritonavir. Important substrates of CYP3A4 are:

- Amiodarone
- Terfenadine, Astemizole, Cisapride
- Cyclosporine, Tacrolimus
- Lovastatin and other statins
- Calcium channel blockers
- Midazolam
- Protease inhibitors

2. Ans. (c) Phenobarbitone (Ref: *KK Sharma 2/e p46*)

Phenobarbitone is a barbiturate which is a derivative of barbituric acid (weakly acidic drug) and its excretion can be enhanced by making the urine alkaline. Morphine, atropine and amphetamines are basic drugs.

3. Ans. (c) CYP2C10 (Ref: *ncbi.nlm.nih.gov*)

Clopidogrel and proton pump inhibitors are metabolized mainly by CYP2C19 and by CYP3A4. Due to this reason there is potential of interaction between these two drugs but none of these enzymes were given in the options. We have no idea what the examiner want a student to learn. Whether student should know the clinically important things or they should go for the most rarest of things.

Anyways, some of these drugs are also metabolized by CYP2C9. On searching a lot, we came to know that this enzyme (CYP2C9) was previously known as CYP2C10. (Ref: <http://www.genecards.org/cgi-bin/carddisp.pl?gene=CYP2C9>). So the answer among the given options should be CYP2C10. But again we will suggest to remember about 2C19 which is clinically more relevant.

4. Ans. (d) Simvastatin: Glucuronide conjugation (Ref: *Goodman and Gilman 12/e p159, 1976*)

Table 7-3 in Goodman and Gilman 12/e p159 clearly writes that CYP2D6 is involved in metabolism of beta blockers and CYP3A4 in calcium channel blockers' metabolism. P-glycoprotein polymorphism decreases AUC of digoxin.

Pg 1976 of Goodman and Gilman writes that 'irreversible oxidative metabolites of simvastatin are produced by CYP3A enzymes.' Another important thing that a student may get confused with is that simvastatin metabolites can be glucuronide conjugated. This is true but the drug no longer remains simvastatin. Clinical importance of this is that if another drug or substance induces UGT glucuronyl transferase, it will not affect the activity of simvastatin. On the other hand if a drug is directly conjugated with glucuronide molecules, the inducers of UGT enzyme will affect the plasma concentration of the drug.

5. Ans. (a) Enalapril (Ref: *KDT 7/e p23-24*)

All ACE inhibitors are prodrugs except captopril and lisinopril.

6. Ans. (a) Ketoconazole (Ref: *KDT 7/e p26*)

- Ketoconazole is a powerful microsomal enzyme inhibitor whereas rifampicin, phenobarbitone and phenytoin are enzyme inducers.

7. Ans. (c) Conjugation (Ref: *KDT 7/e p22-24*)

Metabolic reactions may be classified into phase I (non-synthetic) and phase II (synthetic) reactions. *Phase I reactions include oxidation, reduction, hydrolysis, cyclization and decyclization etc. whereas phase II reactions include glucuronidation, acetylation, methylation, sulfation and glycine conjugation etc.*

8. Ans. (d) Sex steroid hormones do not bind to any protein in plasma (Ref: *KDT 7/e p19-20*)

- Acidic drugs mainly bind to albumin and basic drugs to alpha-1 acid glycoprotein. Drugs having high PPB like sulfonamides can displace other drugs bound to same site and may result in toxicity.
- Sex steroids bind to steroid hormone binding globulin as well as albumin.

9. Ans. (a) Barbiturates (Ref: KDT 7/e p29)

For acidic drug poisonings (like barbiturates, salicylates and methotrexate), urinary alkalinizing agents are prescribed whereas for basic drug poisonings, (morphine, amphetamine, atropine etc.) urinary acidifying agents are administered.

10. Ans. (c) Cytochrome oxidase (Ref: Katzung 11/e p55)

- Drugs can be metabolized by cytochrome P450 dependent oxidations and cytochrome P450 independent oxidations (i.e., by monooxygenases)
- NADPH cytochrome P450 reductase is same as flavin monooxygenase
- Cytochrome oxidase is involved in respiratory chain and not in drug metabolism.
- CYP3A4 is responsible for the metabolism of 50% of prescription drugs metabolised by the liver.

11. Ans. (a) Clopidogrel (Ref: KDT 6/e p609, 610)

- ADP receptor antagonists, ticlopidine and clopidogrel are prodrugs.

12. Ans. (a) Is excreted mainly by the kidneys (Ref: KDT 7/e p29)

Ionized molecules cannot cross the biological membranes. Therefore, these are less likely to be absorbed. Entry of these molecules through blood brain barrier and blood placental barrier is also restricted. These drugs cannot be reabsorbed in the nephron, thus are excreted by the kidneys.

13. Ans. (b) Small changes of pH near the pKa of a weak acidic drug will not affect its degree of ionization (Ref: Katzung 11/e p9, 11)

- pKa is the pH at which half of the drug is in the ionized form. There is maximum variation in the ionization of a drug at pH near its pKa value.
- Phenobarbitone is an acidic drug having pKa of 7.2. Therefore, at pH = 7.2, 50% of drug is ionized and 50% un-ionized. In acidic medium, more of it will be unionized (because it is acidic in nature). In plasma (pH = 7.4), more will be ionized (60%) and less (40%) un-ionized.

14. Ans. (c) Low oral bioavailability always and necessarily mean poor absorption (Ref: Katzung 11/e p43-44; KDT 6/e p17)

- Low oral bioavailability can also be due to high first pass metabolism. For detail see text.

15. Ans. (b) Salicylates (Ref: Katzung 11/e p1019)

Salicylates stay in the blood whereas digoxin, diazepam and organophosphates are distributed widely.

16. Ans. (d) Binding sites are non specific and one drug can displace the other (Ref: Katzung 10/e p47, 48)

- Acidic drugs bind to albumin whereas basic drugs bind to α_1 acid glycoprotein.
- It is the free form of the drug that is metabolized or excreted. Bound form is not available for either metabolism or excretion.
- Many drugs can bind to the same plasma protein binding site resulting in the displacement reactions.
- When plasma concentration increases, both free as well as bound drug will increase in plasma.

17. Ans. (b) Morphine (Ref: Katzung 12/e p39-40)

All drugs listed in the options are highly plasma protein bound (>90%) whereas morphine has only 35% binding to plasma proteins.

18. Ans. (a) Active transport; (b) Passive transport (Ref: KDT 7/e p11-13)

Drugs are transported across the membranes by:

- Passive diffusion and filtration
- Specialized transport

Specialized transports are of two types:

- Active transport
- Facilitated diffusion

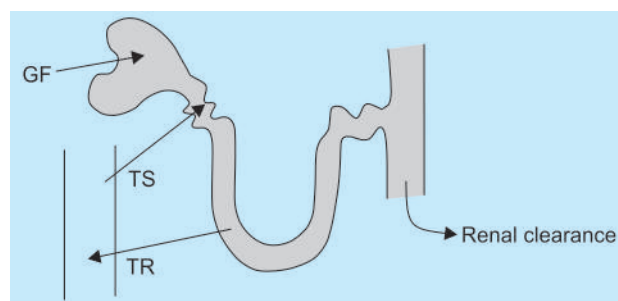
19. Ans. All (Ref: KDT 7/e p20, 30-33)

- High protein binding of a drug make it restricted to vascular compartment and thus has tendency to lower volume of distribution. It behaves as a long acting drug as bound fraction is not available for metabolism or excretion.

- Other factors that affect duration of action of IV drugs are:
 - Clearance
 - Half Life
 - Volume of distribution which depends on lipid solubility, ionization at physiological pH, protein binding affinity of tissues and regional blood flow.
20. **Ans. (a) High first pass metabolism** (Ref: KDT 7/e p16)
- The causes of low bioavailability are:
 1. Reduced absorption
 2. High first pass metabolism
21. **Ans. (b) Phenytoin; (c) Carbamazepine** (Ref: KDT 7/e p26)
- CYP3A4 carry out biotransformation of large number of drugs. The inhibition of this isoenzyme by erythromycin, clarithromycin, ketoconazole, itraconazole etc. is responsible for important drug interactions with terfenadine, as-temizole and cisapride. Rifampicin, barbiturates and other anticonvulsants are important inducers.
22. **Ans. (a) If a drug is administered rectally it follow 1st order kinetics; (b) If a drug is administered I.M. it follows zero order kinetics; (c) If a drug is administered I.V. it follows 1st order kinetics** (Ref: KDT 7/e p30-31)
- The order of kinetics of drugs does not depend upon the route of administration. It depends upon the type of drugs.
 - In case of i.v. injection bioavailability is 100%, but is frequently lower in oral ingestion.
23. **Ans. (c) Phenobarbitone; (d) DDT** (Ref: KDT 7/e p26)
- P-450 inducers are:
 - Phenobarbitone, rifampicin, phenytoin, chloral hydrate, phenylbutazone, griseofulvin, DDT, and chronic alcohol ingestion.
 - Ketoconazole and cimetidine inhibit the drug metabolizing enzymes.
24. **Ans. (a) Plasma protein binding; (b) Lipid solubility; (c) Degree of blood flow; (d) Age** (Ref: KDT 7/e p17-18)
- **Factors affecting drugs distribution:**

– Lipid solubility of drugs.	– Regional blood flow.
– Ionization at physiological pH.	– Fat: lean body mass ratio (changes with age).
– Degree of plasma protein binding.	– Disease like CHF, uremia, cirrhosis.
– Affinity for different tissues.	
25. **Ans. (b) I.M. administration needs sterile technique; (c) I.D. injection produces local tissue necrosis and irritation** (Ref: KDT 7/e p8-9)
- 100% bioavailability is seen in case of IV route.
 - Sterile technique is needed in case of I.V. and I.M. administration.
 - Irritation and local tissue necrosis is seen in case of intradermal (ID) route.
 - In inhalational route, absorption of drugs takes place from vast surfaces of alveoli-so bioavailability is high and action is very rapid. [KDT 6/e p9]
26. **Ans. (a) Obesity; (c) Pregnancy; (d) Older age; (e) Neonate** (Ref: KDT 7/e p17-18)
- In elderly patients, the V_d is more because of increased total body fat content and decreased plasma protein binding of drugs.
 - In paediatric patients also, there is greater volume of extracellular fluid and this provides a larger volume of distribution of highly ionized drugs. Therefore, a larger initial dose may be required to achieve the desired blood level.
 - In obese patients because of greater than normal adipose content, V_d is increased.
 - In Pregnancy also blood volume increases about 30-40%. Although the total protein is increased, but plasma protein concentration is decreased, thus altering V_d .
27. **Ans. (a) Mercaptopurine; (b) Dipivefrine; (c) Enalapril** (Ref: KDT 7/e p23)
- | Prodrug | Active form |
|------------------|------------------------|
| • Enalapril | • Enalaprilat |
| • Dipivefrine | • Epinephrine |
| • Mercaptopurine | • Methylmercaptopurine |
28. **Ans. (a) Lignocaine; (b) Propanolol; (c) Salbutamol** (Ref: KDT 7/e p27)

29. Ans. (b) Sulfation; (c) Methylation; (d) Glucuronidation (Ref: KDT 7/e p34)
30. Ans. (a) Propranolol; (b) Lidocaine; (d) Imipramine; (e) Theophylline (Ref: KDT 6/e p28)
- High hepatic extraction ratio means that most of the drug reaching the liver (via blood vessels) is removed by liver. These drugs have either high first pass metabolism or high systemic metabolism.
 - Propranolol and lidocaine undergo high first pass hepatic metabolism.
 - Theophylline is extensively metabolized in liver by demethylation and oxidation.
 - TCAs (tricyclic antidepressants) are extensively metabolized in liver; the major route for imipramine and amitriptyline is demethylation whereby active metabolites-desipramine and nortriptyline respectively are formed.
 - **Ampicillin is partly excreted in bile** and enterohepatic circulation occurs. However, **primary channel of excretion is kidney**.
31. Ans. (c) Hepatic metabolism and renal excretion are the two most important mechanisms involved (Ref: KDT 6/e p23)
- Action of a drug can be terminated either by hepatic metabolism or by renal excretion. Most of the drugs are inactivated by metabolism. However, some drugs may be activated from inactive form (pro-drugs) and others may produce active metabolites.
 - Some drugs may act away from blood e.g. digoxin leaves blood stream and enters the heart to produce its action.
32. Ans. (b) First pass effect (Ref: Katzung 10/e p41)
- Reduction in the amount of drug before it enters the systemic circulation is called first pass metabolism (also known as first pass effect) whereas if the amount of drug decreases after entry into the systemic circulation, it is called elimination. Latter includes excretion and metabolism.**
33. Ans. (b) Elimination (Ref: Katzung 10/e p41)
34. Ans. (c) Inhalational (Ref: KDT 6/e p9)
- Inhalational anesthetic agents like halothane are used in the clinical practice by titration of dose with response.
35. Ans. (b) Weak acid (Ref: Katzung 10/e p7, 8)
- Strong electrolytes (strong acid and strong base) are ionized in all media, whether it is acidic or basic. Weak acids are ionized in the alkaline medium and are easily excreted.
36. Ans. (b) Diclofenac sodium (Ref: Katzung 10/e p7, 8; KDT 6/e p193)
- Diclofenac is an acidic drug and is non-ionized in the acidic medium of stomach. Therefore, it has the maximum chances of absorption from the stomach. Other drugs given in the options are basic drugs that are ionized at gastric pH.
37. Ans. (a) High plasma protein binding (Ref: Katzung 10/e p34, 35)
- If a drug is highly bound to plasma proteins, it is more likely to stay in the blood. Thus, its V_d will be less.
 - Low ionization favors the distribution of a drug because unionized molecules can cross the membranes of blood vessels and the tissues.
 - More lipid soluble drugs can easily cross the membranes and are more likely to be highly distributed.
38. Ans. (b) Desmopressin (Ref: KDT 6/e p9)
39. Ans. (a) Passive diffusion (Ref: Katzung 10/e p6)
40. Ans. (a) More than the GFR (Ref: KDT 6/e p30)



After filtration from glomerulus, a drug may undergo two processes (tubular reabsorption and tubular secretion) before going out from the body i.e. renal clearance.

- Suppose 100 mg of a drug is filtered by glomerulus and the renal clearance is 150 mg, it means 50 mg is coming from somewhere else, i.e. tubular secretion must be present. However, we cannot say that reabsorption is not occurring because if 20 mg is reabsorbed and 70 mg is secreted, same thing can happen.

- Suppose, 100 mg of a drug is filtered but renal clearance is 50 mg. Therefore, 50 mg must have gone somewhere i.e. tubular reabsorption must be occurring, Again, we cannot say that tubular secretion is not present.

41. Ans. (c) Conversion of lipid soluble drugs to water soluble metabolites (Ref: *Katzung 10/e p50*)

After metabolism most of the drugs become inactive and are excreted through the kidney. Lipid soluble drugs will be reabsorbed whereas water soluble drugs are easily excreted. Thus, metabolism of drugs helps in the conversion of lipid soluble drugs to water soluble metabolites.

42. Ans. (d) Redistribution (Ref: *KDT 6/e p19*)

Highly lipid soluble drugs like thiopentone are quickly distributed to the tissue having high blood supply (like brain). If the target organ is also having high blood supply, drug action will be very quick. This is the case with general anaesthetics like thiopentone. Now, the drug will be distributed to less vascular tissues like fat and muscle. Movement of the drug outside the brain results in the termination of its action. This is called redistribution.

43. Ans. (a) They produce high peak plasma concentration of the drug (Ref: *KDT 6/e p9*)

Transdermal route is employed for highly lipid soluble drugs that can traverse intact skin. The size of the pores in transdermal patch is adjusted to produce a uniform and smooth absorption of the drug. This will thus, produce a delayed and smaller peak in the plasma concentration. As the drug is going directly in the blood stream, first pass metabolism is avoided.

44. Ans. (a) Highly lipid soluble drugs (Ref: *KDT 6/e p19*)

45. Ans. (b) These are excreted faster in acidic urine (Ref: *Katzung 10/e p7, 8*)

46. Ans. (d) High plasma protein binding decreases the volume of distribution (Ref: *Katzung 10/e p47*)

When a drug is highly bound to plasma proteins, it is more likely to stay in blood and thus V_d is less. *Glomerular filtration depends on renal blood flow and plasma protein binding.* Highly protein bound drugs are less likely to be filtered by the glomerulus. Due to non-specific binding sites on plasma proteins these drugs are subjected to several drug interactions.

47. Ans. (a) Glucuronidation (Ref: *KDT 6/e p25*)

48. Ans. (b) Acetylation (Ref: *KDT 6/e p25*)

Most of the phase I reactions and glucuronide conjugation (Phase II reaction) are catalyzed by microsomal enzymes. These enzymes can be induced or inhibited by drugs. Acetylation is carried out by N-acetyl transferase, a non-microsomal enzyme.

49. Ans. (b) Plasma protein binding (Ref: *KDT 6/e p29, 30, 31*)

As discussed in question no. 121, glomerular filtration is dependent on renal blood flow and plasma protein binding. It does not depend on the lipid solubility.

50. Ans. (b) Chronic administration of cimetidine with the drug (Ref: *KDT 6/e p24*)

- Cimetidine is a microsomal enzyme inhibiting drug. It increases the duration of action of the drugs metabolized by these enzymes. On the other hand, rifampicin and phenobarbitone are enzyme inducers and will decrease the duration of action of such drugs.
- Displacement from binding sites increases the free drug that can be quickly metabolized.

51. Ans. (a) Urinary excretion would be accelerated by administration of NH_4Cl , an acidifying agent (Ref: *Katzung 10/e p7, 8*)

This question can be solved by the knowledge that basic drugs are ionized in the acidic medium and vice-a-versa. This antihistaminic drug is a weak base and will be highly ionized in the acidic urine. As ionized drugs cannot be reabsorbed in the nephron, urinary acidifying agents like NH_4Cl will accelerate the excretion of this agent. On the other hand, NaHCO_3 will decrease its excretion by increasing the unionized form.

Blood pH is slightly alkaline (7.4) whereas gastric pH is highly acidic. Basic drugs are ionized more in the acidic pH, therefore option (c) is false.

Only unionized molecules can cross the membranes, therefore more drug will be absorbed by the small intestine (alkaline pH) than by the stomach.

52. Ans. (b) The first pass effect is the result of elimination of a drug after administration and before it enters systemic circulation (Ref: *Katzung 10/e p41*)

- Inhalational route provides localized delivery to respiratory system and thus is associated with lesser adverse effects than the systemic routes like oral. Option (a) is thus false.
- Option (b) is the definition of first pass metabolism as given in the text.
- When a drug is administered by rectal route, first pass metabolism is less than oral route. But sublingual administration completely avoids first pass metabolism. Therefore, option c is also wrong.

- Transdermal route is associated with slower absorption of a drug because the pore size is smaller. However, first pass metabolism is avoided because the drug directly enters the systemic circulation.

53. Ans. (c) Lower volumes of distribution (Ref: KDT 6/e p20-21)

- The clinically significant implications of plasma protein binding are:
 1. Plasma protein binding causes restriction of drugs in the vascular compartment and thus *lower volume of distribution*.
 2. *Longer duration of action* – as the protein-bound fraction is not available for metabolism or excretion.
 3. Plasma protein bound drugs tend to have *more drug interactions* due to displacement of a drug with lower affinity by a drug with higher affinity for plasma proteins.
 4. Hypoalbuminemia can lead to high concentration of free drug and thus drug toxicity.

54. Ans. (a) Cimetidine (Ref: KDT 6/e p27-28)

55. Ans. (c) Levodopa (Ref: KDT 6/e p24)

56. Ans. (d) Lisinopril (Ref: KDT 6/e p485)

- Captopril and lisinopril are ACE inhibitors that are not prodrugs.
- Diazepam produce many active metabolites like oxazepam.
- Propranolol can produce 4-hydroxypropranolol which has β -antagonist activity.
- Allopurinol gives rise to oxypurinol which can inhibit xanthine oxidase.

57. Ans. (c) Insulin (Ref: KDT 6/e p28)

58. Ans. (c) Carbimazole (Ref: KDT 6/e p250)

59. Ans. (a) Insulin (Ref: KDT 6/e p28)

60. Ans. (b) Lisinopril (Ref: KDT 6/e p485)

61. Ans. (a) Sequestered in body tissues (Ref: KDT 6/e p18-19)

- Apparent volume of distribution (V_d) is more for drugs sequestered in tissues.
- Lipid insoluble drugs do not enter cells, V_d approximates ECF volume.

62. Ans. (b) Cimetidine (Ref: KDT 6/e p27)

63. Ans. (a) Phenobarbitone (Ref: KDT 6/e p27)

64. Ans. (b) Sodium bicarbonate (Ref: KDT 6/e p30)

65. Ans. (c) Propranolol (Ref: KDT 6/e p28)

66. Ans. (a) Study of absorption, distribution, binding/storage/biotransformation and excretion of the drug (Ref: Katzung 11/e p37)

67. Ans. (c) Levodopa (Ref: KDT 6/e p24)

68. Ans. (b) Enalapril (Ref: KDT 6/e p24)

69. Ans. (b) The percentage of drug that is detected in the systemic circulation after its administration (Ref: KDT 6/e p17)

70. Ans. (a) $V_d = \frac{\text{Dose administered by I.V. route}}{\text{Plasma concentration}}$ (Ref: KDT 6/e p18)

71. Ans. (c) Thiopentone (Ref: KDT 6/e p119)

72. Ans. (a) Acetylation (Ref: KDT 6/e p683)

73. Ans. (d) Blood brain barrier is deficient at the chemoreceptor trigger zone (Ref: KDT 6/e p20)

74. Ans. (d) Oxidation (Ref: KDT 6/e p24-25)

75. Ans. (b) Imipramine (Ref: KDT 6/e p24)

76. Ans. (a) To achieve Steady State concentration in short time (Ref: KDT 6/e p34)

77. Ans. (a) Weak acid drugs (Ref: KDT 6/e p30)
78. Ans. (c) Clearance of the drug (Ref: KDT 6/e p34)
79. Ans. (d) Glucuronidation (Ref: KDT 6/e p24)
80. Ans. (a) Hydroxylation (Ref: Katzung 11/56)
81. Ans. (a) Phase I reactions (hydrolysis, oxidation, reduction etc.) only (Ref: Katzung 11/e p56)
Cytochrome P450 enzymes are responsible for phase I reactions only whereas microsomal enzymes can be involved in phase II also (glucuronide conjugation)
82. Ans. (b) The rate of absorption (Ref: Katzung 11/e p44)
83. Ans. (c) Sodium valproate (Ref: Katzung 11/e p414)
84. Ans. (a) d-tubocurarine (Ref: Katzung 12/e p39, 40)
Tubocurarine is not absorbed orally whereas oral bioavailability of morphine, ampicillin and phenytoin are 24%, 62% and 90% respectively.
85. Ans. (c) Rifampicin (Ref: KDT 6/e p27)
86. Ans. (b) Amphetamine (Ref: KDT 6/e p127)
87. Ans. (a) CYP 3A4 (Ref: KDT 6/e p24)
88. Ans. (a) Penicillin (Ref: KDT 6/e p20)
- Acidic drugs bind to albumin whereas basic drugs bind to α_1 acid glycoprotein.
 - Penicillin is an acidic drug, so it binds to albumin.
89. Ans. (a) Ketoconazole (Ref: KDT 6/e p27)
90. Ans. (a) Clearance (Ref: KDT 7/e p30)
Clearance of a drug is the theoretical volume of plasma from which the drug is completely removed in unit time.
91. Ans. (d) The rate of elimination is proportional to the plasma concentration (Ref: Goodman and Gilman 12/e p34)
Drugs may follow zero order or first order kinetics. It depends on the following formula:
Rate of Elimination $\propto$ [Plasma Concentration]^{order}
- Thus, if a drug follows zero order kinetics, [Plasma Concentration]⁰ is equal to one, in other words rate of elimination is independent of plasma concentration or rate of elimination is constant.
 - From the above formula, rate of elimination is proportional to plasma concentration for the drugs following first order kinetics.
92. Ans. (a) Volume of distribution (Ref: KDT 6/e p34)
- **Loading dose is given to saturate the tissue stores so it is mainly dependent on volume of distribution;** Whereas maintenance dose depends on the clearance. Loading dose is used for drugs having very long $t_{1/2}$ (or high V_d). It is calculated as $LD = V_d \times \text{Target PC}$
 - **Volume of distribution and clearance are primary pharmacokinetic parameters. All other parameters (e.g. half-life) can be calculated from these.**
93. Ans. (b) A constant proportion of plasma concentration is eliminated per unit time (Ref: KDT 7/e p30-31)
In first order kinetics, rate of elimination is proportional to plasma concentration of the drug. Half life and clearance are constant in first order kinetics.
94. Ans. (a) Lipid solubility; (b) Volume of distribution; (c) Clearance; (d) Drug concentration (Ref: KDT 7/e p30-31)
- Elimination of a drug depends upon:
 - Volume of distribution
 - Clearance
 - Volume of distribution is more with highly lipid soluble drugs.
 - In case of drugs following first order kinetics; rate of elimination is directly proportional to plasma concentration.
95. Ans. (c) k is 0.0693 and (e) CL is 0.2 L/hr (Ref: KDT 7/e p31-32)
- In this patients total dose of drug administered

$$= 70 \times 100 \text{ mg}$$

$$= 7000 \text{ mg}$$

Plasma concentration is 1.9 mg/ml

So, volume of distribution (V_d)

$$= \frac{\text{Total dose administered}}{\text{Plasma concentration}}$$

$$= \frac{7000}{1.9}$$

Again,

$$t_{1/2} = 0.693 \times \frac{V_d}{CL} \text{ where,}$$

V_d = Volume of distribution

CL = Clearance

Thus,

$$CL = 0.693 \times \frac{V}{t_{1/2}}$$

$$= \frac{0.693}{10} \times \frac{7000}{1.9}$$

$$= 255.3 \text{ ml/hr}$$

$$\sim 0.2 \text{ L/hr}$$

Further

$$t_{1/2} = \frac{0.693}{k}$$

Or

$$k = \frac{0.693}{t_{1/2}}$$

$$= \frac{0.693}{10} = 0.0693$$

96. Ans. (b) 80 L (Ref: Katzung 10/e p34)

$$V_d = \frac{\text{Amount administered}}{\text{Plasma concentration}}$$

$$= \frac{4 \text{ g}}{50 \text{ } \mu\text{g/ml}} = 80 \text{ L}$$

97. Ans. (d) Total body clearance (Ref: KDT 6/e p34)

- Maintenance dose is determined by clearance.

$$\text{Maintenance dose} = CL \times \text{Plasma concentration required}$$

98. Ans. (b) 2.0 L/hr (Ref: Katzung 10/e p35)

$$\text{Clearance} = \frac{\text{Rate of elimination}}{\text{Plasma concentration}}$$

$$= \frac{20 \text{ mg/hr}}{10 \text{ mg/L}} = 2 \text{ L/hr}$$

99. Ans. (b) 4 mg/dl (Ref: Katzung 10/e p44)

Dose Rate = Clearance $\times$ Steady state plasma concentration

- This means plasma concentration at steady state is a direct function of the dose rate, if clearance is constant. In first order kinetics (clearance is constant), plasma concentration attained is directly proportional to the dose rate. Thus, doubling of dose rate from 10 to 20 mg/min, will double the steady state plasma concentration (from 2 to 4 mg/dl).

100. Ans. (d) 160 mg (Ref: Katzung 10/e p45)

Loading dose = $V_d \times$ target plasma conc.

$$= 40 \text{ L} \times 4 \text{ mg/L}$$

$$= 160 \text{ mg}$$

Clearance plays no role in the determination of loading dose. It is given to confuse you.

101. Ans. (c) 3.2 days (See below)

We want to decrease the plasma concentration of digoxin from 4 ng/ml to 1 ng/ml. It will take two half lives. Thus time required will be $2 \times t_{1/2}$ i.e. $2 \times 1.6 = 3.2$ days.

102. Ans. (d) Constant intravenous infusion (Ref: Katzung, 10/e p40, 43, 44)

- When a drug is administered less frequently, it produces marked variation in the plasma concentrations. In this question the drug has a half life of 6 hours. If we repeat the dose at 6 hourly intervals, there will be 100% variation in the plasma concentration.
- More frequent dosing will minimize the variation between maximum and minimum plasma concentrations. As the margin of safety of this drug (given in the question) is very low (maximum tolerable concentration is only 1.5 times the effective concentration), constant i.v. infusion is the best route.

103. Ans. (d) Approximately 32 hours

(See below)

- For a drug following first order kinetics, rise in plasma concentration as well as fall in plasma concentration is similar. When the steady state is attained and the drug administration is stopped, it will be eliminated from the body. 50% will be eliminated in one half life, 75% in $2 t_{1/2}$, 87.5% ($50 + 25 + 12.5\%$) in $3 t_{1/2}$ and 93.75% ($50 + 25 + 12.5 + 6.25\%$) in four half lives.
- When constant i.v. infusion is administered, plasma concentration increases in the same manner. In one half life, it is 50% of the steady state and to reach 93.75% of steady state, 4 half lives will be required.
- As half life of this drug is 8 hours, approximately 32 hours (4×8) will be taken.

104. Ans. (b) 4 mg/L (Ref: Katzung, 10/e p40, 43, 44)

- Half life of this drug is 2 hours and its plasma concentration is 3 mg/L after 4 hours (9AM to 1 PM).
- This means, after 2 half lives (4 hours) plasma concentration is 3 mg/L. We know, by constant i.v. infusion, plasma concentration attained is 75% of the steady state in 2 half lives. So, if 3 mg/L is 75% of steady state, it will amount to 4 mg/L.

105. Ans. (c) 40 hr (Ref: Katzung, 10/e p38, 39)

$$t_{1/2} = 0.693 \frac{V_d}{CL}$$

106. Ans. (b) 30 mg/hr (Ref: Goodman and Gilman 12/e p36-37)

In this question 80 percent of drug is eliminated by renal route and 20 percent by non-renal routes (10 percent by hepatic metabolism and 10 percent by biliary secretion).

This patient has 50 percent renal function (60 ml/min of GFR instead of 120 ml/min). Thus, the drug that can be eliminated in this person is 20 percent (Non-renal route) + 40 percent (Renal route; 50 percent of 80 percent) = 60 percent

Thus, the dose rate should be 60 percent of the original.

i.e. $50 \text{ mg/hr} \times 60 \text{ percent} = 30 \text{ mg/hr}$.

107. Ans. (c) Increasing rate of elimination as plasma concentration increases. (Ref: Katzung 10/e p38)

108. Ans. (b) 93% (Ref: KDT 6/e p32)

- Drugs elimination after different $t_{1/2}$:

Half Life	Elimination
First	50%
Second	75% ($50 + 25$)
Third	87.5% ($50 + 25 + 12.5$)
Fourth	93.75% ($50 + 25 + 12.5 + 6.25$)

109. Ans. (b) Barbiturates (Ref: KDT 6/e p31)

110. Ans. (b) Phenytoin (Ref: KDT 6/e p31)

111. Ans. (a) 6.25% (Ref: KDT 6/e p32)
112. Ans. (a) Half life of drug (Ref: KDT 6/e p32)
113. Ans. (b) Half life of drug (Ref: KDT 6/e p32)
- After a dosage regimen, concentration of the drug to reach the steady state (when the elimination balances the input) is called **steady state plasma concentration C_{pss}** .
 - C_{pss} is reached in about 4-5 half lives.
 - The amplitude of fluctuations in C_{pss} depends on the dose interval relative to $t_{1/2}$.
114. Ans. (d) Methotrexate (Ref: KDT 6/e p31)
115. Ans. (a) Zero order kinetics (Ref: KDT 6/e p383)
116. Ans. (a) Volume of plasma which is cleared of drug in unit of time (Ref: KDT 6/e p31)
117. Ans. (a) Phenytoin and Theophylline (Ref: KDT 6/e p31, 138)
118. Ans. (a) A constant amount of drug is eliminated per unit time (Ref: KDT 6/e p31)
119. Ans. (a) Clearance remains constant (Ref: KDT 6/e p31)
120. (b) Penicillin (Ref: Harrison 18/e p2735)
Important drugs causing SLE like syndrome include:
- | | |
|---|--------------|
| S | Sulfonamides |
| H | Hydralazine |
| I | Isoniazid |
| P | Procainamide |
121. Ans. (c) Seven pass transmembrane receptors (Ref: Goodman and Gilman 12/e p52-53)
These neurotransmitters (A, NA, DA) act through G-protein coupled receptors which are also known as seven-transmembrane domain receptors, heptahelical receptors and serpentine receptors.
122. Ans. (d) Increased cAMP (Ref: Harper, 28/e p447)
For Details, see text.
123. Ans. (c) Insulin binds to a transmembrane receptor at the outer surface of the plasma membrane, which activates the tyrosine kinase that is the cytosolic domain of the receptor. (Ref: Goodman and Gilman 12/e p1241)
Enzymatic Receptors have two sites, the drug binds on the extracellular site and the intracellular site has enzymatic activity (mostly tyrosine kinase). This enzyme can be activated via JAK-STAT pathway. Insulin, growth hormone, prolactin and cytokines act via enzymatic receptors.
124. Ans. (c) G proteins act as inhibitory and excitatory because of difference in alpha subunit (Ref: Harper 26/e p458; Lippincott Biochem 3/e p93; Ganong 22/e p41; KDT 6/e p46)
- G proteins are so-called because they bind the guanine nucleotides GDP and GTP. They are heterotrimers (i.e., made of three different subunits)
 - The three subunits are: $G\alpha$, $G\beta$ and $G\gamma$.
 - In the inactive state G protein has GDP bound to its $G\alpha$ subunit.
 - When a hormone or other ligand binds to the associated receptor (GPCR), the GDP is exchanged for GTP.
 - GTP activates $G\alpha$ causing it to dissociate from $G\beta\gamma$ (which remain linked as a dimer).
 - Activated $G\alpha$ in turn activates an effector molecule like adenylyl cyclase, which catalyzes the conversion of ATP to the "second messenger" cyclic AMP).
 - G_s , G_i and G_q are different types of G-proteins due to different α -subunits.
 - G_s and G_q are stimulatory whereas G_i is inhibitory G-protein.
125. Ans. (d) Metoclopropamide (Ref: KDT 7/e p24)
- Important drugs metabolized by acetylation are
- | | |
|---|--------------------------------|
| S | Sulfonamides including dapsone |
| H | Hydralazine |
| I | Isoniazid |
| P | Procainamide |

126. Ans. (c) Breakdown of GTP to GDP (Ref: KDT 7/e p46)

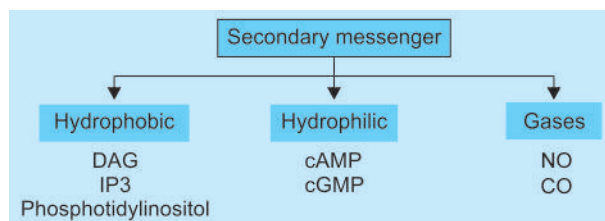
Alpha subunit of G protein contains GTPase activity and thus dissociates GTP to form GDP. This results in re-uniting α subunit with β and γ subunit

127. Ans. (b) Guanylyl Cyclase (Ref: KDT 7/e p47-48)

Remember that guanylyl cyclase is an enzyme while cGMP is a secondary messenger

Types of second messengers

There are three basic types of secondary messenger molecules:



Note: Calcium in the setting of G proteins is considered as the third messenger whereas the drug itself is considered as the first messenger.

128. Ans. (c) Decreases V_{max} (Ref: KDT 7/e p39)

- Competitive inhibitors increase K_m value whereas non-competitive inhibitors decrease V_{max} of an enzyme

129. Ans. (c) Activation of protein kinase (Ref: KDT 7/e p46)

- Cyclic AMP exerts most of its effects by stimulating cAMP-dependent protein kinases. These phosphorylate enzymes resulting in their activation or inhibition.

130. Ans. (d) Pyrimethamine (Ref: KDT 7/e p66)

- Important drugs causing hemolysis in G-6-PD deficiency are

- Primaquine	- Dapsone	- Sulfonamides
- Nitrofurantoin	- Aspirin	- Menadione
- Chloroquine	- Quinine	- Nalidixic acid

- Sulfonamides can cause hemolysis in patients with G-6-PD deficiency and not pyrimethamine.

131. Ans. (c) Insulin (Ref: Katzung 11/e p730)

For Details, see text.

132. Ans. (c) ED_{50} of the drug corresponds to the efficacy (Ref: Katzung 11/e p30-31)

ED_{50} corresponds to potency of a drug, not its efficacy. All other statements are true.

133. Ans. (b) Binds to the receptor and causes opposite action (Ref: KDT 7/e p40)

134. Ans. (a) Adenosine deaminase deficiency (Ref: KDT 7/e p66)

135. Ans. (a) High affinity (Ref: KDT 6/e p42)

136. Ans. (d) Ceftriaxone (Ref: KDT 7/e p66)

137. Ans. (c) The substrate concentration at half maximal velocity (Ref: KDT 7/e p38)

K_m of an enzyme is similar to potency of a drug. It is the substrate concentration at which the velocity reaches half of the maximum known as V_{max} . (similar to efficacy of a drug). Higher is the K_m , lesser is the speed of the reaction.

138. Ans. (d) Adrenaline and histamine; (e) Salbutamol and leukotrienes (Ref: Katzung 12/e p20)

- Physiological antagonists are those drugs that produce opposite action by acting on different receptors.
- Adrenaline reverses the bronchoconstrictor action of histamine (via H_1 receptors) by causing bronchodilation (through β_2 receptors). Therefore, these are physiological antagonists.
- Salbutamol reverses the bronchoconstrictor action of leukotrienes (via cysteinyl leukotriene receptors) through its action on β_2 receptors. Therefore, it is also a physiological antagonism.
- Isoprenaline (β_1 and β_2 agonist) and propranolol (β_1 and β_2 antagonist) are pharmacological antagonists because they are acting on same receptors.
- Isoprenaline and salbutamol or adrenaline are not antagonists at all.

139. Ans. (a) Chloroquine; (b) Quinine; (c) Sulfamethoxazole; (d) Nitrofurantoin; (e) Primaquine (Ref: KDT 7/e p66)

Primaquine, sulfonamides and nitrofurantoin possess high risk of causing hemolysis in patients with G-6-PD deficiency.

- Chloroquine and quinine can also cause hemolysis in G-6-PD deficiency but the risk is low.

140. Ans. (a) Variability of enzyme action; (c) Individual variability in oral absorption; (e) Different DRC in different individuals (Ref: KDT 7/e p65-66)

- Pharmacogenetics is associated with identification of difference in drug response or metabolism; as a function of genetic background.

141. Ans. (a) INH; (b) Hydralazine; (c) Procainamide (Ref: CMDT 2010/752)

For details, see text.

142. Ans. (c) Physiological antagonist (Ref: Katzung 10/e p16)

Drugs producing opposite action by acting on different receptors are called physiological antagonists.

143. Ans. (a) Pharmacological antagonist (Ref: Katzung 10/e p16)

144. Ans. (c) Diffusion across the membrane and binding to an intracellular receptor (Ref: KDT 6/e p51)

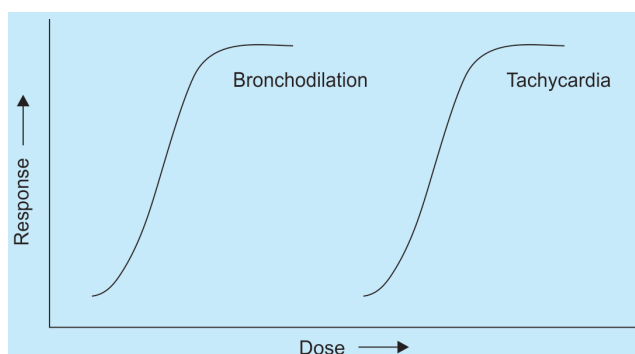
Steroid hormones are lipid soluble and act on cytoplasmic receptors after crossing the plasma membrane.

145. Ans. (d) Primaquine induced hemolytic anemia (Ref: KDT 6/e p853)

Primaquine is an oxidant drug. It can cause hemolytic anemia in subjects having deficiency of G-6-PD enzyme. This condition is genetically determined.

146. Ans. (d) Highly selective drug (Ref: Katzung 10/e p28, 29)

Wide separation of two curves on DRC suggests that the dose required to produce one action is much higher than the other.



DRC of salbutamol for bronchodilation and tachycardia.

From the Figure, it is seen that bronchodilation (β_2 action) appears at low doses whereas tachycardia (β_1 action) is present only at high doses. Thus, it shows that the drug is highly selective for β_2 receptors.

147. Ans. (c) Intrinsic ion channel opening (Ref: Katzung 10/e p21; KDT 6/e p40)

Drugs acting via ionotropic receptors are fastest acting whereas those acting through nuclear receptors are slowest in action.

148. Ans. (b) Nicotinic cholinergic receptor (Ref: KDT 6/e p48)

149. Ans. (a) High affinity but low intrinsic activity (Ref: KDT 6/e p42)

150. Ans. (d) Salbutamol (Ref: KDT 6/e p45)

GPCRs are heptahelical or serpentine receptors. Salbutamol acts through β_2 receptors which are GPCRs.

151. Ans. (d) G Proteins (Ref: KDT 6/e p48)

Cyclic AMP, IP_3 and DAG are second messengers whereas G Proteins are the first messengers. IP_3 and DAG increase the release of Ca^{2+} that acts as a third messenger.

152. Ans. (b) The maximal intensity of response that can be produced by the drug (Ref: Katzung 10/e p29)

153. Ans. (b) Drug A is more potent than drug B (Ref: Katzung 10/e p28, 29)

The drug producing the same response at lower dose is more potent. In this question, drug A is 10 times more potent than drug B. This data does not indicate anything about efficacy, safety or duration of action.

154. Ans. (d) Cortisol (Ref: KDT 6/e p280)
155. Ans. (b) An antagonist has affinity but no intrinsic activity (Ref: KDT 6/e p41)
156. Ans. (a) Epinephrine (Ref: KDT 6/e p48)
157. Ans. (a) Metabotropic receptors (Ref: Katzung 11/e p359)
158. Ans. (b) Binds to the same receptor binding-site as an agonist for that receptor but exerts the opposite pharmacological effect (Ref: KDT 6/e p41)
159. Ans. (a) Competitive antagonism (Ref: KDT 6/e p58)
160. Ans. (a) Concentration of drug at which the reaction velocity is half of maximum (Ref: KDT 6/e p55)
161. Ans. (a) Physiological antagonism (Ref: KDT 6/e p56)
162. Ans. (a) Affinity with intrinsic activity is 1 (Ref: KDT 6/e p41)
163. Ans. (a) Warfarin (Ref: Goodman Gilman 12/e p37-38)
Therapeutic drug monitoring is not required for oral anticoagulants like warfarin. The effect of warfarin is monitored by measuring prothrombin time or INR (International Normalized Ratio).
164. Ans. (d) When the clinical response cannot be easily monitored. (Ref: KDT 7/e p34)

Therapeutic Drug Monitoring (TDM)

- TDM is a process by which the dose of a drug is adjusted according to its plasma concentration.
- For performing TDM, there should be good relation between drug concentration and response. Note that there may not be good relation between dose and plasma concentration.
- It is done for drugs having wide variation in pharmacokinetics (absorption, metabolism or excretion), both intra as well as inter-individual.
- It is done for the drugs having low therapeutic index like theophylline, lithium, antiepileptics, immunomodulators and antiarrhythmics etc.
- TDM is done for those drugs whose effect cannot be easily measured (like effect of antihypertensive drugs can be easily measured by monitoring BP, so TDM is not used).
- TDM is **not done** for the drugs which are activated in the body or produce active metabolites, when pharmacological tolerance is suspected and when there is poor relation between drug concentration and effect.

165. Ans. (a) Safety (Ref: KDT 7/e p56)
- Therapeutic index is a measure of margin of safety of a drug
 - It is defined as the ratio of median lethal dose and median effective dose

$$T.I. = \frac{LD_{50}}{ED_{50}}$$

166. Ans. (b) Metformin (Ref: KDT 7/e p34)
- We can easily monitor blood glucose levels as an effect of metformin, thus TDM is not required.
 - TDM is required for lithium, digitalis, phenytoin, immunosuppressants and anti-arrhythmics etc.
167. Ans. (a) Lithium; (c) Phenytoin (e) Tricyclic antidepressants (Ref: KDT 7/e p34)
168. Ans. (c) Lithium carbonate (Ref: KDT 6/e p434, 435)
169. Ans. (b) It is easier to measure the effect of these drugs (Ref: KDT 6/e p34, 35)
TDM is done for drugs (with narrow therapeutic index) whose response cannot be monitored by clinical examination. Antihypertensive effect can be easily measured, therefore TDM is not required.
170. Ans. (a) Lithium (Ref: KDT 6/e p35)
171. Ans. (b) Lithium (Ref: KDT 6/e p435-436)
172. Ans. (b) Phenytoin (Ref: KDT 6/e p404)
173. Ans. (d) Margin of safety (Ref: KDT 6/e p53, 55)

174. Ans. (b) $\frac{LD_{50}}{ED_{50}}$ (Ref: KDT 6/e p55)
175. Ans. (c) Therapeutic index (Ref: KDT 6/e p55)
176. Ans. (b) Drug with low safety margin (Ref: KDT 6/e p43)
177. Ans. (a) Potency (Ref: Katzung 11/30)
178. Ans. (c) Phase I trial (Ref: Katzung 12/e p75)
Phase I trial is designed as a dose-escalation study to determine the maximum tolerable dosage (MTD), that is, the maximum dose associated with an acceptable level of dose-limiting toxicity.
179. Ans. (c) Phase III
"The purpose of phase III trials is to obtain adequate data about the efficacy and safety of drugs in a larger number of patients of either sex in multiple centres usually in comparison with the standard drug."
180. Ans. (a) Monitoring of drug safety (Ref: KDT 7/e p82-83)
Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.
181. Ans. (c) Drugs used for rare diseases (Ref: KDT 7/e p5)
Orphan drugs are the drugs that are used for the treatment of rare diseases. e.g. N-acetylcysteine for paracetamol poisoning. Other examples include fomepizole, sodium nitrite, digibind etc.
182. Ans. (c) Used to determine efficacy (Ref: Katzung 11/e p72)
For details, see text.
183. Ans. (a) Efficacy (Ref: Katzung, 11/e p31)
 - Efficacy is the maximum effect of a drug regardless of dose. It is determined under controlled conditions in clinical trials.
 - Effectiveness is the response of a drug in clinical set up. It may not yield the maximum benefit.
184. Ans. (d) Phase IV (Ref: KDT 6/e p77, Katzung 11/e p72-73)
185. Ans. (a) Preclinical Phase (Ref: KDT 7/e p79)
 - GCP guidelines are made to safeguard the interest of subjects in clinical trials. These have to be adhered to in all phases of clinical trials.
 - Preclinical trials are performed in animals for which different regulations are given by CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals).
186. Ans. (a) Placebo is a dummy medication (Ref: KDT 6/e p65)
Placebo plays a very important role in the clinical trials. To know, whether the effect is produced by a drug or it is just by chance, a dummy medication known as placebo is given to the control group. Placebo may or may not produce an effect in a subject.
187. Ans. (d) It is a drug required for treatment or prevention of a rare disease (Ref: KDT 6/e p6)
Orphan drugs are used for rare diseases e.g. erythropoietin for the treatment of anemia in patients with chronic renal failure.
188. Ans. (a) Phase I involves the study of a small number of normal volunteers by highly trained clinical pharmacologists (Ref: KDT 6/e p77)
 - Phase I is carried out in healthy volunteers whereas other phases are conducted in patients.
 - Phase II is performed in small number of patients and phase III is a multicentric trial requiring large number of patients.
 - Phase IV is a post marketing trial conducted for every drug. It is done to know the rare adverse effects.
189. Ans. (a) Phase-I (Ref: KDT 6/e p77)
190. Ans. (c) Side effects (Ref: KDT 6/e p79-80)
"Side effects are unwanted but often-unavoidable pharmacodynamic effects that occur at therapeutic dose" (less than toxic dose)

Intolerance is the appearance of characteristic toxic effects of a drug in an individual at therapeutic doses.

Toxic effects are the result of excess pharmacological action of the drug due to overdose or prolonged use. Effects are predictable and dose related.

191. **Ans. (d) Safety and comparisons with other medicines** (Ref: *Katzung 11/e p72-73*)
 192. **Ans. (d) Phase IV** (Ref: *KDT 6/e p77*)
 193. **Ans. (a) Qualitatively abnormal responses to the drug** (Ref: *Principles of Pharmacology by HL Sharma and KK Sharma, 1st/71; KDT 6/e p78*)
 194. **Ans. (c) Propylthiouracil** (Ref: *KDT 7/e p964*)
 - Among the given options, the best answer seems to be propylthiouracil. Although, the latter can cause hepatotoxicity in mother.
 195. **Ans. (b) Thalidomide** (Ref: *KDT 7/e p89*)
Thalidomide is highly teratogenic drug that can result in phocomelia as congenital anomaly.
 196. **Ans. (a) Propylthiouracil** (Ref: *KDT 7/e p964*)
 - Methotrexate, warfarin and tetracycline are contra-indicated in pregnancy.
 197. **Ans. (c) Penicillin G** (Ref: *KDT 7/e p30*)
Penicillins are secreted by renal tubules. Probenecid competitively inhibits the secretion of penicillins and is used to increase the effectiveness of these antibiotics.
 198. **Ans. (d) Heparin** (Ref: *KDT 7/e p964*)
 199. **Ans. (c) Have increased baroreceptor sensitivity** (Ref: *KDT 7/e p64*)
 - Baroreceptor Sensitivity is reduced in elderly.
 - Total body water, lean body mass and body fat are reduced in the elderly patients leading to decrease in the volume of distribution. Renal function is depressed in the elderly patients and for some drugs, hepatic metabolism is also reduced. Baroreceptor and other reflexes are blunted in the elderly as compared to a young person.
- Note:** Receptor sensitivity to drugs (Particularly CNS drugs) is increased whereas baroreceptor sensitivity is reduced in elderly
200. **Ans. (b) Heparin is highly teratogenic drug** (Ref: *KDT 7/e p89*)
Teratogenicity is the development of characteristic set of malformations by the use of a drug during pregnancy. Different drugs have specificity for a particular phase of development of fetus. The risk of teratogenesis is dose dependent. Heparin cannot cross the placenta and is thus safe during pregnancy.
 201. **Ans. (a) Specificity** (Ref: *Katzung 10/e p28, 29*)
It can be understood from the example given below:
Atropine is a non specific antagonist of muscarinic receptors. It can be used in the management of bronchial asthma by virtue of its M_3 blocking action (bronchodilation). But it can cause tachycardia as an adverse effect due to blockade of cardiac M_2 receptors. A more specific drug like tiotropium bromide (selective M_3 antagonist) is less likely to produce this adverse effect.
 202. **Ans. (c) Antacids** (Ref: *KDT 7/e p53*)
 - Alcohol promotes $GABA_A$ receptor mediated synaptic inhibition (through chloride channel opening) as well as NMDA and kainate type of excitatory amino acid receptors
 - Benzodiazepines acts through BZD receptors which is the integral part of the $GABA_A$ receptor-chloride channel complex.
 - Most antipsychotics (except clozapine) have potent dopamine D_2 receptor blocking properties.
 - Local anesthetics acts with the receptors situated within voltage sensitive Na^+ channel.
 - Propofol acts through $GABA$ receptors
 - Drugs which do not have receptor mediated actions are
 - Antacids
 - Chelating agents
 - Antimetabolites
 - Mesna
 - Mannitol

203. Ans. (b) Propanolol; (d) Physostigmine (Ref: KDT 7/e p18-19)

- Lipid soluble drugs can penetrate blood brain barriers (BBB). These include
 - Levodopa
 - Physostigmine
 - Organophosphates
- Streptomycin, neostigmine, hexamethonium, glycopyrrolate, dopamine cannot cross BBB.

204. Ans. (b) Quinine; (c) Chloroquine (Ref: KDT 6/e p908)

- Primaquine is avoided during pregnancy, because fetus is G-6PD deficient; thereby can cause hemolysis.
- Tetracyclines are contra-indicated in pregnancy and in children.
- Sulfonamides (antifolate) are also contra-indicated in pregnancy.

205. Ans. (a) Antihistaminics; (b) Antithyroid drugs; (c) Penicillin; (d) Diazepam; (e) Antiepileptics (Ref: KDT 6/e p911-914)

- Benzodiazepines cross placenta and are secreted in milk.
- Antithyroid (e.g. carbimazole), antihistaminics, penicillin and antiepileptics are also secreted in milk.

206. Ans. (d) An antihypertensive with a plasma half life of 3 hours (See below)

Sustained release formulations of a drug are used for the drugs having short duration of action requiring prolonged administration.

- PSVT is an acute condition and requires a short and fast acting drug. Adenosine is therefore, the drug of choice for this condition.
- Option (b) describes a drug having long half life (24 hours). This drug need not be administered as sustained release preparation.
- For a hypnotic drug, action required is brief i.e. to induce sleep. Therefore, it should not be given as a sustained release preparation.
- Treatment of hypertension is life long. Drug with half life of 3 hours, needs to be administered several times a day, therefore sustained release oral dosage form is best utilized for this drug.

207. Ans. (c) Ion trapping of acidic drugs occur in pregnancy: (Ref: Goodman & Gilman 11/e p9-10)

- Heparin and insulin are anticoagulant and antidiabetic drugs of choice, respectively, in pregnancy, because these have minimum entry across placenta.
- Fetal plasma is slightly more acidic than that of mother (pH 7.0 as compared to 7.4 of mother), so ion trapping of basic drugs occur.
- Placenta contain P-glycoprotein that can act as an efflux pump for drugs.
- Placental transfer of most drugs is greater in late pregnancy than in early pregnancy because uterine circulation increases and trophoblastic layer becomes thinner as the pregnancy advances.

208. Ans. (c) Lithium (Ref: KDT 6/e p435)

209. Ans. (c) Renal clearance (Ref: Katzung 11/e p1039)

210. Ans. (a) Orphan drugs (Ref: KDT 6/e p6)

211. Ans. (b) Dopamine (Ref: KDT 6/e p415)

212. Ans. (c) Radioactive isotopes (Ref: KDT 6/e p252)

213. Ans. (a) Glycopyrrolate (Ref: KDT 6/e p110)

214. Ans. (b) Insulin (Ref: Katzung. 11/e p734)

ANSWERS OF RECENT QUESTIONS ASKED BY NATIONAL BOARD

1. Ans (b) Allergic effect of the drug (Ref: KDT 7th/83)
2. Ans (b) Penicillin (Ref: KDT 7th/56)
3. Ans (a) Valproate (Ref: KDT 7th/26)
4. Ans (a) Enalapril (Ref: KDT 7th/502)
5. Ans. (d) Physiological antagonism (Ref: KDT 7/e p58)

6. Ans. (b) β (Beta) receptor (Ref: KDT 7/e p46)
7. Ans. (b) Sequestered in tissues (Ref: KDT 7/e p18)
8. Ans. (b) Single compound (Ref: KDT 7/e p4)
9. Ans. (c) Corticosteroids (Ref: KDT 7/e p66)
10. Ans. (b) Post marketing surveillance (Ref: KDT 7/e p80)
11. Ans. (b) Enzyme inhibitor (Ref: Goodman Gilman 12/e p139)
 - Grapefruit juice contains furano coumarins and naringin that are CYP 3A4 inhibitors.
12. Ans. (b) Prostacycline-Thromboxane (Ref: KDT 7/e p58)
13. Ans. (b) Neostigmine (Ref: KDT 7/e p105)
14. Ans. (c) Safety (Ref: KDT 7/e p56)
15. Ans. (b) Schedule H (Ref: KDT 7/e p5)
16. Ans. (d) Metoclopramide (Ref: KDT 7/e p89)
17. Ans. (b) Insulin (Ref: KDT 7/e p49)
 - Nicotine acts on N_M and N_N receptors which are inotropic receptors.
 - Diazepam acts on GABA-BZD-CL channel complex that mediates entry of chloride.
 - Glibenclamide is a sulfonylurea that acts on ACh sensitive K^+ channels.
 - Insulin acts on enzymatic receptors.
18. Ans. (d) Maximum response a drug can produce (Ref: KDT 7/e p54)
19. Ans. (a) Defect in development of long bones (Ref: KDT 7/e p89)
20. Ans. (c) Drug toxicity (Ref: KDT 7/e p80)
21. Ans. (a) Hydralazine (Ref: KDT 7/e p66)
22. Ans. (b) Rifampicin (Ref: KDT 7/e p326)
23. Ans. (c) Inverse agonist (Ref: KDT 7/e p42)
24. Ans. (a) Pharmacogenomics (Ref: KDT 7/e p65)
25. Ans. (d) Alcohol and theophylline (Ref: KDT 7/e p31)
26. Ans. (d) Body surface area (Ref: KDT 7/e p63)
27. Ans. (b) Metformin (Ref: KDT 7/e p34)
28. Ans. (a) Cimetidine (Ref: KDT 7/e p26)
29. Ans. (c) Corrosive acid poisoning (Ref: KDT 7/e p85)
30. Ans. (b) Nitrate induced headache (Ref: KDT 7/e p86)
31. Ans. (b) After a drug is marketed (Ref: KDT 7/e p80)
32. Ans. (a) Phenobarbitone (Ref: KDT 7/e p29)
33. Ans. (a) Propylthiouracil (Ref: KDT 7/e p89)
34. Ans. (c) Agonists and antagonists bind to the same receptor (Ref: KDT 7/e p39)
35. Ans. (b) Transdermal (Ref: KDT 7/e p6)
36. Ans. (c) That satisfy the priority health care needs of the population (Ref: KDT 7/e p4)
37. Ans. (a) Competitive inhibitor (Ref: KDT 7/e p39)
38. Ans. (a) Phase I of clinical trial (Ref: KDT 7/e p63)
39. Ans. (d) Drugs for rare disease (Ref: KDT 7/e p5)
40. Ans. (d) Digoxin poisoning (Ref: KDT 7/e p18)

41. Ans. (c) 87.5% (Ref: KDT 7/e p30)
42. Ans. (a) 12.5% (Ref: KDT 7/e p30)
43. Ans. (a) First pass metabolism (Ref: KDT 7/e p16)
44. Ans. (a) Amount of drug that reach the systemic circulation (Ref: KDT 7/e p18)
45. Ans. (a) Drug safety (Ref: KDT 7/e p55-56)
46. Ans. (c) Low intrinsic activity and high affinity (Ref: KDT 7/e p42)
47. Ans. (c) More fat soluble metabolites are formed (Ref: KDT 7/e p22)
48. Ans. (d) Amoxicillin (Ref: KDT 7/e p23)
49. Ans. (b) Enalapril (Ref: KDT 7/e p23)
50. Ans. (d) Mechanism of action (Ref: KDT 7/e p1)

Autonomic Nervous System

Autonomic Nervous System (ANS) is involuntary in nature and the activities of this system are maintained autonomically. In contrast to somatic nervous system, organs supplied by ANS *do not atrophy* even after the section of an autonomic nerve (rather, denervation supersensitivity of receptors occur). ANS is divided into **three main divisions**.

- Sympathetic
- Parasympathetic
- Enteric nervous system.

Neurotransmitter (NT) secreted at **somatic** nerves (at neuromuscular junction) as well as at **all preganglionic** autonomic (sympathetic as well as parasympathetic) nerves is *acetylcholine* (ACh). This substance stimulates N_M nicotinic receptors at neuromuscular junction (N_{MJ}) and N_N nicotinic receptors at the ganglia.

Division of ANS into sympathetic and parasympathetic system is *anatomical* in origin. Fibres of sympathetic system originates from thoracic and lumbar spinal cord (*thoracolumbar outflow*) whereas parasympathetic system originates from cranial nerves (III, VII, IX and X) and sacral ($S_{2,3,4}$) spinal cord (*craniosacral outflow*). All autonomic fibres form a synapse in the ganglion before supplying the organ and thus can be divided into pre and post-ganglionic fibres. In *sympathetic* system, *postganglionic* fibres are either equal to or longer than preganglionic fibres whereas in *parasympathetic* system *preganglionic* fibres are much longer than postganglionic fibres (ganglia are closer to the organs).

- **Acetylcholine (ACh)** is the principal NT at NMJ as well as at all preganglionic fibres.
- In *parasympathetic* system, NT released at *postganglionic* fibres is also ACh.
- In *sympathetic* system, at most of the postganglionic fibres, NT secreted is *nor-adrenaline* (NA) but it can be *dopamine* (renal and mesenteric vasculature), *ACh* (sweat glands; sympathetic cholinergic) or *adrenaline* (adrenal medulla).

Impulse is conducted along the axon till it reaches the cell body forming the synapse. Cell body releases the NT that acts on the receptors present on the post-synaptic membrane (post-synaptic receptors) as well as on the pre-synaptic membrane (pre-synaptic receptors). Pre-synaptic receptors increase (**nicotinic**, β) or decrease (**muscarinic**, α_2) the release of neurotransmitter from their own neuron (autoreceptors) or from adjoining neurons (heteroreceptors).

Acetylcholine (ACh) is the principal neurotransmitter at neuromuscular junction as well as at all preganglionic fibres.

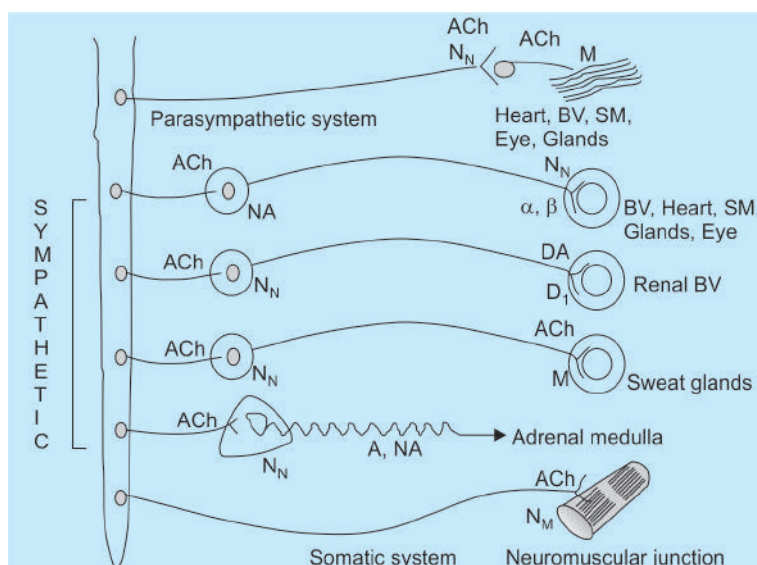


Fig. 3.1: Divisions of autonomic nervous system

Most of the actions of sympathetic and parasympathetic systems are opposite. To remember major actions, we can assume that sympathy is related to heart, so sympathetic system stimulates it (i.e. tachycardia, positive inotropic action etc.). On the other hand, parasympathetic system has opposite action, so depress heart. At most other parts action is reverse i.e. sympathetic system inhibits and parasympathetic system stimulates.

Site	Action of Sympathetic System	Action of Parasympathetic System
Heart	Stimulates ($\uparrow$ HR, $\uparrow$ Contractility, $\uparrow$ Conduction)	Depresses ($\downarrow$ HR, $\downarrow$ Conduction)
Bronchus	Relax (Bronchodilation)	Stimulates (Bronchoconstriction)
GIT	Relax ($\downarrow$ Movements)	Stimulates ($\uparrow$ Movements)
Bladder	Relax ($\downarrow$ Urine outflow)	Stimulates ($\uparrow$ Urine outflow)
Pupil	Relax (Mydriasis)	Stimulates (Miosis)
Glands	Depress ($\downarrow$ Secretions except sweating)	Stimulates ($\uparrow$ Secretions)

PARASYMPATHETIC NERVOUS SYSTEM

In parasympathetic system, **acetylcholine is the principal NT** secreted by preganglionic as well as postganglionic fibres. Therefore, it is also known as cholinergic nervous system. ACh is synthesized (from acetyl Co-A and choline) and stored within the cholinergic neurons.

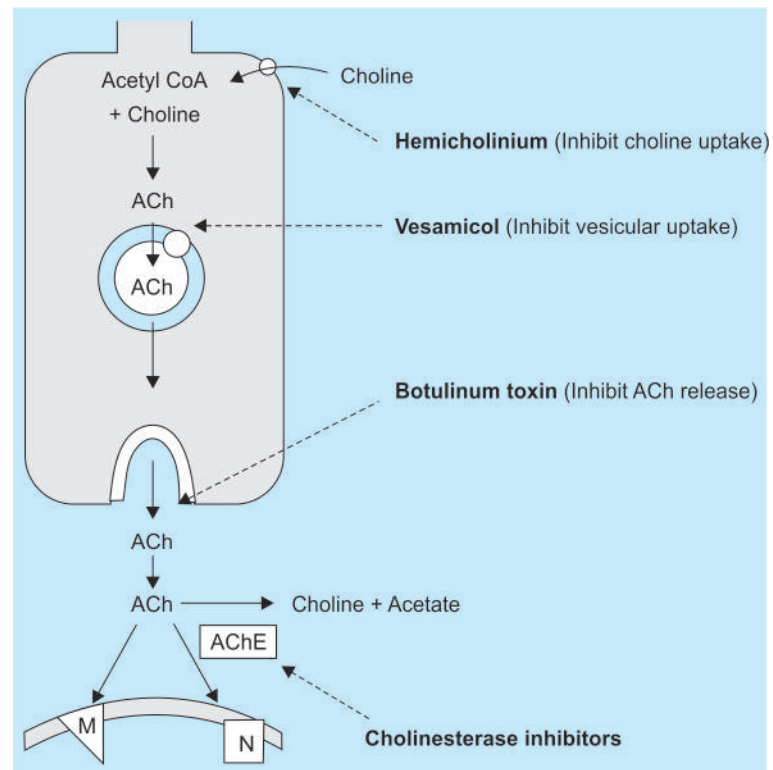
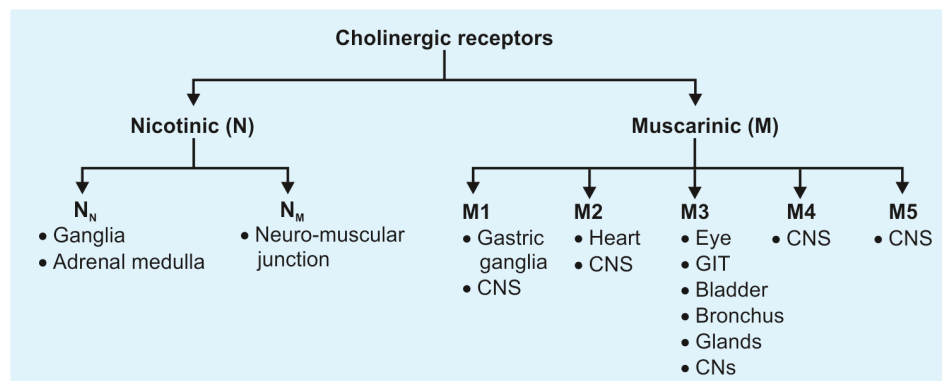


Fig. 3.2: Drugs acting at cholinergic neurons

Uptake of choline by the neurons is the rate limiting step in the biosynthesis of acetylcholine.

Uptake of choline by the neurons is the rate limiting step in the biosynthesis of this NT. After its synthesis, ACh is stored in the vesicles. It is released in the synaptic cleft (by exocytosis) when nerve impulse stimulates the neuron. Here, it stimulates post-ganglionic as well as pre-ganglionic cholinergic receptors and produces the response.



FUNCTIONS OF CHOLINERGIC SYSTEM

Sympathetic and parasympathetic systems have opposite actions on most of the organs. At almost all organs except heart, cholinergic system has excitatory activity and adrenergic system has relaxing properties.

Muscarinic Actions

- **Heart:** Parasympathetic system has *inhibitory effect on the heart* (M_2) and is responsible for the negative chronotropic (decreased heart rate) and dromotropic (decreased conduction) effects. Anticholinergic drugs stimulate the heart by decreasing the inhibitory effect of ACh on heart.
- **Blood vessels:** No direct cholinergic supply is present in blood vessels but cholinergic receptors (M_3) are present on endothelium of blood vessels. Stimulation of these receptors causes *release of NO* from endothelium *resulting in vasodilation*. Additional mechanism of vasodilation is inhibitory action of ACh on nor-adrenaline release from tonically active vasoconstrictor nerve endings. However, if endothelium is damaged, ACh can stimulate M_3 receptors in the vascular smooth muscle leading to vasoconstriction.
- **Eye:** Cholinergic system stimulates sphincter pupillae (circular muscle of eye) and thus results in *miosis* (M_3). ACh also causes contraction of ciliary muscle of the eye and thus accommodation is possible. Anticholinergic drugs result in mydriasis and loss of accommodation (blurred vision).
- **Glands:** Cholinergic system stimulates the secretion of glands and results in the *increased salivation, lacrimation as well as sweating* (M_3). On the other hand anticholinergic drugs will result in dry mouth, dry eyes and difficulty in swallowing (due to decreased saliva).
- **Urinary bladder:** Cholinergic drugs *stimulate detrusor and relax the trigone* (sphincter) of urinary bladder resulting in increased micturition (M_3). Anticholinergic drugs may result in urinary retention.
- **Gastro-intestinal tract:** Hydrochloric acid secretion in the stomach (M_1 and M_3) is stimulated by parasympathetic system and thus increases the *risk of peptic ulcer disease*. Peristalsis of GIT is increased and sphincters are relaxed by the cholinergic drugs. Anticholinergic drugs can be used as spasmolytic agents for intestinal colic.
- **Bronchus:** Cholinergic system causes *bronchoconstriction* (M_3) and anticholinergic drugs may lead to bronchodilation.
- **Male sex organs:** Due to vasodilation, cholinergic system is responsible for *erection* of the male organ.

Nicotinic Actions

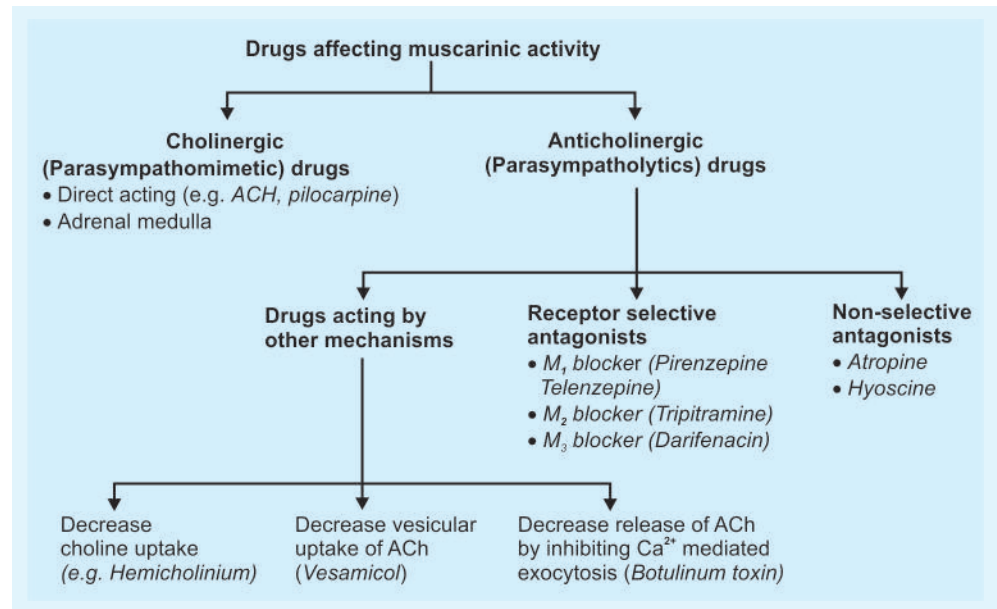
- **Autonomic ganglia:** Both sympathetic and parasympathetic ganglia are stimulated by ACh through the stimulation of N_N receptors.
- **Neuromuscular junction:** ACh stimulates skeletal muscle contraction by its action on NMJ (N_M receptors).

M

To remember location of cholinergic receptors, read in Hindi
- Pehle khao, Phir dil lagao, Baki kaam bad mein
i.e. M_1 in stomach, M_2 in heart and M_3 at all other places.

🔑

No direct cholinergic supply is present in blood vessels but cholinergic receptors (M_3) are present on endothelium of blood vessels.

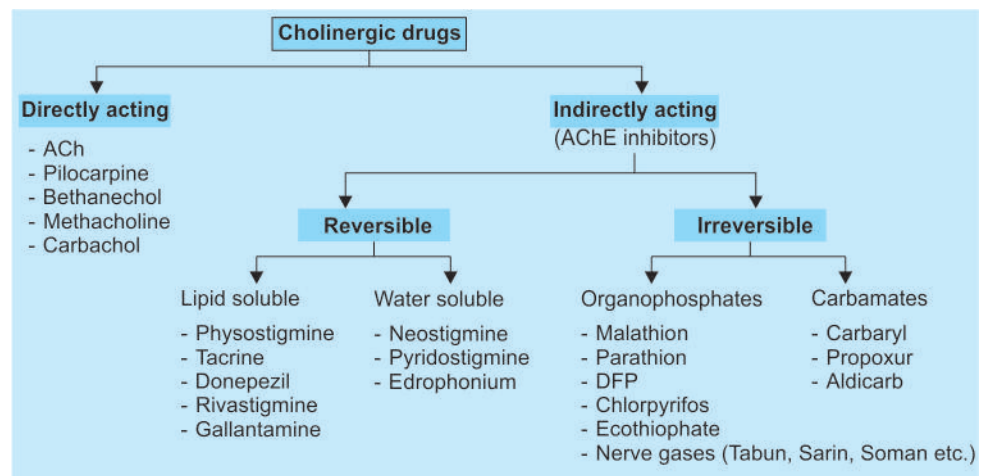


Parasympathomimetic Drugs

These drugs may directly activate the muscarinic receptors (directly acting) or may act by increasing the availability of ACh at the synaptic cleft (indirectly acting).



Saxitoxin (obtained from dinoflagellates) is a sodium channel blocker whereas α -bungarotoxin (component of venom of banded krait) is irreversible antagonist at N_M receptors.



DIRECTLY ACTING DRUGS

These are the esters of choline and may be **natural alkaloids** (ACh, muscarine, nicotine, pilocarpine and arecoline) or **synthetic derivatives** (methacholine, carbachol and bethanechol).

- Acetylcholine is not used clinically because it is *metabolized very quickly* by cholinesterases in the plasma and is not effective even by i.v. route.
- Methacholine has maximum action on **myocardium**. It can be given inhalationally for the diagnosis of bronchial hyperreactivity in patients who do not have clinically apparent asthma **methacholine challenge test**.
- Bethanechol is mainly used for its action on urinary **bladder** and has no nicotinic activity.
- Pilocarpine is used in glaucoma due to its **pupillary constrictor** (miotic) action. However because of its *very short duration of action*, intraocular tension may increase even if one or two doses are missed.

- Carbachol has common activity on nicotinic and muscarinic receptors.
- Pilocarpine and Cevimeline are used to treat dry mouth associated with Sjogren syndrome and that caused by radiation damage of salivary glands.

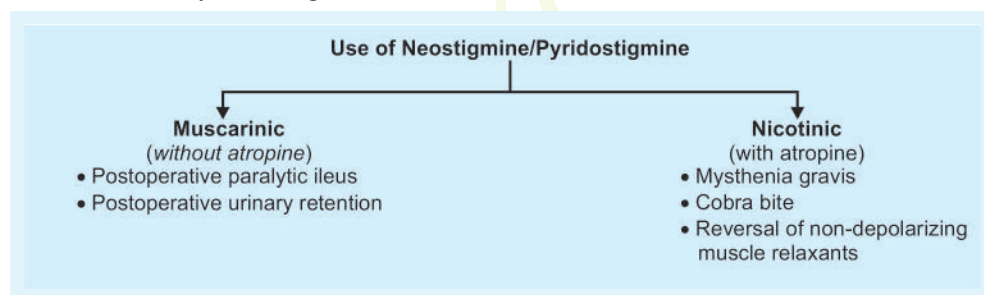
INDIRECTLY ACTING DRUGS

These drugs act by *inhibiting the enzyme acetylcholinesterase*, thus increasing the availability and prolonging the action of ACh. These drugs are also known as anticholinesterases. Cholinesterase inhibitors may be reversible or irreversible.

Reversible Anticholinesterases

Physostigmine, neostigmine, pyridostigmine, edrophonium, tacrine, donepezil, galantamine and rivastigmine are the important drugs in this group. These drugs inhibit the enzyme AChE reversibly and prolong the duration of action of ACh.

- **Physostigmine** is naturally occurring *tertiary amine* and is *lipid soluble*. Tacrine, donepezil, rivastigmine and galantamine are also lipid soluble drugs. **All other** reversible anti-cholinesterases are synthetic *quarternary* compounds and are *lipid insoluble*. Due to high lipid solubility, physostigmine can be administered orally and it can cross blood brain barrier and corneal membrane. Lipid insoluble compounds are ineffective orally and do not enter CNS or eye.
- *Physostigmine is used in glaucoma as a miotic drug and in belladonna (atropine) poisoning as a specific antidote.*
- **Neostigmine** is preferred for the treatment of *myasthenia gravis*. It does not produce adverse effects in the CNS (does not cross BBB) and it also has *direct N_M receptor agonistic action*. It can also be used for the *treatment of cobra bite* (cobra venom contain the compounds that cause skeletal muscle paralysis), *post operative paralytic ileus*, *atony of urinary bladder* and the *reversal of competitive skeletal muscle relaxants*.
- **Pyridostigmine** is *longer acting* than neostigmine and can be used for all these indications. Atropine is added to neostigmine therapy when action is required on N_M receptors [to avoid adverse effects due to muscarinic receptor stimulation] as in case of myasthenia gravis and cobra bite.



- **Edrophonium** is a short acting synthetic anticholinesterase and is useful in the *diagnosis of myasthenia gravis*. 1-2 mg i.v. dose of edrophonium improves skeletal muscle activity if the weakness is due to myasthenia whereas it will worsen the condition if it is due to cholinergic crisis. (**Tensilon test**)
- **Tacrine** was the drug of choice for Alzheimer's disease but due to several limitations (*frequent dosing requirement, hepatotoxicity, diarrhea*), other drugs like donepezil, rivastigmine and galantamine are now the preferred agent.
- **Rivastigmine** has been approved for the treatment of dementia in Alzheimer's as well as Parkinson's disease.

Irreversible Anticholinesterases

This group includes **organophosphates** (*malathion, parathion, ecothiophate, chlorpyrifos, nerve gases like tabun, sarin, soman etc. and diflos*) and **carbmates** (*carbaryl and propoxur*).

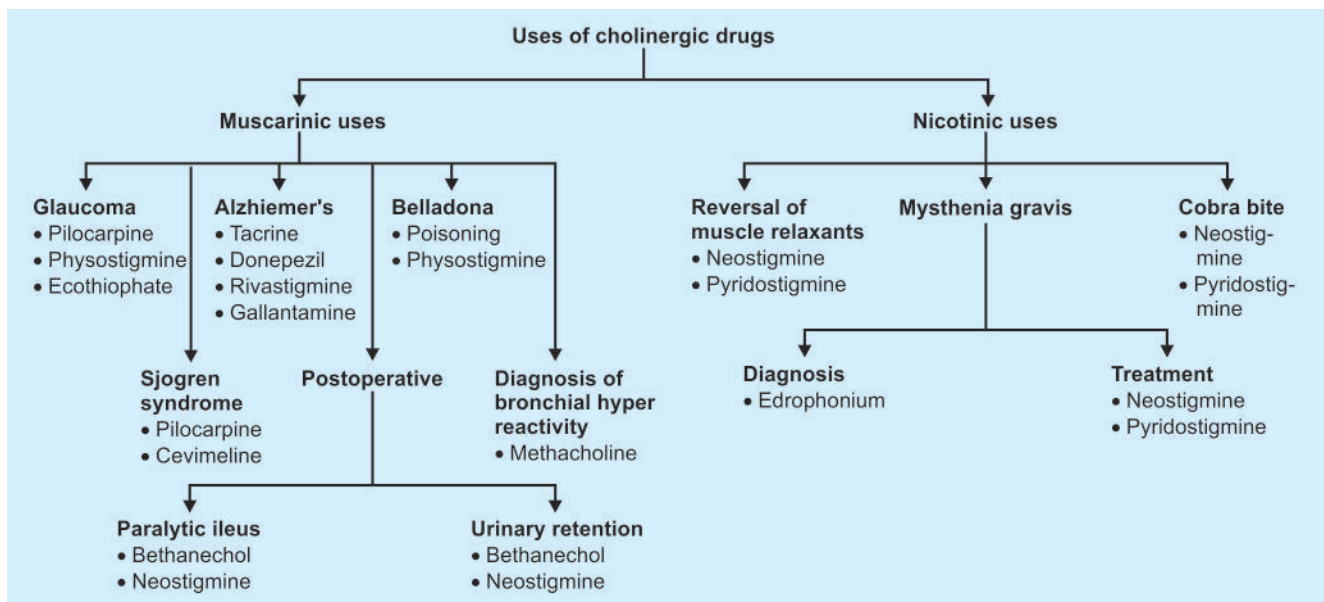
Uses of neostigmine

1. Nicotinic actions
 - a. Myasthenia gravis
 - b. Cobra bite
 - c. Reversal of muscle relaxants
2. Muscarinic actions
 - a. Post operative paralytic ileus
 - b. Post operative urinary retention

Atropine is an antidote of choice for both organophosphate and carbamate poisoning.

Oximes should not be given in carbamate poisoning.

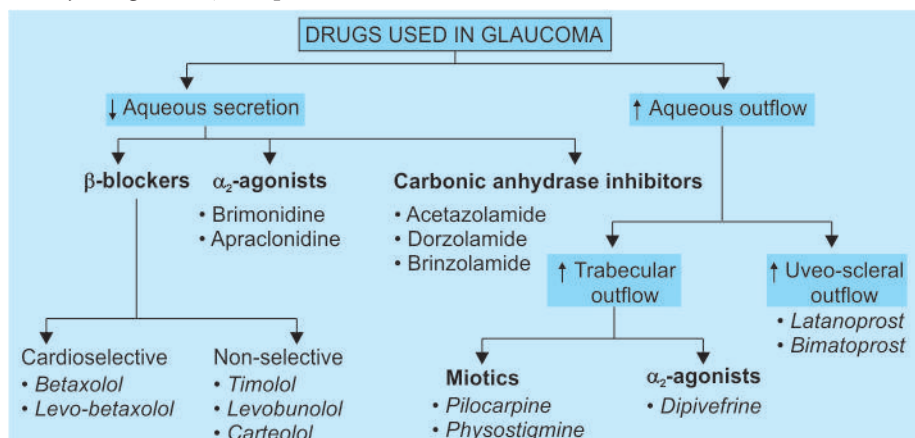
- Except ecothiophate these are *not used therapeutically*. Ecothiophate is useful in glaucoma.
- Other drugs are used as insecticides and are important due to their potential to cause poisoning.
- **Symptoms of anti-cholinesterase poisoning** are simply the extension of the pharmacological actions of ACh and are manifested as *pin-point pupil, salivation, lacrimation, sweating, bronchoconstriction, diarrhea, urination, bradycardia, hypotension and coma*. Blood pressure and heart rate may increase rarely due to stimulation of nicotinic receptors.
- **Atropine** is an *antidote of choice* for both organophosphate and carbamate poisoning.
- **Enzyme reactivators** like *pralidoxime, obidoxime and diacetylmonoxime* can be used to regenerate AChE in the organophosphate poisoning but are *contra-indicated* in the carbamate poisoning. Principle indications of oximes are **muscle weakness and respiratory depression**. The site on which oximes bind and reactivate the enzyme (anionic site) is occupied by carbamates whereas it is free in the organophosphate poisoning. (organophosphates binds to esteritic site only whereas carbamates bind to both esteritic as well as anionic sites) Further *oximes themselves possess weak AChE inhibitory action*. Due to these two reasons, oximes should not be given in carbamate poisoning.
- *Diacetylmonoxime* can cross BBB and regenerate AChE in the brain whereas pralidoxime and obidoxime cannot cross BBB.
- Chronic exposure to certain organophosphates e.g. triorthocresyl phosphate (additive in lubricating oils) may cause:
 - *Delayed neuropathy* (appear 1-2 weeks after exposure) associated with demyelination of axons. It is not caused by cholinesterase inhibition but rather by NTE (neuropathy target esterase) inhibition.
 - *Intermediate syndrome* (occurs after 1-4 days) caused by cholinesterase inhibition.



Glaucoma

- Glaucoma is characterized by progressive damage to optic nerve associated with raised intraocular pressure (> 21 mm Hg). Rise in intraocular tension is either due to excessive production or due to less drainage of aqueous humor. So, the drugs

used for glaucoma act by either **decreasing the secretion** (β -blockers, α_2 agonists and carbonic anhydrase inhibitors) or by **increasing the outflow** (miotics, dipivefrine and prostaglandins) of aqueous humor.



Latanoprost causes **growth of eyelashes** as an adverse effect which can be utilized for treatment of hypotrichosis.

Apraclonidine can cause **lid retraction** whereas brimonidine is associated with anterior uveitis. Both of these can cause drowsiness.

PGF_{2α} analogs can cause cystoid macular edema in aphakics

• Various drugs useful in **primary open angle glaucoma (POAG)** are:

- **β-blockers:** These are among the first line drugs for POAG. Ciliary processes contain β_2 (vasodilatory) and α_2 (vasoconstrictor) receptors. Whenever vasodilation occurs, amount of blood reaching in the ciliary body increases resulting in excessive secretion of aqueous humor. Therefore, **β-blockers and α agonists can decrease the secretion of aqueous. Timolol, betaxolol, levobetaxolol, levobunolol, carteolol and metipranolol** have been approved for use in glaucoma. *Levobunolol is longest acting* whereas betaxolol is cardioselective (therefore less efficacious but safe in asthmatics) β-blocker.
- **Prostaglandin analogs:** PGF_{2α} increases uveoscleral outflow. **Latanoprost, bimatoprost and unoprostone** are PGF_{2α} derivatives useful in glaucoma. These are **now the drug of choice for POAG**. *Bimatoprost causes growth of eyelashes as an adverse effect which can be utilized for treatment of hypotrichosis.*
- **α-Agonists:** **Dipivefrine** (prodrug of adrenaline) and adrenaline act by increasing trabecular outflow whereas **apraclonidine and brimonidine** (selective α_2 agonists) act by decreasing aqueous secretion. *Apraclonidine can cause lid retraction whereas brimonidine is associated with anterior uveitis. Both of these can cause drowsiness. Dipivefrine can cause cystoid macular edema in aphakics.*
- **Carbonic anhydrase inhibitors:** **Acetazolamide (oral), brinzolamide and dorzolamide (both topical)** act by decreasing the secretion of aqueous humor.
- **Miotics:** **Pilocarpine** (directly acting cholinomimetic) and **physostigmine** (indirectly acting cholinomimetic) increase aqueous outflow by causing miosis. *Pilocarpine is short acting, therefore requires frequent daily dosing. Demcarium and ecothiophate (both are long acting cholinomimetics) are rarely used because they accelerate cataract development.*

- For closed-angle glaucoma, definitive treatment is surgery (Laser peripheral iridotomy or surgical peripheral iridectomy). The only drugs used to control intraocular tension preceding surgery are cholinomimetics (miotics), acetazolamide and osmotic diuretics (e.g. mannitol). The onset of other agents is too slow in this situation. Initial treatment of choice in acute cases is **intravenous acetazolamide**.

Note: All patients with primary acute angle-closure glaucoma should undergo prophylactic laser peripheral iridotomy to the unaffected eye.

MIOTICS
Cataract
Stenosis (Punctal)

Beta blockers
Blepharoconjunctivitis

PG F_{2α} analogs
Pigmentation of iris
Growth of eyelashes

APRACLONIDINE
LID retraction

BRIMONIDINE
Brain depression
Iridocyclitis

DRUGS USED IN GLAUCOMA

Group	Drugs	Mechanism	Adverse effect	Special points
1. MIOTICS – Directly acting muscarinic agonist – AChE inhibitor	Pilocarpine Physostigmine Echothiophate	Increase trabecular outflow	- Blurred vision due to induced myopia - Headache and brow pain - AChE inhibitors can lead to cataract formation	- Pilocarpine is short acting and can result in fluctuations in IOP - Miotics increase the risk of retinal tears in susceptible individuals - Can cause punctal stenosis of nasolacrimal system
2. BETA BLOCKERS – Non-selective ($\beta_1 + \beta_2$) blockers – Cardioselective (β_1) blockers	Timolol Levobunolol Carteolol Metipranolol Betaxolol	↓ Formation of aqueous humor	- Allergic blepharoconjunctivitis - Precipitates asthma - Transient stinging and burning in eye	- Should be avoided in: - Asthma - Bradycardia - CHF - Diabetes - Betaxolol is less likely to precipitate asthma but is less efficacious
3. PGF _{2α} ANALOGS	Latanoprost Bimatoprost Travoprost Tafluprost Unoprostone	↑ Uveoscleral outflow	Iris pigmentation Growth of eyelashes - Macular edema in aphakics (Latanoprost) - Reactivation of uveitis (Latanoprost)	Drug of choice for POAG
4. α_2 AGONISTS	Apraclonidine Brimonidine	↓ Aqueous formation	Lid retraction - Dry Mouth - Ocular burning and allergic conjunctivitis	- Brimonidine is less likely to cause ocular allergy - These can cause CNS depression and apnea in neonates and are contraindicated in children < 2 years
5. α_1 AGONISTS	Dipivefrine Adrenaline	↑ Trabecular and uveoscleral outflow	- Conjunctival hyperemia (Red Eye) - Ocular allergy	
6. CARBONIC ANHYDRASE INHIBITORS	Dorzolamide Brinzolamide	↓ Aqueous formation	- Ocular allergy - Corneal edema - Bitter taste	

Anticholinergic Drugs

These drugs act by blocking muscarinic (*antimuscarinic*) or nicotinic receptors. Drugs blocking N_M receptors are called *neuromuscular blocking* agents and those blocking N_N receptors are called *ganglion blockers*.

Atropine (obtained from *Atropa belladonna*) and scopolamine (l-hyoscyne) are natural alkaloids that act as non-selective antagonists at all muscarinic receptors.

ACTIONS OF ANTIMUSCARINIC AGENTS

Central Nervous System

- Atropine is a CNS stimulant whereas scopolamine causes CNS depression.
 - Due to its amnesic and CNS depressant action, hyoscyne induces “twilight sleep” and has been used as a *lie detector* or *truth serum* in suspects.
 - Transdermal patch* of scopolamine (applied behind the pinna) is used for prevention of *motion sickness*.

Triopcamide is the shortest acting mydriatic.

- Central anticholinergic agents like *trihexiphenidyl* (benzhexol), *benztropine* and *biperidin* are *drugs of choice* for the treatment and prevention of *drug induced Parkinsonism*.

Eye

- Anticholinergic drugs cause mydriasis and cycloplegia.
 - *Atropine, homatropine, cyclopentolate and tropicamide* are used as *mydriatic* and *cycloplegic* agents. Mydriatic action is useful in fundus examination [maximum part of retina can be visualized] whereas cycloplegic action allows correct assessment of refractive error [due to loss of error resulting from accommodation]. Further, pain in iridocyclitis occur due to spasm of ciliary muscle which can be relieved due to cycloplegic action. *Atropine has very long duration of action* (3-5 days) in the eye (therefore avoided in adults) whereas it has shorter action in other organs. *Hyoscine* possess *similar cycloplegic action* and *more potent mydriatic action* as compared to *atropine*. Its duration of action is also quite long (but less than atropine).
 - Conventional systemic doses of *atropine* has little effect on eye whereas equal dose of *scopolamine* produce definite *mydriasis* and *cycloplegia* (Ref: Goodman & Gilman 12th/228).
 - *Tropicamide* is the *shortest acting mydriatic*.
 - Anticholinergic agents are *contra-indicated* in *glaucoma*.

Atropine is longest acting mydriatic

Cardiovascular System

- Atropine causes *bradycardia* initially due to inhibition of presynaptic muscarinic receptors (M_2) but further increase in dose causes *tachycardia* due to inhibition of post-synaptic M_2 receptors. Atropine is useful in the treatment of arrhythmias like AV block and digitalis induced bradycardia. It has negligible effect on BP and cardiac contractility.

Respiratory system

- Anticholinergic drugs *reverse the bronchoconstriction* caused by stimulation of M_3 receptors. **Ipratropium and tiotropium** are muscarinic receptor antagonists useful in the *treatment of COPD* and bronchial asthma. *Ipratropium* has *non-selective action* on all muscarinic receptors whereas *tiotropium* is somewhat selective blocker of M_1 and M_3 receptors. **Glycopyrrolate** is used as a *pre-anaesthetic medication* to decrease the secretions and reflex bronchospasm during general anaesthesia.

Gastro-intestinal tract

- Anticholinergic drugs decrease the motility, tone and secretions in the gastrointestinal tract.
 - *Pirenzepine and telenzepine* are *selective M_1 blockers* useful in *peptic ulcer disease*.
 - *Hyoscine, dicyclomine, propantheline, oxyphenonium and clidinium* are useful as *anti-spasmodic* agents for the treatment of intestinal colic.
 - *Darifenacin and solefenacin* are *selective M_3 blockers* useful for irritable bowel syndrome and overactive bladder.

M

Onabotulinum toxin A has recently been approved to prevent headaches in adult patients with chronic migraine.

Genitourinary tract:

- Anticholinergic drugs decrease the motility of urinary tract and thus may *result in urinary retention* (therefore contra-indicated in BHP).
 - *Dicyclomine, flavoxate and oxybutynin* are useful for the *treatment of urinary incontinence* [detrussor instability] and renal colic.
 - *Tolterodine, fesoterodine* (a prodrug of tolterodine), *darifenacin* and *solefenacin* (selective M_3 antagonist) are also useful for urinary incontinence.

M

S – Solefenacin
O – Oxybutynin
F – Flavoxate, Fesoterodine
T – Tolterodine, Trospium
blat DAR - DAR ifenacin

Soft bladder means bladder is relaxed, so these can be used for overactive bladder.



Tropium has minimum CNS penetration among drugs used in overactive bladder



Solefancin is longest acting and oxybutynin is shortest acting drug among this group

- **Oxybutynin** has maximum risk of **dry mouth** and other anticholinergic adverse effects.
- **Tropium** has **minimum CNS penetration** because of quaternary amine structure. It has thus *lesser risk of causing impairment of cognition* and is safe in elderly also. It is the only drug from this group that **can be used with AChE inhibitors**.
- **Tolterodine, solefencin and darifenacin** are vesicoselective M_3 antagonists and thus are less likely to block M_1 muscarinic receptors present in CNS. These also can be used in elderly and cognitive impaired person.
- **Tropium** is the only drug in this group that is *not metabolized by liver*. Thus, it is safe to be used with CYP inhibitors.
- **Oxybutynin** is *shortest acting* and **solefencin** is *longest acting* drug from this group.
- **Mirabegron** is a newer drug approved for overactive bladder. It *acts by stimulating β_3 receptors*.
- In refractory cases, intrabladder injection of botulinum toxin A can be done.
- *Behavioural therapy* (bladder training, pelvic floor exercises, fluid management) is *first line of treatment for overactive bladder* whereas antimuscarinic drugs are second line treatment.
- Any antimuscarinic drug may be used because these have similar efficacy. If both extended release (ER) and immediate release (IR) preparations are available, ER is preferred.

Glands

- Anticholinergic drugs decrease the secretions and *cause dry mouth*, reduced sweating, salivation and lacrimation. **Atropine is contra-indicated in children due to the risk of hyperthermia** (due to decreased sweating).

Other uses

- **Botulinum toxin type A** has been approved for *treatment of strabismus, blepharospasm, cervical dystonia and glabellar lines* whereas botulinum toxin **type B** has been approved for the treatment of *cervical dystonia*. *Onabotulinum toxin A* has recently been approved to prevent headaches in adult patients with chronic migraine (given every 12 weeks as multiple injections).
- *Atropine* is the drug of choice for early mushroom poisoning due to *Inocybe* species. (It is *contra-indicated* in poisoning due to *Amanita muscaria*). Thiocetic acid is useful for late mushroom poisoning due to *Amanita phalloides*.
 - It is also the drug of choice for *organophosphate and carbamate poisoning*.
 - It is used along with *neostigmine* (to decrease its muscarinic side effects) for the treatment of Myasthenia gravis and cobra bite.
 - It is also added to diphenoxylate (anti-motility drug) to reduce its addictive potential.

Mushroom poisoning (Mycetism) (Goodman & Gilman 12th/225)

- **Early mushroom poisoning** is due to *Inocybe* and *clitocybe* species. Symptoms manifest within thirty minutes and are of cholinergic excess (like diarrhea, lacrimation, bradycardia etc.) Therefore, **drug of choice is atropine**.
- *Amanita muscaria* poisoning do not manifest as cholinergic excess (because muscarine content is too low to produce symptoms), rather, the symptoms produced are due to other contents like *muscimol, ibotenic acid and other isoxazole derivatives*. These agents *stimulate excitatory and inhibitory neurotransmitters*.

- Therefore, symptoms range from irritability, restlessness, ataxia, hallucinations and delirium to drowsiness and sedation. Treatment is mainly supportive; benzodiazepines are indicated when excitation predominates, whereas **atropine** is **contra-indicated** because it may exacerbate delirium.
- **Delayed mushroom poisoning** is due to *Amanita phalloides* and *Galerina* species. Principal toxins are *amatoxins* and act by inhibiting mRNA synthesis. Renal and hepatic dysfunction results. Treatment is largely supportive and *penicillin*, *thioctic acid* and *silibinin* may be effective antidotes.

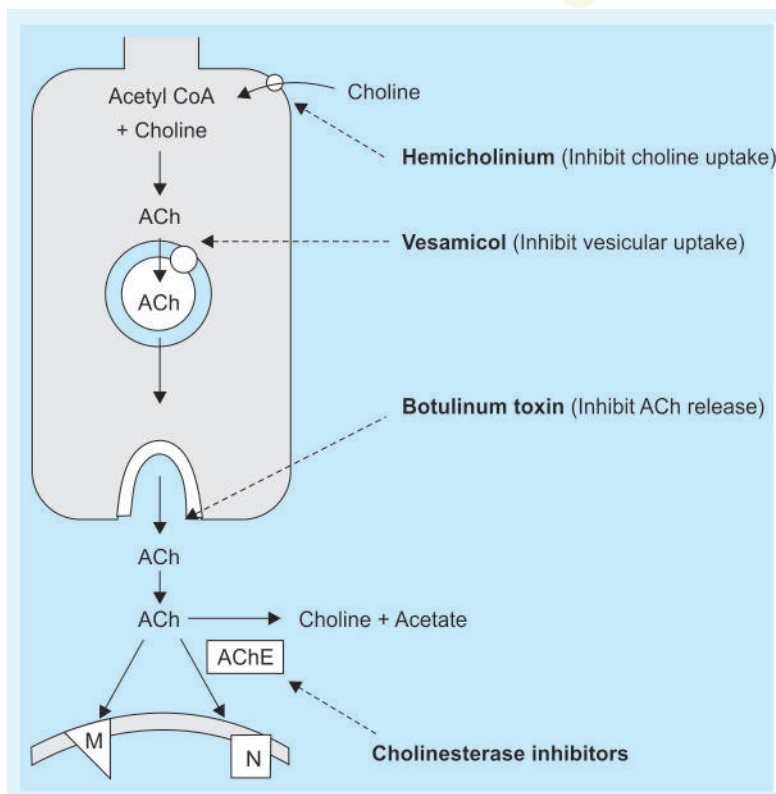
ADVERSE EFFECTS

These include *dry mouth*, *blurred vision* (due to mydriasis and cycloplegia), *urinary retention*, *constipation*, *hyperthermia*, *confusion*, *delirium* and *restlessness* etc. Anticholinergic drugs are **contra-indicated** in **glaucoma** and **BHP**.

SYMPATHETIC NERVOUS SYSTEM

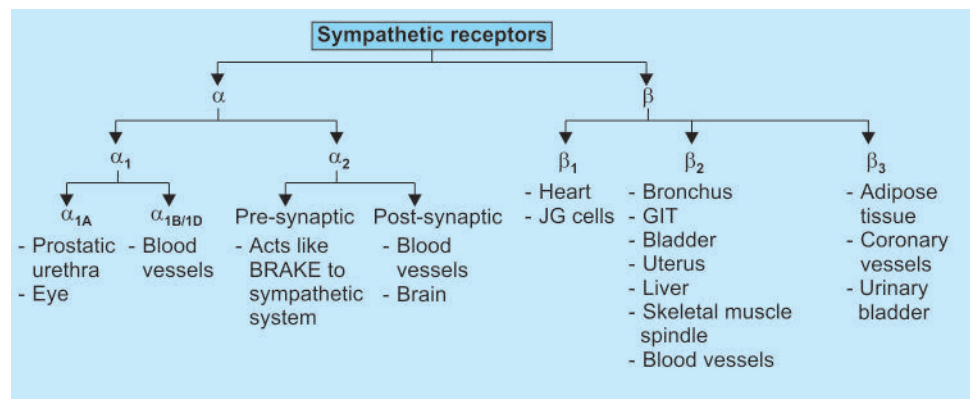
In this part of ANS, *nor-adrenaline* is the neurotransmitter at most of the sites. Circulating tyrosine is transported into the neuronal cytoplasm where it is hydroxylated to form L-dopa (di hydroxy phenylalanine). This *rate limiting step* is catalysed by an enzyme, *tyrosine hydroxylase* that is amenable to inhibition by **metyrosine**. Latter can be used to control the discharge of catecholamines during surgical removal of the tumor in patients with pheochromocytoma. L-dopa is converted to dopamine by the action of a *non specific decarboxylase* (that also decarboxylates 5-hydroxytryptophan to serotonin), which can be *inhibited* by *carbidopa* and *benserazide*. Dopamine is transported to the storage vesicles (inhibited by reserpine), where

Rate limiting enzyme in catecholamine biosynthesis is tyrosine hydroxylase



it is converted to nor-adrenaline by dopamine β hydroxylase. This enzyme is inhibited by disulfiram. Action of NA is terminated mainly by reuptake in the vesicles (inhibited by cocaine and TCA) and partly by the metabolism through MAO and COMT. Further conversion of NA to adrenaline (A) is carried out in the adrenal medulla. This methylation step occurs in the cytoplasm with the help of phenyl ethanolamine-N-methyl transferase. Sympathetic neurons lack this enzyme; therefore catecholamine synthesis is stopped at NA level.

NA remains stored in the vesicles. Stimulation of this neuron by the action potential increases the influx of Ca^{2+} and results in exocytosis of NA in the synaptic cleft. *Exocytosis is inhibited by bretylium and guanethidine.* NA released in the synapse acts on post-synaptic receptors (to produce various effects) as well as presynaptic receptors (to modulate its own release).



ACTIONS OF SYMPATHETIC SYSTEM

- **Heart:** Positive chronotropic, ionotropic and dromotropic effects are seen due to stimulation of β_1 receptors.
- **Blood vessels:** Stimulation of α_1 receptors causes *vasoconstriction* whereas β_2 stimulation leads to *dilation of blood vessels*. Effect of sympathetic system depends on the predominant type of receptor (α_1 or β_2) present in a particular vascular bed. Skin, mucosal and splanchnic blood vessels are constricted due to predominance of α_1 receptors whereas skeletal muscular blood vessels and coronaries are dilated because of the presence of β_2 receptors in excess. Renal vessels contain both α_1 (vasoconstriction) and D_1 (vasodilator) receptors and sympathetic stimulation cause less increase in vascular resistance here than in other vascular beds.
- **GIT:** Smooth muscles of GIT are relaxed by direct action of β_2 receptors and indirect action of α_2 receptors. Latter are present presynaptically on the cholinergic neurons (heteroreceptors) and results in decreased release of ACh.
- **Urinary system:** Urinary retention can occur due to *relaxation of detrusor* by β_2 action and *contraction of trigone (sphincter)* by α_1 action.
- **Genital system:** Pregnant uterus is relaxed by β_2 stimulation. Activation of α_1 receptors in vas deferens, seminal vesicle and prostate facilitates ejaculation.
- **Bronchus:** Bronchial smooth muscle contains β_2 receptors but no sympathetic supply. Exogenous drugs can cause *bronchodilation* by stimulation of β_2 receptors. Mucosal vasoconstriction (by action on α_1 receptors) further increases the luminal diameter of bronchus.

Stimulation of β_2 receptors initially causes efflux of K^+ from liver (hyperkalemia) that is followed by hypokalemia (due to uptake by skeletal muscles).

- **Eye:** Stimulation of α_1 receptors present on the dilator pupillary muscle causes *mydriasis*. Ciliary vasodilation by stimulation of β_2 receptors *increases the formation of aqueous humor* whereas α receptor stimulation *decreases the secretion*. Thus β blockers and α agonists are useful in the treatment of glaucoma.
- **Glands:** Secretion of salivary glands becomes thick. *Sweating is stimulated by sympathetic cholinergic receptors (M_3 action).*
- **Metabolic effects:** Stimulation of β_3 receptors causes breakdown of triglycerides to free fatty acids. Hyperglycemia is caused by promotion of *glycogenolysis and gluconeogenesis on β_2 stimulation*. Initially it causes efflux of K^+ from liver (*hyperkalemia*) that is followed by *hypokalemia* (due to uptake by skeletal muscles). α_2 stimulation also contributes to hyperglycemia by *reducing the release of insulin* from β cells. Minor β_2 mediated increase in glucagon secretion also is responsible for the elevation in blood glucose.
- **Other effects:** Stimulation of β_1 receptors in the JG cells of kidney is responsible for *renin release*. β_2 stimulation can cause *tremors*.

Mnemonics:

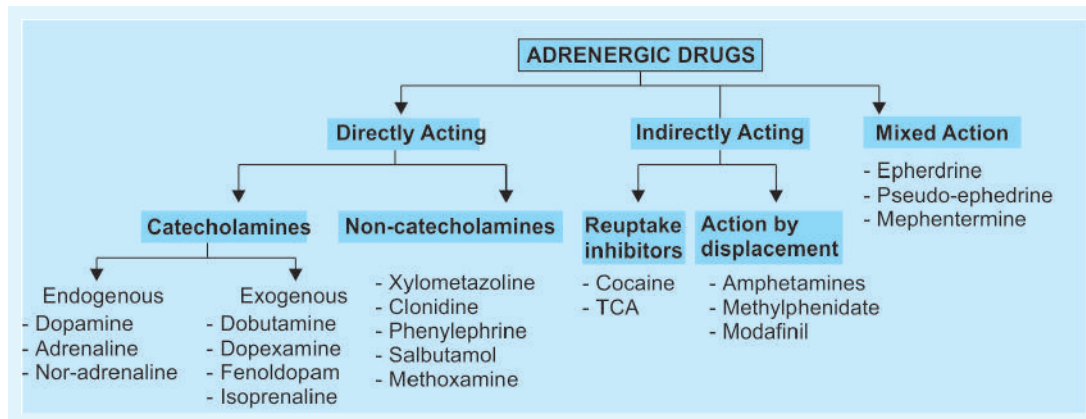
1. We have one heart and two lungs i.e. β_1 is in heart and β_2 is in lungs (bronchus).
2. Sympathetic system stimulates heart and inhibits at other places. In heart, we have β_1 receptor, so its function is to stimulate (i.e. tachycardia etc) whereas at other places, we have β_2 , so it relaxes (i.e. bronchodilation, tocolytic action, relaxation of GIT and bladder).
3. In emergencies, we require sympathy. Thus, the tremors occurring during fear are due to β_2 receptor stimulation.
4. Blood vessels contain α_1 receptors (causing vasoconstriction) and β_2 receptor (causing vasodilation). To remember, we have ABCD.
A (Alpha 1) $\rightarrow$ C (Constriction)
B (Beta 2) $\rightarrow$ D (Dilation)
5. When sympathetic system is stimulated, both α_1 and β_2 receptors are stimulated, so what will happen to blood vessels? It depends upon the relative number of receptors. If a blood vessel contain more α_1 receptors, it contracts whereas those having more β_2 receptors will dilate. To remember this,

When we see a lion, we require sympathy, so sympathetic system is activated. We need to run now, so, muscles require more blood. They get this because blood vessels of skeletal muscle contain more β_2 receptors. At this time of emergency, blood requirement in skin and internal organs is minimal, so vasoconstriction occur here due to more α_1 receptors.

6. Hypoglycemia is an emergency. Sympathetic system protect from it by:
 - Causing warning symptoms (tachycardia, palpitations via β_1 stimulation) and tremors by β_2 activation.
 - Beta-2 receptor in liver reverse hypoglycemia by increasing the formation (stimulate gluconeogenesis and glycogenolysis) of glucose.

Sympathomimetic Drugs

These drugs increase the activity of adrenergic system and may be divided into directly acting, indirectly acting and mixed action sympathomimetics. Directly acting drugs stimulates alpha and beta receptors directly whereas indirectly acting drugs increase the amount of NA in the synapse. Mixed action sympathomimetics possess both of these actions.



DIRECTLY ACTING SYMPATHOMIMETICS

These drugs may be catecholamines (containing di hydroxy benzene nucleus) or non-catecholamines. A, NA and dopamine (DA) are the endogenous catecholamines whereas isoprenaline, dobutamine, dopexamine and fenoldopam are synthetic catecholamines. Non-catecholamines may act as selective agonists of α_1 , α_2 , β_1 and β_2 receptors.

Catecholamines

A, NA and DA are high potency compounds with short half life (due to rapid inactivation by MAO and COMT). Being polar, these drugs have poor penetration in the CNS. Metabolism in intestine (by MAO and COMT) and liver (by MAO) precludes their oral use.

Adrenaline acts on α_1 , α_2 , β_1 and β_2 receptors whereas NA has poor β_2 activity (i.e. α_1 , α_2 and β_1) and isoprenaline possess little α activity (β_1 and β_2 only). Effect of these drugs on the heart rate and blood pressure are given below:

Systolic blood pressure (SBP) is determined by cardiac output (β_1 action) whereas diastolic BP (DBP) depends on the state of blood vessels. Stimulation of α_1 increases DBP by causing vasoconstriction whereas β_2 activation results in reduction of DBP due to vasodilation. Increased DBP stimulates baroreceptor mediated release of ACh (reflex action) that decreases heart rate via activation of M_2 receptors. Reduction in DBP increases central sympathetic outflow and thereby increases heart rate. NA normally decreases heart rate but if given after a dose of atropine, increase in heart rate will be seen (reflex action is abolished).

	SBP (β_1)	DBP (β_2 and α)	Heart Rate		
			Direct Action (β_1)	Reflex action (M_2)	Net effect
A	↑↑	Nil	↑	Nil	↑
NA	↑↑	↑↑	↑	↓↓	↓
Iso	↑↑	↓↓	↑	↑	↑↑

- **Adrenaline** is the drug of choice for anaphylactic shock. It is given as 0.5 ml of 1:1000 solution (i.e. 0.5 mg) i.m./s.c. injection. **Intramuscular route** (on Lateral thigh) is preferred because of variability in absorption from s.c. sites. Intravenous route is avoided but can be used rarely in much lower concentration (1:10,000).
- Adrenaline is also used to prolong the duration of action and decrease the systemic toxicity of local anaesthetics.
- Adrenaline is also used in patients with cardiac arrest. The preferred route is i.v. followed by intra-osseous and endotracheal.

Adrenaline is the drug of choice for anaphylactic shock.

Dopamine is the drug of choice for cardiogenic shock with oliguric renal failure.

- **Dopamine** is the drug of choice for cardiogenic shock with oliguric renal failure. It acts on D_1 (at a dose of 1-2 $\mu\text{g/kg/min.}$), β_1 (at 2-10 $\mu\text{g/kg/min.}$) and α_1 (at > 10 $\mu\text{g/kg/min.}$) receptors. It causes renal vasodilation by acting on D_1 receptors and maintains renal perfusion and GFR. Other inotropic agents like NA cause renal vasoconstriction and thus worsen renal failure.
- **Ibopamine** has similar properties as DA.
- **Dobutamine** is relatively selective β_1 agonist with no action on DA receptors. It increases cardiac output with little action on heart rate.
- **Dopexamine** combines β_2 and D_1 agonistic activity with NA reuptake inhibitory action.
- **Fenoldopam** is D_1 agonist useful in hypertensive emergencies.

Concentration of adrenaline for different routes and indications

Route and Indication	Concentration of Adrenaline required
Bronchial asthma, inhalational	1:100
Anaphylactic shock, intramuscular	1:1000
Anaphylactic shock, subcutaneous	1:1000
Anaphylactic shock, intravenous	1:10000
Cardiac arrest, intravenous	1:1000
With Local anaesthetics, subcutaneous	1:200000

Non Catecholamines

α_1 agonists: These drugs can be used as nasal decongestants like *naphazoline*, *oxymetazoline* and *xylometazoline*. When effect of these drugs subside, after-congestion is seen. If used for prolonged periods, these can result in **atrophic rhinitis** (*Rhinitis medicamentosa*). *Phenylephrine* can also be used as a mydriatic (*does not cause cycloplegia*). *Methoxamine* and *mephentermine* can be used to increase BP in hypotensive states. **Midodrine** is a prodrug (active metabolite is *desglymidodrine*) used for the treatment of orthostatic hypotension.

- Phenylpropanolamine was banned due to risk of hemorrhagic stroke

α_2 agonists: *Clonidine* and α *methyldopa* (a prodrug) are α_2 agonists that can be used for the treatment of hypertension. Other uses of clonidine include:

- To control diarrhea in diabetic patients with autonomic neuropathy.
- Prophylaxis of migraine.
- Management of withdrawal symptoms of alcohol, nicotine and opioids.
- Epidurally, in combination with opioids for relief of pain.
- For treatment of ADHD [as monotherapy or adjunctive to other drugs]

Apraclonidine and *brimonidine* are selective α_2 agonists used topically for the treatment of glaucoma. *Dexmedetomidine* (central α_2 agonist) is used for pre-anaesthetic medication. It is also indicated for sedation of initially intubated and mechanically ventilated patients during treatment in ICU. *Guanfacine* and *guanabenz* are α_2 agonists similar to clonidine and are rarely used now. *Tizanidine* is used as a muscle relaxant.

β_1 agonists: *Prenaltrenol* is the only non-catecholamine β_1 selective agent. It has been promoted recently for the reversal of β blockade.

β_2 agonists: *Salbutamol* (albuterol), *levalbuterol*, *bitolterol*, *fenoterol*, *metaproterenol*, *terbutaline*, *pirbuterol*, *salmeterol*, *formoterol*, *arformoterol*, *carmoterol* and *indacaterol* are selective β_2 agonists useful in bronchial asthma. *Ritodrine* and *isoxsuprine* are agonists useful as tocolytic (uterine relaxant) agents.

β_3 agonists: *Mirabegron* is a new drug that acts by stimulating β_3 receptors in urinary bladder. It is indicated for treatment of overactive bladder.

Uses of clonidine:

- Hypertension
- To control diarrhea in diabetic patients with autonomic neuropathy.
- Prophylaxis of migraine.
- Management of withdrawal symptoms of alcohol, nicotine and opioids.
- Epidurally, in combination with opioids for relief of pain.
- For treatment of ADHD [as monotherapy or adjunctive to other drugs]

M

Mirabegron is a new drug approved for overactive bladder. It acts by stimulating β_3 receptors

Modafinil is approved for treatment of

- Narcolepsy.
- In shift workers
- To relieve fatigue in multiple sclerosis
- An adjunct in obstructive sleep apnea.

Ephedrine is the vasopressor of choice in pregnancy

INDIRECTLY ACTING SYMPATHOMIMETICS

These drugs act by increasing the release of NA in the synaptic cleft or by inhibiting the reuptake of NA. These agents *enter the neuronal cytoplasm by the same transporter that is responsible for the reuptake of NA*. From the cytoplasm, these drugs enter the storage vesicles and displace and release the stored NA (because each vesicle has fixed storage capacity). Released NA activates adrenergic receptors. On repeated dosing at short intervals, *tachyphylaxis* (rapid development of tolerance) is seen with these drugs.

- *Tyramine* is normally present in certain foods and can lead to *cheese reaction* in patients taking MAO inhibitors
- *Methylphenidate* is the preferred drug for the treatment of *attention deficit hyperkinetic disorder* (ADHD). Other drugs used for this indication are *amphetamines*, *atomoxetine* and *pemoline*. **Pemoline** has been withdrawn due to life threatening **hepatotoxicity**.
- *Amphetamines* are addictive substances and can result in tolerance and dependence. As these are basic drugs, *urinary acidification* (with NH_4Cl) is employed for the treatment of their toxicity. On the other hand, amphetamine addicts use sodium bicarbonate to obtain the "kick".
- **Modafinil** is approved for treatment of *narcolepsy*, in shift workers, to relieve fatigue in multiple sclerosis and as an adjunct in obstructive sleep apnea.

MIXED ACTION SYMPATHOMIMETICS

These drugs enhance the release of NA (like indirectly acting drugs) apart from activating α and β receptors directly. Ephedrine and pseudoephedrine are present in the cold remedies for nasal decongestant and bronchodilator action. **Ephedrine** can also be used for the treatment of bronchial asthma. It is the *vasopressor of choice in pregnancy* because due to β_2 mediated vasodilatory action, it does not interfere with placental circulation [methoxamine, mephentermine and other selective α_1 agonists can cause placental vasoconstriction and compromise fetal circulation].

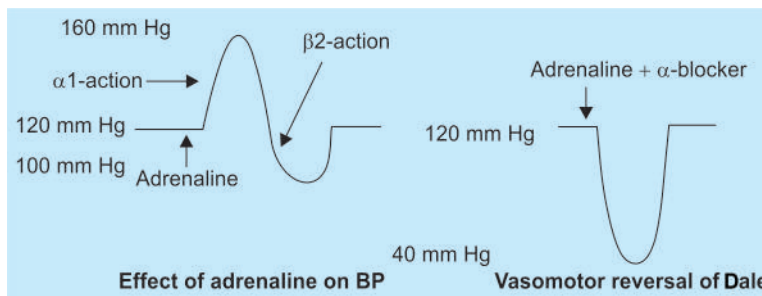
Sympatholytic Drugs

These drugs may act by blocking α and/or β -adrenergic receptors.

ALPHA BLOCKERS

Nonselective α -Blockers

Phenoxybenzamine is an *irreversible antagonist* whereas *phentolamine* and *tolazoline* are reversible blockers of α_1 and α_2 receptors. These agents result in *vasodilation and postural hypotension* (due to antagonism of vasoconstrictor α_1 receptors). Reflex increase in sympathetic discharge and increased sympathetic outflow (due to blockade of α_2 receptors) are responsible for *marked tachycardia* seen with the use of these agents. Use of these drugs before adrenaline results in **vasomotor reversal of Dale**. Intravenous injection of adrenaline normally causes increase in blood pressure (α effect) followed by prolonged fall (β_2 effect). If it is administered after giving α blockers, only fall in BP is seen (*vasomotor reversal of Dale*).



- *Phenoxybenzamine* is used to prevent hypertensive episodes during operative manipulation of tumor in *pheochromocytoma*.
- *Phentolamine* and *tolazoline* are preferred agents for the treatment of hypertensive crisis in *clonidine withdrawal* and *cheese reaction*.

Selective α_1 -Blockers

These drugs (*prazosin, terazosin, doxazosin* and *alfuzosin*) cause decrease in blood pressure with lesser tachycardia than non selective blockers (due to lack of α_2 blocking action, sympathetic outflow is not increased).

- Selective α_1 blockers have **favorable effect on lipid profile** (increase HDL and decrease LDL and TG)
- Due to relaxation of smooth muscle in the neck of urinary bladder and prostatic urethra, urinary flow is improved by these drugs. Therefore, selective α_1 blockers are *drugs of choice for patients with hypertension and benign hyperplasia of prostate* (BHP).
- **Prazosin** (and other α_1 blockers) are useful for the treatment of **scorpion sting**.
- **Major adverse effect** of these drugs is *postural hypotension*. It is seen with first few doses or on dose escalation (*First dose effect*). If used continuously, tolerance develops to this adverse effect. **Inhibition of ejaculation** is another side effect of these agents.
- **Tamsulosin** and **Silodosin** selectively inhibits subtype of α_1 receptors present in the prostate (α_{1A}) without affecting those present in the blood vessels. These are therefore preferred for the treatment of BHP because of their reduced propensity to cause postural hypotension. These has been found to cause intra-operative '**floppy iris syndrome**' during cataract surgery.
- **Indoramin** and **urapidil** are occasionally used for *hypertensive emergencies*.

Selective α_1 blockers have favorable effect on lipid profile (increase HDL and decrease LDL and TG)

Tamsulosin and Silodosin are selective α_{1A} blockers and are preferred for the treatment of BHP because of reduced propensity to cause postural hypotension.

Tamsulosin and silodisin have been found to cause intra-operative '**floppy iris syndrome**' during cataract surgery.

Selective α_2 -Blockers

Yohimbine and *idazoxan* are blockers of α_2 receptors having no established clinical role.

BETA BLOCKERS

Nonselective β -Blockers [First generation β -blockers]

Drugs in this category are *propanolol, timolol, nadolol, pindolol, alprenolol* and *oxprenolol*.

Important effects of these drugs are:

- Myocardial oxygen demand is decreased due to blockade of β_1 receptors in the heart (*useful in classical angina*) but coronary vasoconstriction can occur due to blockade of vasodilatory β_2 receptors (*contraindicated in variant angina*).
- *Decrease in blood pressure* (mainly due to β_1 blockade).
- *Bronchoconstriction* may occur due to blockade of β_2 receptors (*contraindicated in asthmatics*).
- *Dyslipidemia* characterized by increase in LDL and decrease in HDL may be seen (β_2 blockade).
- Decreased chances of *reversal of hypoglycemia in patients on insulin and other hypoglycemic agents* (β_2 blockade).
- Decreased production of aqueous humor (*useful in glaucoma*) by β_2 blocking action.
- *Impaired exercise capacity* due to blockade of β_2 receptors in blood vessels of skeletal muscle.
- *Abolishes sympathetic tremors* (β_2 blockade).

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Contra-indications of non-selective β -blockers
A – Asthma
B – Block (AV)
C – CHF
D – Diabetes

Limitations of Non-selective β -Blockers

- Contraindicated in bronchial asthma due to their *bronchoconstrictor action*.

- Hypoglycemia is commonly observed in diabetic patients receiving insulin and oral hypoglycemic drugs. Symptoms of hypoglycemia (like tachycardia, sweating and tremors) are due to sympathetic stimulation that act as warning signs for the patient. *Beta blockers mask these symptoms (except sweating because it is mediated by sympathetic cholinergic system) and patient can go directly into coma. Further, these agents delay the recovery from hypoglycemia due to inhibition of β_2 mediated hyperglycemia. These drugs are therefore contraindicated in diabetic patients.*
- On long term use non selective β blockers can *adversely affect serum lipid profile and can cause glucose intolerance.*
- By causing vasoconstriction (β_2 is vasodilatory), these drugs can *worsen peripheral vascular disease* (contraindicated in Raynaud's disease).
- These drugs can *impair exercise capacity* due to blockade of skeletal vascular β_2 receptors.

Cardioselective (Selective β_1) β -Blockers [Also known as second generation β -blockers]

- These agents are *preferred in patients with diabetes mellitus, bronchial asthma, peripheral vascular disease or hyperlipidemia.* The drugs in this group are:

Advantages of cardioselective β -blockers

- Safe in asthma
- Safe in diabetes
- Safe in PVD
- Less likely to impair exercise capacity
- Less risk of hyperglycemia
- Less risk of dyslipidemia

* New	– Nebivolol (Most cardioselective)
* Beta	– Betaxolol
* Blockers	– Bisoprolol
* Acting	– Acebutolol
* Exclusively	– Esmolol
* At	– Atenolol
* Myo	– Metoprolol
* Cardium	– Celiprolol

Beta-Blockers with Intrinsic Sympathomimetic Activity (ISA)

These drugs are partial agonists at β_1 receptors (apart from having β blocking property). These are preferred in the *patients prone to develop severe bradycardia with β blocker therapy.* However, these drugs are less useful in angina (because of stimulation of heart by β_1 receptors). The drugs can be remembered as

* COntain	– Celiprolol, Oxprenolol
* Partial	– Pindolol, Penbutolol
* Agonistic	– Alprenolol
* Activity	– Acebutolol

Beta-Blockers with Membrane Stabilizing Activity

These drugs possess Na^+ channel blocking (local anaesthetic) activity. It can contribute to *antiarrhythmic action.* These drugs should be *avoided in glaucoma* due to the risk of corneal anaesthesia. The drugs are:

* Possess	– Propanolol (maximum)
* Membrane stabilizing or	– Metoprolol
* Local	– Labetalol
* Anaesthetic	– Acebutolol
* Property	– Pindolol

Lipid Insoluble β -Blockers

These agents are mainly *excreted by kidney* and are therefore *contraindicated in renal failure*. Most of these have *long duration of action*

*Not	– Nadolol (<i>longest acting β blocker</i>)
*Soluble	– Sotalol
*A	– Atenolol
	– Acebutolol
*B	– Betaxolol
	– Bisoprolol
*C	– Celiprolol

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Beta blockers contra-indicated in renal failure

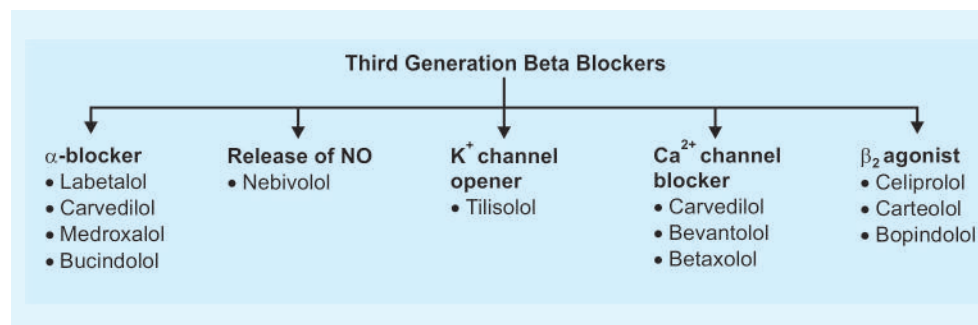
A – Atenolol
N – Nadolol
S – Sotalol

Other β blockers are metabolized mainly by liver and are short acting (**shortest acting β blocker is esmolol**)

Note: Acebutolol possesses all activities i.e. cardioselectivity, ISA, membrane stabilizing action and lipid insolubility.

Third Generation β -Blockers

These drugs possess *additional vasodilatory property*. It may be due to α blockade (*labetalol, carvedilol*), β_2 agonism (*celiprolol, carteolol, bopindolol*), release of NO (*nebivolol, nipradilol*), opening of K^+ channels (*tilisolol*) or inhibition of Ca^{2+} channels (*carvedilol, bevantolol, betaxolol*).



USES OF β -BLOCKERS

Cardiac (due to β_1 blockade)	Extra cardiac (due to β_2 blockade)
Hypertension	Pheochromocytoma (after α blockade)
Classical angina	Hyperthyroidism
Myocardial infarction	Performance anxiety
Supraventricular arrhythmias	Tremors
Chronic CHF	Akathisia
Hypertrophic obstructive cardiomyopathy (DOC)	Prophylaxis of migraine
Emergency management of symptoms of TOF	Glaucoma (<i>timolol and betaxolol</i>)
Mitral valve prolapse	Alcohol and opioid withdrawal
	Prophylaxis of bleeding in portal hypertension

COMBINED ALPHA AND BETA BLOCKERS

Labetalol and carvedilol are the important drugs in this group. These are useful for the control of hypertensive episodes in *pheochromocytoma*. **Carvedilol** is the *most commonly used beta blocker in chronic CHF* due to its **antioxidant and antimitogenic properties**. Other drugs having both α and β blocking activity are *medroxalol* and *bucindolol*.

Note: Carvedilol has maximum plasma protein binding (98%) whereas celiprolol has minimum (< 5%).

DRUG OF CHOICE	
Condition	Drug Of Choice
• Mushroom poisoning	
– Early (Inocybe sp.)	Atropine
– Delayed (Amanita sp.)	Thioctic acid
• Glaucoma	
– Open angle	Latanoprost
– Angle closure	Acetazolamide
• Myasthenia gravis	
– Diagnosis	Edrophonium
– Treatment	Neostigmine/pyridostigmine
• Belladonna poisoning	Physostigmine
• Atropine poisoning	Physostigmine
• Dhatura poisoning	Physostigmine
• Alzheimer's dementia	Donepezil/Rivastigmine/Gallantamine
• Cobra bite	Anti-venom
• Anticholinesterase poisoning	
– Organophosphate	Atropine
– Carbamate	Atropine
• Colicky pain	Anticholinergics like hyoscine/dicyclomine
• Bronchial asthma	salbutamol
• Refraction testing	
– In adults	Tropicamide
– In children	Atropine
• Fundoscopy	Phenylephrine
• Uveitis	
– Iridocyclitis	Atropine + steroids
– Posterior uveitis	steroids
– Panuveitis	steroids
• Bradycardia	atropine
• Atrioventricular block	atropine
• Drug induced Parkinsonism	Anticholinergics like benzhexol
• Shock	
– Cardiogenic	Nor-adrenaline or dopamine
– with oligourea	Dopamine
– Anaphylactic	Adrenaline
– Distributive	Nor-adrenaline or phenylephrine
– Septic	Broad spectrum antimicrobials
– Shock due to adrenal insufficiency	Corticosteroids
– Hypovolumic	Fluids (crystalloids)
– Secondary	Prazosin (α -blockers)
• Postural hypotension	Fludrocortisone
• Attention deficit hyperkinetic disorder	Methylphenidate

Contd...

Contd...

Condition	Drug Of Choice
• Narcolepsy	Modafinil or armodafinil
• Pheochromocytoma	
– Before surgery	Phenoxybenzamine
– Long term	Calcium channel blockers like nifedipine or nicardipine extended release
• Cheese reaction	Phentolamine or tolazoline
• Rebound hypertension due to clonidine withdrawal	Phentolamine or tolazoline
• Raynaud's phenomenon	Calcium channel blockers like nifedipine ER or amlodipine
• Essential tremors	Propanolol
• Akathisia	Propanolol
• Hypertrophic obstructive cardiomyopathy	Propanolol
• Beta blocker poisoning	Glucagon
• Benign hyperplasia of prostate	
– Without hypertension	Tamsulosin
– With hypertension	Prazosin or doxazosin
• Performance anxiety	Propanolol

MULTIPLE CHOICE QUESTIONS

■ PARASYMPATHOMIMETICS AND GLAUCOMA

- Cholinomimetics are not used in** (AIIMS Nov 2013)
 - Glaucoma
 - Myasthenia gravis
 - Post operative atony
 - Partial heart block
- Correct match of drug and mechanism of action is** (AIIMS May 2013)
 - Brimonidine: Decrease aqueous production
 - Latanoprost: Carbonic anhydrase inhibitor
 - Pilocarpine: Increases uveoscleral outflow
 - Betaxolol: Increases trabecular outflow
- Cholinomimetic drugs can be used for the treatment of all the following conditions EXCEPT:** (AIIMS Nov 2012)
 - Closed angle Glaucoma
 - Bradycardia
 - Cobra bite
 - Myasthenia gravis
- A patient presents to emergency with pinpoint pupil, salivation, lacrimation, tremors and red tears. Plasma cholinesterase level was 30% of normal. Most probable Diagnosis is:** (AIIMS May 2012)
 - Organophosphate poisoning
 - Datura poisoning
 - Opioid poisoning
 - Pontine hemorrhage
- Lid retraction is caused by?** (AIIMS Nov 2011)
 - Bimatoprost
 - Latanoprost
 - Brimonidine
 - Apraclonidine
- What is the probable diagnosis in a patient with a dilated pupil not responsive to 1% pilocarpine?** (AIIMS Nov 2011)
 - Diabetic 3rd nerve palsy
 - Adie's tonic pupil
 - Uncal herniation
 - Pharmacological block
- Dilator pupillae is supplied by:** (AIIMS Nov 2011)
 - Postganglionic parasympathetic from Edinger Westphal nucleus
 - Postganglionic sympathetic from cervical sympathetic chain
 - Third cranial nerve
 - Sympathetic fibres of fronto-orbital branch of trigeminal nerve
- Which of the following cranial nerves does not carry parasympathetic outflow?** (AIIMS May 2010)
 - Oculomotor
 - Trochlear
 - Facial
 - Glossopharyngeal
- A patient came to the casualty with acute bronchial asthma after treatment for glaucoma. The probable drug may be:** (Delhi PG 2011)
 - Timolol
 - Betaxolol
 - Latanoprost
 - Anticholinesterase
- Which of the following drugs should not be given in a patient with acute angle closure glaucoma:** (AI 2009)
 - Pilocarpine
 - Clozapine
 - Fluphenazine
 - Paroxetine
- Synaptic transmission in the autonomic ganglion is usually:** (DPG 2009)
 - Adrenergic
 - Peptidergic
 - Cholinergic
 - Mediated by substance P
- Which of the following cranial nerve does not contain parasympathetic motor (GVE) fibers?** (DPG 2009, MPPG 2007)
 - III
 - VI
 - IX
 - X
- Major neurotransmitter released at end organ effectors of the sympathetic division of the autonomic nervous system is:** (DPG 2009)
 - Adrenaline
 - Noradrenaline
 - Dopamine
 - Acetylcholine
- All of the following agents are used in glaucoma treatment, except:** (DPG 2009)
 - Apraclonidine
 - Timolol
 - Pilocarpine
 - Metoprolol

15. Which of the following antiglaucoma medication is **UNSAFE** in infants? (DPG 2009)
 - (a) Timolol
 - (b) Brimonidine
 - (c) Latanoprost
 - (d) Dorzolamide
16. Mechanism of action of pralidoxime is: (AI-2008)
 - (a) Stimulation of ACh receptors
 - (b) Inhibition of breakdown of ACh
 - (c) Blockade of ACh receptors
 - (d) Reactivation of AChE enzyme
17. Diagnosis of myasthenia gravis is done by using: (AI 2000)
 - (a) Edrophonium
 - (b) Neostigmine
 - (c) Succinylcholine
 - (d) Atropine
18. Which of the following statements is FALSE?
 - (a) Hemicholinium prevents the release of ACh from storage vesicles (PGI Dec. 2005)
 - (b) Botulinum toxin increase the ACh release
 - (c) Pralidoxime reactivates acetylcholine esterase
 - (d) Vesamicol inhibit the uptake of choline
 - (e) Organophosphates inhibit acetyl-cholinesterase
19. True statements about neostigmine are: (PGI Dec. 2004)
 - (a) It is a quaternary ammonium compound
 - (b) It is metabolised by liver
 - (c) It can cross the blood brain barrier
 - (d) Prominent effect on cardiac muscle
 - (e) It possess agonistic action on N_M receptors
20. All of the following effects are seen with cholinergic muscarinic receptor stimulation EXCEPT:
 - (a) Sweating
 - (b) Rise in blood pressure
 - (c) Bradycardia
 - (d) Urination
21. A patient Raj Kishore was given pilocarpine. All of the following can be the features seen in him EXCEPT:
 - (a) Sweating
 - (b) Salivation
 - (c) Miosis
 - (d) Cycloplegia
22. Which of the following provides the best explanation for neostigmine being preferred over physostigmine for treating myasthenia gravis?
 - (a) It is better absorbed orally
 - (b) It has longer duration of action
 - (c) It has additional direct agonistic action on nicotinic receptors at the muscle end plate
 - (d) It penetrates blood brain barrier
23. Which of the following properties make pyridostigmine different from neostigmine?
 - (a) It is more potent
 - (b) It is longer acting
 - (c) It produces less muscarinic side effects
 - (d) It does not have any direct action on N_M receptors
24. Dr Sunil used edrophonium for differentiating myasthenic crisis from cholinergic crisis. He preferred it over other anticholinesterase agents because of its:
 - (a) Shorter duration of action
 - (b) Longer duration of action
 - (c) Direct action on muscle end plate
 - (d) Selective inhibition of true cholinesterase
25. Agonistic action at which of the following adrenergic receptors results in the reduction of aqueous secretion?
 - (a) β_1 receptor
 - (b) β_2 receptor
 - (c) M_2 receptor
 - (d) α_2 receptor
26. You are in the eye OPD and wish to use a topical beta blocker in a patient. The chosen drug by you should have all the following properties EXCEPT:
 - (a) Strong local anaesthetic activity
 - (b) High lipophilicity
 - (c) High ocular capture
 - (d) Low systemic activity
27. Which of the following is the longest acting ocular beta blocker?
 - (a) Timolol
 - (b) Betaxolol
 - (c) Carteolol
 - (d) Metoprolol
28. Several children at a summer camp were hospitalized with symptoms thought to be due to ingestion of food containing botulinum toxin. The effects of botulinum toxin are likely to include:
 - (a) Bronchospasm
 - (b) Cycloplegia
 - (c) Diarrhea
 - (d) Skeletal muscle spasms
29. A direct acting cholinomimetic that is lipid soluble and has been used in the treatment of glaucoma is:
 - (a) Acetylcholine
 - (b) Physostigmine
 - (c) Pilocarpine
 - (d) Neostigmine
30. Drug of choice for treatment of acute organophosphate poisoning is:
 - (a) Atropine
 - (b) Pralidoxime
 - (c) Neostigmine
 - (d) d- Tubocurarine
31. Sunder Lal, 28 year old farmer is found convulsing in the farm. Heart rate is 100/min and blood pressure is 180/110 mm Hg. Diarrhea, sweating and urination are apparent. Pupils are pin point. Drug poisoning is suspected. Most probable cause is:
 - (a) Acetaminophen overdose
 - (b) Amphetamine toxicity

- (c) Organophosphate poisoning
(d) Atropine poisoning
32. Lallu, a farmer comes to you in the emergency in comatose state. Patient had profuse sweating and lacrimation. Diarrhea and urination were apparent. On examination pupil was constricted and BP of the farmer was 80/60 mm Hg. You make a diagnosis of anticholinesterase poisoning. You decide to administer him atropine. All of the following actions will be reversed by atropine EXCEPT:
- Hypotension
 - Central excitation
 - Muscle paralysis
 - Bronchoconstriction
33. A 28 yr old woman has been treated with several autonomic drugs for about a month. Which of the following signs would distinguish between an overdose of a muscarinic blocker and a ganglionic blocker?
- Blurred vision
 - Dry mouth, constipation
 - Mydriasis
 - Postural hypotension
34. Mr. James has just been diagnosed with myasthenia gravis. You are his physician and are considering different therapies for his disease. Neostigmine and pyridostigmine may cause which one of the following?
- Bronchodilation
 - Diarrhea
 - Cycloplegia
 - Irreversible inhibition of acetylcholinesterase
35. A patient complains of muscle weakness. It was reversed on administration of neostigmine, because:
- It blocks action of acetylcholine (DPG 2010)
 - It interferes with the action of mono amine oxidase
 - It interferes with the action of carbonic anhydrase
 - It interferes with the action of acetylcholine esterase.
36. How would a drug that competes with ACh for receptors at the motor end plate affect skeletal muscle? It would: (Karnataka 2009)
- Produce uncontrolled muscle spasms
 - Cause the muscles to contract and be unable to relax
 - Cause muscles to relax and be unable to contract
 - Make the muscles more excitable
37. All are cholinergic agents EXCEPT: (DELHI-PG-2008)
- Gallantamine
 - Donepezil
 - Tacrine
 - Memantine
38. Neostigmine is not able to cross blood brain barrier because of its: (DELHI-PG-2008)
- Primary structure
 - Secondary structure
 - Tertiary structure
 - Quarternary structure
39. Besides stimulation of M_3 receptors located on endothelial cells, the main mechanism of vasodilatory actions of acetylcholine includes which of the following?
- Decrease in endothelin by acetylcholine released from cholinergic nerves in blood vessels
 - Inhibition of norepinephrine release from adrenergic nerve endings
 - Stimulation of vascular smooth muscle cells
 - Effects on autoregulation particularly in coronary vascular beds.
40. True statement about pralidoxime is: (DPG-2007)
- Signs of atropinization occur more slowly when pralidoxime is used as compared to the use of atropine alone
 - It can be used for chlorinated pesticides
 - It should not used for nerve gases used in chemical warfare
 - Therapy with pralidoxime should ideally be monitored by measuring blood cholinesterase concentration
41. Which drug is not used now in Alzheimer's disease? (DPG 2004)
- Tacrine
 - Galantamine
 - Donepezil
 - Rivastigmine
42. Organophosphates bind to: (DPG 2004)
- Anionic site of AChEs
 - Esteratic site of AChEs
 - ACh
 - None
43. Drug used in ameliorative test for myasthenia gravis is: (DPG 2003)
- Physostigmine
 - Edrophonium
 - Tacrine
 - Pyridostigmine
44. Atropine is useful in organophosphate poisoning because it: (DPG 2000)
- Reactivates acetylcholinesterase
 - Competes with acetylcholine release
 - Binds with both nicotinic and muscarinic acetylcholine receptors
 - Is a competitive antagonist of acetylcholine
45. 2-PAM (Pralidoxime) is useful in treatment of: (MPPG 2007, MPPG 2004)
- Paracetamol overdose
 - DDT Poisoning
 - Malathion Poisoning
 - Lead Poisoning
46. Pin-point pupil suggests poisoning with: (MPPG 2007)
- DDT
 - Opiates

- (c) Belladonna
- (d) Barbiturates

47. **Drug of choice in treatment of myasthenia gravis is:** (MPPG 2002)
- (a) d-Tubocurarine
 - (b) Hexamethonium
 - (c) Neostigmine
 - (d) Gallamine
48. **Which of the following does not cross the blood brain barrier?** (UP 2005)
- (a) Pralidoxime
 - (b) Obidoxime
 - (c) Diacetyl-monoxime
 - (d) Physostigmine
49. **Anti-cholinesterases are ineffective against:** (UP 2005)
- (a) Belladonna poisoning
 - (b) Carbamate poisoning
 - (c) Postoperative ileus
 - (d) Cobra bite
50. **Acetylcholine is not used commercially because:** (UP 2006)
- (a) Long duration of action
 - (b) Costly
 - (c) Rapidly destroyed in the body
 - (d) Crosses blood brain barrier
51. **Which one of the following acts commonly both on parasympathetic and sympathetic division?** (AP 1986) (JIPMER 1986) (TN 1989) (TN 2003)
- (a) Atropine
 - (b) Pilocarpine
 - (c) Acetylcholine
 - (d) Adrenaline
52. **The short acting anticholinesterase drug is:** (TN 2004)
- (a) Edrophonium
 - (b) Demecarium
 - (c) Dyflos
 - (d) Ectothiophate
53. **Anticholinesterase with effect on CNS is:** (TN 2005)
- (a) Neostigmine
 - (b) Pyridostigmine
 - (c) Physostigmine
 - (d) Edrophonium
54. **Which of the following anticholinesterase is derived from natural source?** (TN 2006)
- (a) Physostigmine
 - (b) Neostigmine
 - (c) Pyridostigmine
 - (d) Tacrine
55. **The α_2 agonist used in glaucoma is:** (TN 2008)
- (a) Guanacare
 - (b) Guanabenz
 - (c) Brimonidine
 - (d) Tizanidine
56. **Blood brain barrier is crossed by:** (RJ 2001)
- (a) Physostigmine
 - (b) Neostigmine
 - (c) Acarbose
 - (d) All
57. **Which antiglaucoma drug can be used in an asthmatic patient?** (RJ 2005)
- (a) Timolol
 - (b) Betaxolol
 - (c) Propanolol
 - (d) All
58. **Cholinesterase activators are useful for treatment of which poisoning?** (MH 2000, 2007)
- (a) Paraquat
 - (b) Parathion
 - (c) Carbamates
 - (d) Organochloro compounds
59. **Neostigmine used in treatment of myasthenia gravis acts by:** (MH 2002)
- (a) Increasing the number of receptors for acetylcholine
 - (b) Increasing synthesis of acetylcholine
 - (c) Decreasing breakdown of acetylcholine
 - (d) Increasing acetylcholine degradation
60. **Which of the following drug binds only with the anionic site of cholinesterase?** (MH 2008)
- (a) Physostigmine
 - (b) Neostigmine
 - (c) Edrophonium
 - (d) Pyridostigmine
61. **Which among the following is contraindicated in a myasthenic patient?** (Jharkhand 2006)
- (a) Aminoglycosides
 - (b) Sulphonamides
 - (c) Penicillin
 - (d) All
62. **A patient requires mild cholinomimetic stimulation following surgery. Physostigmine and bethanechol in small doses have significantly different effects on which of the following?** (Karnataka 2005)
- (a) Gastric secretion
 - (b) Neuromuscular junction
 - (c) Sweat glands
 - (d) Ureteral tone
63. **In oral poisoning with carbamate insecticides may be hazardous:** (Karnataka 2001)
- (a) Pralidoxime
 - (b) Atropine
 - (c) Magnesium sulfate purgative
 - (d) Gastric lavage with activated charcoal

PARASYMPATHOLYTICS

64. **Which of the following drugs does not cross blood placental barrier?**
- (a) Atropine
 - (b) Glycopyrolate

- (c) Physostigmine
(d) Hyoscine hydro bromide
65. All of the following are actions of muscarinic antagonists except: (AI 2011)
(a) Decreases gastric secretion
(b) Prolongs A-V conduction
(c) Decreases tracheobronchial secretions
(d) Causes contraction of radial muscle of iris
66. Which of the following drug is used for overactive bladder? (AIIMS Nov 2010)
(a) Duloxetine
(b) Darifenacin
(c) Oxybutynin
(d) Flavoxate
67. A patient presented in emergency with tachycardia, hyperthermia, bronchial dilatation and constipation. The person is likely to be suffering from overdose of: (AIIMS Nov 2010)
(a) Atropine
(b) Organophosphorus compound
(c) Mushroom
(d) Paracetamol
68. A child presented with history of ingestion of some unknown plant and developed mydriasis, tachycardia, dry mouth, warm skin and delirium. Which of the following group of drugs is likely to be responsible for the symptoms of this child? (AIIMS May 2010)
(a) Anticholinergic
(b) Sympathomimetic
(c) Opioid
(d) Benzodiazepine
69. Which of the following drug is commonly used in narcoanalysis? (AI 2010)
(a) Atropine sulfate
(b) Scopolamine hydrochloride
(c) Phenobarbitone
(d) Morphine
70. All of the following drugs are useful in detrusor instability EXCEPT: (AIIMS Nov 2008)
(a) Solifenacin
(b) Tolterodine
(c) Flavoxate
(d) Duloxetine
71. Botulinum toxin blocks neuromuscular transmission by which of the following mechanism: (DPG 2009)
(a) Closure of Ca^{++} channels at presynaptic membrane
(b) Closure of Na^{+} channels at the postsynaptic membrane
(c) Opening of K^{+} channels at the presynaptic membrane
(d) Opening of Cl^{-} channels at the postsynaptic membrane
72. Botulinum toxin produces skeletal muscle paralysis by: (DPG 2009)
(a) Enhancing release of norepinephrine
(b) Inhibiting release of acetylcholine
(c) Direct damage to nerve endings
(d) Producing hemolysis
73. Use of tiotropium is contra-indicated in: (AI-2008)
(a) Bronchial asthma
(b) Hypertension
(c) Urinary retention
(d) Peptic ulcer disease
74. All of the following drugs are used for the treatment of urinary incontinence EXCEPT: (AI-2008)
(a) Oxybutynin
(b) Ipratropium
(c) Darifenacin
(d) Tolterodine
75. Drug of choice for mushroom poisoning is: (AI 2007)
(a) Atropine
(b) Physostigmine
(c) Adrenaline
(d) Carbachol
76. Which of the following drugs increases gastro-intestinal motility? (AI 2005)
(a) Glycopyrrolate
(b) Atropine
(c) Neostigmine
(d) Fentanyl
77. Which one of the following drugs does not produce central anticholinergic syndrome? (AIIMS Nov, 2005)
(a) Atropine sulphate
(b) Glycopyrrolate
(c) Antihistaminics
(d) Tricyclic antidepressants
78. Atropine can cause: (PGI Dec. 2001)
(a) Decreased cardiac output
(b) Heart block
(c) Hypertension
(d) Mydriasis
(e) Sweating
79. Intramuscular injection of atropine causes initial bradycardia. The reason for this effect being seen is:
(a) Stimulation of medullary vagal centre
(b) Stimulation of vagal ganglia
(c) Blockade of M_2 receptors of SA nodal cells
(d) Blockade of muscarinic autoreceptor on vagal nerve endings
80. The difference between hyoscine and atropine is that hyoscine:
(a) Exerts depressant effects on the CNS at relatively low doses
(b) Exerts more potent effects on the heart than on the eye

- (c) Is longer acting
(d) Has weaker antinausea activity
81. A drug 'X' belongs to the anticholinergic drug group. It is primarily used in pre anesthetic medication and also during surgery. Which of the following can be 'X'?
- Glycopyrrolate
 - Pipenzolate methyl bromide
 - Isopropamide
 - Dicyclomine
82. You are being asked to give your expert opinion as a toxicologist regarding an effective antidote for belladonna poisoning. Which of the following agents would you suggest?
- Neostigmine
 - Physostigmine
 - Pilocarpine
 - Methacholine
83. What is the most dangerous effect of belladonna in very young children?
- Dehydration
 - Hallucination
 - Hypertension
 - Hyperthermia
84. Which of the following best describes the mechanism of action of scopolamine?
- Irreversible antagonist at nicotinic receptors
 - Irreversible antagonist at muscarinic receptors
 - Reversible antagonist at muscarinic receptors
 - Reversible antagonist at nicotinic receptors
85. Accepted therapeutic indications for the use of antimuscarinic drugs include all of the following EXCEPT:
- Hypertension
 - Motion sickness
 - Parkinson's disease
 - To produce mydriasis and cycloplegia
86. In which of the following organs, the effect of atropine on parasympathetic system is of the longest duration?
- Eye
 - Heart
 - Salivary glands
 - Urinary bladder
87. Which is the shortest acting mydriatic? (DPG 2010)
- Atropine
 - Tropicamide
 - Cyclopentolate
 - Homatropine
88. Oxybutynin acts by: (DPG 2004)
- Nicotine receptor stimulation
 - Muscarinic receptor stimulation
 - Muscarinic receptor inhibition
 - α receptor inhibition
89. Atropine does not cause: (DPG 2004, MPPG 2004)
- Increase bowel sound
 - Decrease bowel sound
 - Dryness
 - Tachycardia
90. Atropine poisoning causes all, EXCEPT: (DPG 2003)
- Dilated pupil
 - Excitement
 - Excessive salivation
 - Hot skin
91. Which of the following drugs is useful in prophylaxis of motion sickness? (DPG 2000)
- Hyoscine
 - Metoclopramide
 - Prochlorperazine
 - Ondansetron
92. Clinical signs of atropine intoxication are as follows, EXCEPT: (MPPG 2007)
- Decreased bowel sounds
 - Dry skin
 - Scarlet flushing of face
 - Increased bowel sounds
93. Atropine is substituted by phenylephrine to facilitate fundus examination when: (MPPG 2003)
- Mydriasis is required without cycloplegia
 - Cycloplegia is required
 - Mydriasis and cycloplegia both are required
 - Cycloplegia and Mydriasis both are not required
94. Treatment of atropine toxicity is: (MPPG 2003)
- 2-Pralidoxime
 - Naloxone
 - Flumazenil
 - Physostigmine
95. Short acting mydriatic used in fundoscopy is: (UP 2007, 2006, RJ 2006)
- Atropine
 - Homatropine
 - Cyclopentolate
 - Tropicamide
96. The following drug is a selective blocker (antagonist) of M1 muscarinic receptors: (TN 2004)
- Methacholine
 - Bethanechol
 - Methoctramine
 - Pirenzepine
97. All of the following are anticholinergics, except: (TN 2007)
- Ipratropium bromide
 - Dicyclomine
 - Atropine
 - Amphetamine
98. Which of the following drugs has no cycloplegic action? (MH 2005)
- Atropine
 - Cyclopentolate

- (c) Tropicamide
- (d) Phenylephrine

99. The main mechanism of hyperpyrexia induced by atropine includes: (DPG 2007)

- (a) Vasodilation
- (b) Inhibition of sweating
- (c) Through central actions
- (d) Increase in basal metabolic rate

100. Pirenzepine acts on which receptor? (RJ 2000)

- (a) Muscarinic
- (b) Nicotinic
- (c) Alfa
- (d) Beta

ADRENERGIC DRUGS

101. Which of the following drug acts as combined alpha and beta adrenergic receptor agonist?

- (a) Dobutamine
- (b) Phenylephrine
- (c) Fenoldopam
- (d) Noradrenaline

102. Which of these is an FDA approved indication for use of modafinil as an adjunct? (AI 2009)

- (a) Major depression and associated lethargy
- (b) Narcolepsy
- (c) Obstructive sleep apnea
- (d) Shift work disorder

103. Which of the following agent is not used in erectile dysfunction: (AIIMS Nov. 2012)

- (a) PGE₂
- (b) Vardenafil
- (c) Phenylephrine
- (d) Alprostadil

104. Which is True about dobutamine? (AIIMS Nov. 2012)

- (a) Dobutamine decreases peripheral resistance
- (b) Acts on D₁ and D₂ receptors
- (c) Decrease kidney circulation
- (d) Has no effect on coronary circulation

105. Which of the following concentrations of epinephrine does not correspond to the respective route of administration? (Delhi PG 2011)

- (a) 1 : 10000 for intravenous route
- (b) 1 : 1000 for inhalational route
- (c) 1 : 1000 for intramuscular route
- (d) 1 : 1000 for subcutaneous route

106. Tolazoline is used as: (AIIMS May 2009)

- (a) A thrombin inhibitor in peripheral angiography
- (b) A vasodilator in treating coronary artery stenosis during angio procedures
- (c) A vasoconstrictor in treatment of varices
- (d) An antispasmodic during biliary spasm

107. Which of the following drug is a long acting beta-2 agonist? (AIIMS May 2008, AIIMS Nov. 2006)

- (a) Albuterol
- (b) Salmeterol
- (c) Pirbuterol
- (d) Orciprenaline

108. Drug used to perform stress ECHO is: (AIIMS May 2008)

- (a) Thallium
- (b) Dobutamine
- (c) Adrenaline
- (d) Adenosine

109. Vasopressor of choice in pregnancy is? (AIIMS Nov 2008)

- (a) Ephedrine
- (b) Phenylephrine
- (c) Methoxamine
- (d) Mephentermine

110. One of the following activities is not mediated through β_2 adrenergic receptors: (DPG 2009)

- (a) Stimulation of lipolysis
- (b) Increased hepatic gluconeogenesis
- (c) Increased muscle glycogenolysis
- (d) Smooth muscle relaxation

111. Fenoldopam is used in the management of: (DPG 2009)

- (a) Hypertensive emergencies
- (b) Congestive heart failure
- (c) Migraine prophylaxis
- (d) Tachyarrhythmia

112. The rate limiting step for norepinephrine synthesis is:

- (a) Conversion of phenylalanine to tyrosine (DPG 2009)
- (b) Conversion of tyrosine to DOPA
- (c) Conversion of DOPA to dopamine
- (d) Conversion of dopamine to norepinephrine

113. Which of the following is an adverse effect of β_2 agonists? (AI 2007)

- (a) Hypoglycemia
- (b) Hypomagnesemia
- (c) Hypophosphatemia
- (d) Hypokalemia

114. A child on β_2 agonists for treatment of bronchial asthma may exhibit all of the following features EXCEPT: (AI 2007)

- (a) Tremors
- (b) Hypoglycemia
- (c) Hypokalemia
- (d) Bronchodilation

115. Sympathomimetic drugs are useful in the therapy of all the following conditions EXCEPT: (AI 2004)

- (a) Acute decompensated heart failure
- (b) Hypotension
- (c) Hypertension
- (d) Erectile dysfunction

116. All of the following are correct statements EXCEPT:

- (a) IV noradrenaline increases systolic and diastolic BP and causes tachycardia (AI 2001)

- (b) IV adrenaline increases systolic, decreases diastolic BP and causes tachycardia
 (c) IV isoproterenol increases systolic, decreases diastolic BP and causes tachycardia
 (d) Dopamine increases peripheral resistance and improves renal perfusion
- 117. Which is not an endogenous catecholamine?** (AIIMS May, 2007)
 (a) Dopamine
 (b) Dobutamine
 (c) Adrenaline
 (d) Noradrenaline
- 118. Which of the following is NOT an alpha adrenoceptor agonist?** (AIIMS May, 2005)
 (a) Clonidine
 (b) Methyldopa
 (c) Guanabenz
 (d) Guanfacine
- 119. Uses of α_2 agonists are all EXCEPT:**
 (a) To produce sedation
 (b) Glaucoma
 (c) Benign hyperplasia of prostate
 (d) Hypertension
- 120. True statement(s) out of the following is/are:** (PGI June, 2001)
 (a) β_1 receptors in heart stimulate its contractions
 (b) β_2 receptors in heart stimulate its contractions
 (c) β_2 receptors are present in smooth muscles
 (d) α_1 receptors cause preganglionic stimulation
 (e) α_2 receptors cause postganglionic feedback inhibition
- 121. True about tachyphylaxis is:** (PGI Dec. 2006)
 (a) Direct sympathomimetics involved
 (b) Mechanism clearly understood
 (c) Ephedrine tachyphylaxis reversed with dopamine
 (d) Indirect sympathomimetics involved
 (e) It is an anaphylactic reaction
- 122. A patient, Harish came to the emergency after receiving penicillin injection. He was diagnosed to have anaphylactic shock. Which of the following is the only life saving measure to treat him?**
 (a) Intravenous hydrocortisone hemisuccinate
 (b) Intravenous adrenaline hydrochloride
 (c) Intramuscular adrenaline hydrochloride
 (d) Intravenous glucose saline
- 123. The only non-catecholamine sympathomimetic drug out of the following is:**
 (a) Adrenaline
 (b) Ephedrine
 (c) Dopamine
 (d) Isoprenaline
- 124. Which of the following drugs shows the phenomenon of vasomotor reversal of Dale after administration of an α adrenergic blocker?**
 (a) Adrenaline
 (b) Noradrenaline
 (c) Isoprenaline
 (d) All of the above
- 125. A drug is shown to activate dopaminergic D_1 and D_2 and adrenergic α and β_1 but not β_2 receptors. Which of the following can be the drug being talked about?**
 (a) Dopamine
 (b) Dobutamine
 (c) Methoxamine
 (d) Phenylephrine
- 126. A patient in shock comes to you in trauma ward. You examine him and decide not to give him vasoconstrictors. Which is the type of shock your patient is having?**
 (a) Neurogenic shock
 (b) Haemorrhagic shock
 (c) Secondary shock
 (d) Hypotension due to spinal anaesthesia
- 127. The correct statement regarding adrenergic neuron blocking drugs is:**
 (a) Block the action of adrenaline on neuronal α_2 adrenoceptors
 (b) Block both α and β adrenoceptor mediated effects of injected adrenaline
 (c) Do not block any effect of injected adrenaline
 (d) Do not block the effects of sympathetic nerve stimulation
- 128. A child, Ramu has swallowed the contents of 2 bottles of a nasal decongestant whose primary ingredient is α adrenoceptor agonist drug. The signs of α activation that may occur in this patient include:**
 (a) Tachycardia
 (b) Dilatation of pupil
 (c) Vasodilation
 (d) All of the above
- 129. The neurotransmitter agent that is normally released in the SA node of the heart in response to increased blood pressure is:**
 (a) Acetylcholine
 (b) Dopamine
 (c) Adrenaline
 (d) Noradrenaline
- 130. β_2 selective agonists are often effective in:**
 (a) Angina due to coronary insufficiency
 (b) Asthma
 (c) Delayed labour
 (d) All the above
- 131. Which of the following drugs will decrease heart rate in a patient with a normal heart rate but will have little effect on heart rate in a cardiac transplant recipient?**
 (a) Adrenaline
 (b) Noradrenaline
 (c) Isoproterenol
 (d) Phenylephrine

132. A drug that blocks the uptake of dopamine and norepinephrine into presynaptic nerve terminals and also blocks sodium channels in the axonal membrane is:
- Cocaine
 - Ephedrine
 - Imipramine
 - Fluoxetine
133. Intravenous administration of norepinephrine in a patient already taking an effective dose of atropine will often:
- Increase heart rate
 - Decrease total peripheral resistance
 - Decrease pupil size
 - Has no effect on cardiovascular system
134. A patient Pushpa comes to you in the medicine emergency and you diagnose her to be suffering from severe CHF. You choose a drug 'Z' which is a short term inotropic agent having selective adrenergic β_1 agonistic activity but lacking dopaminergic agonistic activity. What can be 'Z'?
- Dopamine
 - Dobutamine
 - Amrinone
 - Salmeterol
135. A patient Ram kali presents with the symptoms suggestive of pheochromocytoma. Her urine metanephrine and vinylmandelic acid levels are above normal but normetanephrine level is less than normal. She later presents to you in emergency with chest pain and severe headache. An ECG indicates MI. Her blood pressure is 220/160 mm Hg and the heart rate is 160/min. On examination she appears to be dehydrated also. The doctor attending her gives her phentolamine i.v. Within 8-10 min, she goes in a state of shock with her blood pressure being 36/0 mm Hg. Vasoconstrictors are ineffective and she dies within 4 hrs. Which of the following best explains the exaggerated response to phentolamine in this patient?
- Escape of the autonomic nervous system control over blood pressure
 - Metastasis of the tumor to the vasomotor centre in medulla
 - Patient's tumor secreting almost pure adrenaline and no noradrenaline
 - Overdose of phentolamine because of the rarity of such cases in the emergency
136. Dopamine is preferred in treatment of shock because of: (DPG 2010) (UP 2008)
- Renal vasodilatory effect
 - Increased cardiac output
 - Peripheral vasoconstriction
 - Prolonged action
137. Which of the following increases systolic and diastolic BP for prolonged period? (DELHI-PG-2008)
- Epinephrine
 - Dopamine
 - Ephedrine
 - All of these
138. TRUE statement regarding use of adrenaline in anaphylactic shock is: (DPG-2007)
- The usual dose is 0.5-1 mg by i.m. route
 - Cerebral hemorrhage never occurs as an adverse effect to epinephrine when used in treatment of anaphylactic shock
 - It is repeated after every 2-4 hours
 - Same solution can be given for s.c. as well as i.v. route
139. Renal dose of dopamine is: (DPG 2005)
- 2.5 $\mu\text{g/kg/min}$
 - 5-10 $\mu\text{g/kg/min}$
 - 10-20 $\mu\text{g/kg/min}$
 - 1-2 $\mu\text{g/kg/min}$
140. Half life of Dobutamine is: (DPG 2004)
- 120 seconds
 - 200 seconds
 - 20 seconds
 - 20 minutes
141. All are side effects of salbutamol EXCEPT: (DPG 2003)
- Palpitation
 - Muscle tremors
 - Sedation
 - Throat irritation
142. Treatment of choice for anaphylactic shock is: (DPG 2003)
- Intravenous hydrocortisone
 - Subcutaneous adrenaline
 - Intravenous aminophylline
 - Subcutaneous antihistaminic
143. Norepinephrine action at the synaptic cleft is terminated by: (DPG 2001)
- Metabolism by COMT
 - Metabolism by MAO
 - Reuptake
 - Metabolism by acetylcholinesterase
144. Epinephrine is most useful in: (DPG 1998)
- Bronchial asthma
 - Anaphylactic shock
 - Peripheral vascular disease
 - Wide angle glaucoma
145. Exogenous adrenaline is metabolized by: (DPG 1998)
- AChE
 - COMT
 - Decarboxylase
 - Acetyl transferase

146. Which of the following is NOT true about adrenergic receptors? (DPG 1997)
- α_1 receptors are usually presynaptic
 - β_1 receptors are predominantly found in heart
 - Noradrenaline stimulates β_1 receptors
 - α_2 receptor stimulation inhibits transmitter release
147. Drug given in cardiogenic shock is: (MPPG 2003)
- Dopamine
 - Phenylephrine
 - Atropine
 - Digoxin
148. Which one of the following is a relatively selective α_2 adrenergic blocker with short duration of action? (TN 2004)
- Prazosin
 - Yohimbine
 - Terazosin
 - Doxazosin
149. Biphasic reaction on blood pressure is seen with the administration of: (TN 2008)
- Adrenaline
 - Nor adrenaline
 - Dopamine
 - Dobutamine
150. Major Metabolite of noradrenaline in urine is: (RJ 2000)
- VMA
 - HVA
 - Normetanephrine
 - Metanephrine
151. Methyl dopa acts on which of the following receptor? (RJ 2001)
- α_2
 - α_1
 - β_1
 - D_1
152. Muscle glycolysis is increased by: (RJ 2003)
- Epinephrine
 - Acetylcholine
 - Histamine
 - Serotonin
153. Salbutamol is preferred over adrenaline in an asthmatic due to: (RJ 2005)
- β_1 selectivity
 - β_2 selectivity
 - α_1 selectivity
 - None
154. Adrenaline increases all of the following blood pressures significantly except: (RJ 2005)
- Systolic
 - Diastolic
 - Mean BP
 - Pulse pressure
155. Most unpleasant side effect of salbutamol is: (MH 2002)
- Tremors
 - Hypertension
 - Rhinorrhoea
 - Headache
156. Methylphenindate is drug of choice for: (MH 2003)
- Obsessive compulsive disorder
 - ADHD (attention deficit hyperkinetic disorder)
 - Enuresis
 - Autism
157. Conversion of norepinephrine to epinephrine occur by: (MH 2007)
- Methylation
 - Decarboxylation
 - Oxidation
 - Sulphation
158. Which of the following statement is not true regarding dobutamine? (MH 2008)
- Agonist of D_1 and D_2 receptors
 - Derivative of dopamine
 - Selective beta-agonistic action
 - Reduced chances of arrhythmia than adrenaline
159. Epinephrine act by stimulating: (Jharkhand 2003)
- Adenyl cyclase
 - Phosphodiesterase
 - Phospholipase
 - None
160. Vasomotor reversal of Dale is due to: (Jharkhand 2004)
- α blocker
 - β -blocker
 - α and β -blocker
 - None
161. Depression occurs as a side effect due to the use of: (AP 2001)
- Reserpine
 - Propanolol
 - Morphine
 - Amphetamine
162. Catecholamine action on α -receptors causes: (AP 2002)
- Increased atrial contraction
 - Increased heart rate
 - Detrusor relaxation
 - Gastrointestinal sphincter contraction
163. Which is not an endogenous catecholamine? (AP 2003)
- Isoprenaline
 - Dopamine
 - Noradrenaline
 - Adrenaline
164. Clonidine has the following attributes except: (MP 2009)
- Acts on α_2 adrenergic receptors
 - Can produce rebound hypertension on abrupt withdrawal
 - Can Produce CNS stimulation
 - Inhibits salivation

165. Clonidine is used for: *(Kolkata 2006)*
 (a) Migraine
 (b) Opioid withdrawal syndrome
 (c) Diabetic diarrhea
 (d) All of the above
166. Which of the following is a non-catecholamine sympathomimetic drug? *(Karnataka 2003)*
 (a) Ephedrine
 (b) Dopamine
 (c) Isoproterenol
 (d) Dobutamine
167. Dobutamine increases: *(Karnataka 2001)*
 (a) Heart rate
 (b) Cardiac output
 (c) Blood pressure
 (d) Plasma volume
168. Lower dose of dopamine in cardiogenic shock will increase: *(Karnataka 2000)*
 (a) Cardiac output
 (b) Urine output
 (c) Heart rate
 (d) Blood pressure
- ADRENERGIC ANTAGONISTS**
169. The most important action of beta-blockers in glaucoma is which of the following: *(Delhi PG 2011)*
 (a) Membrane stabilizing effect
 (b) Retinal neuron protecting effect
 (c) Decrease in the production of aqueous humor
 (d) Pupillary constriction
170. All of the following are therapeutic uses of prazosin, except: *(Delhi PG 2011)*
 (a) Peripheral vascular disease
 (b) Pheochromocytoma
 (c) Lupus Erythematosus
 (d) Scorpion sting
171. All of the following drugs are non-selective β blockers with no pharmacological action on any other receptor EXCEPT: *(AI 2007)*
 (a) Propranolol
 (b) Timolol
 (c) Sotalol
 (d) Carvedilol
172. All of the following are cardioselective beta blockers EXCEPT: *(AI 2002, MPPG 2001)*
 (a) Atenolol
 (b) Esmolol
 (c) Bisoprolol
 (d) Propranolol
173. Beta blockers that can be used in renal failure are all EXCEPT: *(AI 2001)*
 (a) Propranolol
 (b) Pindolol
 (c) Sotalol
 (d) Oxprenolol
174. Beta blocker with peripheral vasodilator action is: *(AI 2000)*
 (a) Carvedilol
 (b) Propranolol
 (c) Atenolol
 (d) Acebutolol
175. The following is NOT true about the use of beta-blockers in heart failure: *(AIIMS May, 2003)*
 (a) It should be initiated at very low dose
 (b) It is most effective in new onset decompensated heart failure
 (c) Slow upward titration of dose is required
 (d) Carvedilol is most widely used in this condition
176. All are true about beta blockers EXCEPT: *(AIIMS May, 2002)*
 (a) Atenolol is longer acting than metoprolol
 (b) Labetalol has both alpha and beta blocking action
 (c) Carvedilol has alpha agonistic and selective β_1 blocking action
 (d) Nadolol has longest half life
177. Combined alpha and beta blockers are: *(PGI June, 2007, PGI June, 2005)*
 (a) Labetalol
 (b) Carvedilol
 (c) Prazosin
 (d) Tamsulosin
 (e) Milrinone
178. True statement about Esmolol is/are: *(PGI June, 2006)*
 (a) It is an α Blocker
 (b) It has a long half life
 (c) It is not cardioselective
 (d) It is used in LV decompensation
 (e) It can cause bradycardia
179. Contraindications of beta blockers are: *(PGI Dec, 2005)*
 (a) Asthma
 (b) Heart block
 (c) Hypertension
 (d) Arrhythmia
180. Which of the following is used in beta-blocker overdose? *(PGI Dec. 2005)*
 (a) Atropine
 (b) Nor-epinephrine
 (c) Glucagon
 (d) Thyroxin
 (e) Calcium chloride
181. Side effects of timolol maleate include: *(PGI Dec. 2004, 2001)*
 (a) Hypertension
 (b) Asthma
 (c) Depression
 (d) Tachycardia
 (e) Hypotension
182. True about carvedilol is: *(PGI Dec. 2004)*
 (a) α_1 blocker
 (b) β_1 blocker

- (c) β_2 blocker
- (d) Antioxidant
- (e) Used in hypertension

183. True about esmolol is: (PGI June, 2003)

- (a) It is an α -blocker
- (b) It has no intrinsic sympathomimetic activity
- (c) It has a long half life
- (d) It is a cardioselective β -blocker
- (e) It can precipitate heart failure

184. True about esmolol is: (PGI June, 2003)

- (a) It is a cardioselective β -blocker
- (b) It increases airway resistance
- (c) It causes tachycardia
- (d) Its $t_{1/2}$ is 4 hrs
- (e) It has negative inotropic activity (PGI Dec. 2002)

185. β -blockers with intrinsic sympathomimetic properties are: (PGI Dec. 2002)

- (a) Propranolol
- (b) Oxprenolol
- (c) Pindolol
- (d) Esmolol
- (e) Butoxamine

186. Properties making cardioselective β -blockers desirable are: (PGI June, 2002)

- (a) Less bronchoconstriction
- (b) Less adverse effect on lipid profile
- (c) Less likely to cause glucose intolerance
- (d) May be used in Raynaud's disease
- (e) Less liable to impair exercise capacity

187. The property which makes betaxolol different from timolol is that betaxolol:

- (a) Is a β_1 selective blocker
- (b) Is more efficacious in glaucoma
- (c) Produces less ocular side effects
- (d) Is shorter acting

188. A drug 'X' is an α adrenergic blocker but paradoxically produces vasoconstriction. 'X' is:

- (a) Phenoxybenzamine
- (b) Ergotamine
- (c) Prazosin
- (d) Tolazoline

189. An old man Baba comes to you and is diagnosed to be having benign hypertrophy of prostate. The drug which provides faster and greater symptomatic relief to this patient will be:

- (a) Terazosin
- (b) Desmopressin
- (c) Finasteride
- (d) Sildenafil

190. Beta adrenergic blocker having cardioselectivity, intrinsic sympathomimetic activity and membrane stabilizing property is:

- (a) Carvedilol
- (b) Atenolol

- (c) Acebutolol
- (d) Metoprolol

191. Propranolol, a non-selective β blocker can be prescribed to decrease anxiety associated with:

- (a) Chronic neurotic disorder
- (b) Schizophrenia
- (c) Short term stressful situations
- (d) Endogenous depression

192. All of the following are features of metoprolol in comparison to propranolol EXCEPT:

- (a) It is ineffective in suppressing muscle tremor
- (b) It is safer in diabetics
- (c) It is less likely to cause bradycardia
- (d) It is less likely to worsen Raynaud's disease

193. Which of the following effects of adrenaline would be blocked by phentolamine but NOT by propranolol?

- (a) Cardiac stimulation
- (b) Relaxation of bronchial smooth muscle
- (c) Relaxation of the uterus
- (d) Contraction of the radial smooth muscle in the iris

194. Propranolol is useful in the treatment of all of the following EXCEPT:

- (a) Angina
- (b) Partial atrioventricular block
- (c) Idiopathic hypertrophic subaortic cardiomyopathy
- (d) Familial tremor

195. Adverse effects that limit the use of adrenoceptor blockers include:

- (a) Bronchoconstriction from α blocking agents
- (b) Heart failure exacerbation from β blockers
- (c) Impaired blood sugar response with α blockers
- (d) Increased intraocular pressure with β blockers

196. An old patient Ram Kishore having asthma and glaucoma is to receive a β blocker. Regarding β blocking drugs: (Karnataka 2005)

- (a) Metoprolol blocks β_2 receptors selectively
- (b) Esmolol's pharmacokinetics are compatible with chronic topical use
- (c) Nadolol lacks β_2 blocking action
- (d) Timolol lacks the local anaesthetic effects of propranolol

197. Which of the following drug is a third generation β -blocker?

- (a) Propranolol
- (b) Timolol
- (c) Nadolol
- (d) Nebivolol

198. In a patient Kishore having hypertension, propranolol was given. Though the drug controlled hypertension but it reduced resting heart rate to 50/min. Which of the following β blockers can be used in this patient

- as an effective substitute which DOES NOT cause bradycardia?
- Pindolol
 - Labetalol
 - Bisoprolol
 - Atenolol
199. Beta blocker without local anaesthetic effect is: (DPG 2010)
- Metoprolol
 - Pindolol
 - Propanolol
 - Timolol
200. Drug used for treatment of scorpion sting is: (DPG-2007)
- Adrenaline
 - Morphine
 - Captopril
 - Prazosin
201. Beta blockers are indicated for all of the following conditions EXCEPT: (DPG-2007)
- Hypothyroidism
 - Alcohol withdrawal
 - Portal hypertension
 - Performance anxiety
202. Propanolol can be used in all of the following conditions EXCEPT: (DPG 2005)
- Thyrotoxicosis
 - Variant angina
 - Migraine
 - Hypertension
203. Propanolol is useful in all EXCEPT: (DPG 2002)
- Atrial flutter
 - Parkinsonian tremor
 - Thyrotoxicosis
 - Hypertrophic cardiomyopathy
204. Timolol is contraindicated in: (DPG 2002)
- Hypertension
 - Glaucoma
 - COPD
 - Aphakia
205. Atenolol is indicated in all EXCEPT: (MPPG 2003)
- Hypertension
 - Partial heart block
 - Hypertrophic obstructive cardiomyopathy
 - Classical angina
206. Which of the following is a selective β_2 antagonist? (UP 2006)
- Esmolol
 - Betaxolol
 - Butoxamine
 - Celiprolol
207. Propanolol is contraindicated in diabetes mellitus because it: (UP 2006)
- Causes hyperglycemia
 - Causes seizures
 - Masks the hypoglycemic symptoms
 - Causes hypotension
208. An ultrashort acting β -blocker devoid of partial agonistic or membrane stabilizing action is: (TN 2002)
- Esmolol
 - Timolol
 - Atenolol
 - Pindolol
209. Which is beta antagonist? (RJ 2009)
- Salbutamol
 - Propanolol
 - Salmeterol
 - Albuterol
210. Which of the following alpha-blocker drug is used in the treatment of benign hypertrophy of prostate without producing significant hypotension? (MH 2003 & 2006)
- Dexazosin
 - Phentolamine
 - Tamsulosin
 - Terazosin
211. Betaxolol is a: (Bihar 2003)
- α blocker
 - β blocker
 - Calcium channel blocker
 - None
212. Old patient taking beta blockers is prone to develop: (Jharkhand 2004)
- Asthma
 - CHF
 - Bradycardia
 - All
213. Beta blocker having both α and β blocking property is: (Jharkhand 2004)
- Carvedilol
 - Sotalol
 - Nadolol
 - Pindolol
214. Heart rate is decreased by: (Kolkata 2008)
- Propanolol
 - Isoprenaline
 - Dopamine
 - Dobutamine
215. Which of the following is a false statement? (Kolkata 2009)
- Esmolol is mainly metabolized in liver
 - Celiprolol has inherent vasodilatory property
 - Nevibolol releases nitric oxide.
 - Metoprolol is used in congestive cardiac failure and prolongs survival
216. Tamsulosin, a competitive α adrenoceptor antagonist has affinity for which of the following receptors? (Karnataka 2006)
- α_{1A}
 - α_{1D}

- (c) None of the above
(d) Both (a) and (b)
217. The beta blocker having intrinsic sympathomimetic activity is: *(Karnataka 2004)*
(a) Propranolol
(b) Atenolol
(c) Sotalol
(d) Pindolol
218. Ideal drug employed in the preoperative preparation for surgical excision of pheochromocytoma is: *(Karnataka 2003)*
(a) Atenolol
(b) Phenoxybenzamine
(c) Reserpine
(d) Clonidine
219. Short elimination half-life (8-10 min) of esmolol (beta-adrenergic blocker) is due to: *(Karnataka 2003)*
(a) Rapid redistribution
(b) Rapid elimination by kidney
(c) Hydrolysis by blood esterase
(d) Rapid protein binding
220. Adverse effects of beta-blockers may include: *(Karnataka 2002)*
(a) Congestive heart failure
(b) Blunting of sympathetic response of oral hypoglycaemic drugs
(c) Bronchial asthma
(d) All of above
221. An example of covalent drug receptor interaction is: *(DPG 2009)*
(a) Noradrenaline binding to β_1 adrenergic receptor
(b) Acetylcholine binding to muscarinic receptor
(c) Prazosin binding to α_1 adrenergic receptor
(d) Phenoxybenzamine binding to alpha adrenergic receptor.
- RECENT QUESTIONS ASKED BY NATIONAL BOARD**
1. All are alpha blockers except :
(a) Atenolol
(b) Prazosin
(c) Indoramine
(d) Idazoxan
2. All of the following statements about dopamine are true Except:
(a) Causes increase in GI Ischemia
(b) Positive inotropic
(c) Improves renal perfusion
(d) Causes Vasoconstriction
3. Beta blockers are not indicated in:
(a) Acute CHF
(b) Hypertension
(c) Chronic CHF
(d) Arrhythmia
4. Most potent cardiac stimulant of the following is:
(a) Adrenaline
(b) Noradrenaline
(c) Ephedrine
(d) Salbutamol
5. Which one of the following drugs increases gastrointestinal motility?
(a) Glycopyrrrolate
(b) Atropine
(c) Neostigmine
(d) Fentanyl
6. Drug of choice for treating anaphylaxis is:
(a) Adrenaline
(b) Corticosteroid
(c) Antihistaminics
(d) Sodium chromoglycate
7. Pralidoxime is ineffective in case of which poisoning?
(a) Organophosphorous
(b) Carbaryl
(c) Both
(d) None
8. Which of the following is not a cardioselective β -blocker:
(a) Acebutol
(b) Atenolol
(c) Pindolol
(d) Metoprolol
9. Which of the following is the most reliable clinical endpoint to indicate adequate atropinisation in organophosphate poisoning:
(a) Pupillary dilatation
(b) Control of diarrhea
(c) Heart rate more than or equal to 100 beats/min
(d) Absence of pulmonary secretions
10. Retinoscopy in 5 year old is best done with:
(a) Atropine
(b) Homatropine
(c) Cyclopentolate
(d) Tropicamide
11. Mechanism of action of clonidine is mediated by which of the following receptors?
(a) Alpha 1
(b) Alpha 2
(c) Beta 1
(d) Beta 2
12. True about therapy of obesity is:
(a) Bariatric surgery is indicated for BMI > 30 kg/m²
(b) Adjuvant pharmacotherapy for BMI > 30 kg/m²
(c) Lifestyle modification not required
(d) Reducing appetite by centrally active drugs is not an option

13. Which of the following drugs is most effective for control of orthostatic hypotension:
 - (a) Clonidine
 - (b) Fludrocortisone
 - (c) Esmolol
 - (d) Phenylephrine
14. Drug of choice for bradycardia due to beta blocker overdose is:
 - (a) Atropine
 - (b) Dopamine
 - (c) Adrenaline
 - (d) Isoprenaline
15. Which of the following is an selective alpha 2 antagonist?
 - (a) Prazosin
 - (b) Labetalol
 - (c) Yohimbine
 - (d) Butoxamine
16. Atropine is most sensitive to:
 - (a) Mucous and pharyngeal secretions
 - (b) Heart
 - (c) Pupil
 - (d) GI tract motility
17. Which is not an effect of atropine?
 - (a) Rise of body temperature
 - (b) Decreased salivary secretion
 - (c) Bradycardia
 - (d) Increased A-V conduction
18. In Anaphylactic shock, epinephrine is given by which route?
 - (a) Intravenous route
 - (b) Oral
 - (c) Subcutaneous
 - (d) Intramuscular
19. Alpha 1a (α_{1A}) adrenergic blocker providing symptomatic relief in BPH is:
 - (a) Tamsulosin
 - (b) Prazosin
 - (c) Doxazosin
 - (d) Tolazoline
20. Alpha I blocker without any effect on blood pressure is:
 - (a) Tamsulosin
 - (b) Prazosin
 - (c) Doxazosin
 - (d) Terazosin
21. Regarding neostigmine, all of the following are correct except:
 - (a) A quaternary ammonium compound
 - (b) Shorter acting than edrophonium
 - (c) Poorly absorbed orally
 - (d) Used in myasthenia gravis
22. Atropine is used in all except:
 - (a) Glaucoma
 - (b) As a mydriatic
 - (c) As a cyclopegic
 - (d) Preanaesthetic medication
23. Alpha blocker useful in BPH is:
 - (a) Phentolamine
 - (b) Prazosin
 - (c) Tolazoline
 - (d) Phenoxybenzamine
24. Beta blockers are contraindicated in:
 - (a) Decompensated CHF
 - (b) Asthma
 - (c) Variant angina
 - (d) All of the above
25. Botulinum toxin acts by:
 - (a) Secretion of Ach
 - (b) Synthesis of Ach
 - (c) Inhibits Ach release
 - (d) Muscle nerve block
26. Pralidoxime is ineffective in case of which poisonings?
 - (a) Organophosphorus
 - (b) Carbaryl
 - (c) Both of the above
 - (d) None of the above
27. Besides its properties of decreasing intraocular pressure, timolol is preferred in the treatment of glaucoma because it:
 - (a) Produces no miosis
 - (b) Possess membrane stabilizing activity
 - (c) Increases outflow of aqueous humor
 - (d) Is a selective beta-adrenoceptor blocker
28. Which β_1 selective blocker is used in glaucoma:
 - (a) Levobunolol
 - (b) Timolol
 - (c) Betaxolol
 - (d) Carteolol
29. Nicotinic receptor sites include all of the following except:
 - (a) Bronchial smooth muscle
 - (b) Adrenal medulla
 - (c) Skeletal muscle
 - (d) Sympathetic ganglia
30. Propranolol is useful for all of the following except:
 - (a) Angina
 - (b) Familial tremor
 - (c) Hypertension
 - (d) Partial AV block

31. **Atropine is added to commercial preparations containing diphenoxylate to:**
- Potentiate its anti-spasmodic effect
 - To reduce excretion of salt and water
 - To prevent overdosage and discourage opioid dependence
 - To prolong its duration of action
32. **Beta-adrenoceptor blocking agent that should be avoided in patients with renal failure is:**
- Atenolol
 - Metoprolol
 - Propranolol
 - Esmolol
33. **The mydriatic drug with short duration of action is:**
- Cyclopentolate
 - Tropicamide
 - Homatropine
 - Atropine
34. **All of the following are used in organophosphorus poisoning except:**
- Pralidoxime
 - Atropine
 - Activated charcoal
 - Naltrexone
35. **A 35 year old man was found unconscious. Examination revealed bilateral constricted pupils, bradycardia, excessive sweating and secretion. Most likely cause is:**
- Opium poisoning
 - Acute alcohol intoxication
 - Organophosphorous poisoning
 - Pontine hemorrhage
36. **Which one of the following drugs does not induce mydriasis:**
- Phentolamine
 - Ephedrine
 - Phenylephrine
 - Cocaine
37. **Blockade of neuromuscular transmission by botulinum toxin is an example of:**
- Depolarizing blockade
 - Competitive blockade
 - Presynaptic blockade
 - Postsynaptic blockade
38. **Atropine when used as a pre-medication causes all of the following symptoms except:**
- Skin flush
 - Bronchoconstriction
 - Prevents bradycardia
 - Dryness of mouth
39. **Patients taking a β -adrenergic receptor blocking drug may experience all of the following except:**
- Exacerbation of existing heart block
 - Precipitation of heart failure
 - Nasal blockage
 - Cold extremities
40. **Beta blocker with peripheral vasodilator action is:**
- Propranolol
 - Carvedilol
 - Atenolol
 - Acebutolol
41. **Which of the following drugs is useful in anaphylactic shock:**
- Isoprenaline
 - Adrenaline
 - Non-adrenaline
 - Terbutaline
42. **A 24 years old farm worker is rushed to a nearby emergency department after an accidental exposure to parathion. Which of the following drugs can be given to increase the activity of his acetyl cholinesterase:**
- Atropine
 - Dimercaprol
 - Physostigmine
 - Pralidoxime
43. **Which of the following drug is not used in treatment of iridocyclitis:**
- Atropine eye ointment
 - Pilocarpine eye drops
 - Timolol eye drops
 - Steroid eye drops
44. **All of the following are the feature of atropine poisoning except:**
- Mydriasis
 - Hallucinations
 - Hypothermia
 - Coma
45. **Catecholamines are synthesized from:**
- Alanine
 - Glycine
 - Cysteine
 - Tyrosine
46. **The drug that is contraindicated in angle closure glaucoma is:**
- Pilocarpine
 - Atropine
 - Dorzolamide
 - Timolol
47. **Pilocarpine reduce the intraocular pressure in persons with closed angle glaucoma by:**
- Reducing aqueous humor secretion
 - Contracting iris sphincter muscle

- (c) Increasing aqueous humor outflow
(d) Relaxing ciliary muscle
- 48. Sweating as a result of exertion is mediated through:**
(a) Adrenal hormones
(b) Sympathetic adrenergic
(c) Parasympathetic cholinergic
(d) Sympathetic cholinergic
- 49. In shock, Dopamine is used at the following dose rate:**
(a) $<1 - 2 \mu\text{g/kg/min}$
(b) $1 - 2 \mu\text{g/kg/min}$
(c) $2 - 10 \mu\text{g/kg/min}$
(d) Greater than $10 \mu\text{g/kg/min}$
- 50. A hypertensive patient has heart rate of 50 beats/min and taking tablet atenolol 200 mg/day in divided doses. After anesthesia, heart rate further fell down to 40 beats/min. What will be the appropriate treatment to improve heart rate:**
(a) IV adrenaline
(b) IV atropine
(c) IV isoprenaline
(d) Dobutamine infusion intravenously
- 51. Which drug is contraindicated in a glaucoma patient suffering from bronchial asthma:**
(a) Timolol maleate
(b) Latanoprost
(c) Betaxolol
(d) Brimonidine
- 52. A 33 years old patient with history of asthma is being treated for symptoms of hypertension. Which of the following beta blocker would be an appropriate therapy for this patient:**
(a) Isoprenaline
(b) Labetalol
(c) Metoprolol
(d) Propanolol
- 53. Stimulation of which receptor will release renin:**
(a) Alpha 1
(b) Alpha 2
(c) Beta 1
(d) Beta 2
- 54. Selective α_2 agonist is:**
(a) Clonidine
(b) Prazosin
(c) Adrenaline
(d) Propanolol
- 55. Propanolol is not used in:**
(a) A-V block
(b) Hypertension
(c) Hypertrophic obstructive cardiomyopathy
(d) Migraine
- 56. Tachyphylaxis is seen after use of:**
(a) Tamoxifen
(b) Ephedrine
(c) Morphine
(d) Chlorpromazine
- 57. Mydriatic which does not cause cycloplegia is:**
(a) Tropicamide
(b) Atropine
(c) Homatropine
(d) Phenylephrine
- 58. Drugs used in treatment of organophosphorus poisoning are all except:**
(a) Sodium bicarbonate
(b) Naloxone
(c) Atropine
(d) Activated charcoal
- 59. Sibutramine is indicated for:**
(a) Smoking cessation
(b) Obesity
(c) Severe weight loss
(d) Mania
- 60. Atropine is contraindicated in:**
(a) Early mushroom poisoning
(b) Myasthenia gravis
(c) Organophosphate poisoning
(d) Glaucoma
- 61. All are cholinergic actions except:**
(a) Bronchoconstriction
(b) Tachycardia
(c) Salivation
(d) Miosis
- 62. Antidote for nicotine poisoning is:**
(a) Neostigmine
(b) Atropine sulphate
(c) Phentolamine
(d) Trimethaphan
- 63. Drug of choice for attention deficit hyperactivity disorder is:**
(a) Fluoxetine
(b) Haloperidol
(c) Deriphylline
(d) Methylphenidate
- 64. Edrophonium test is used in the diagnosis of:**
(a) Marcus Gunn jaw winking Ptosis
(b) Horner's syndrome
(c) Blepharophimosis syndrome
(d) Myasthenic Ptosis

EXPLANATIONS

1. Ans. (d) Partial heart block (Ref: KDT 7/e p108-110)

- Cholinergic drugs decrease the conduction from atrium to ventricle, thus should be avoided in partial heart block
- Cholinergic drugs like pilocarpine and physostigmine are used in angle closure glaucoma
- Neostigmine (acetylcholinesterase inhibitor, a cholinergic drug) is used for treatment of myasthenia gravis
- Neostigmine is also used for post operative paralytic ileus and post operative urinary retention.

2. Ans. (a) Brimonidine: Decrease aqueous production (Ref: KDT 7/e p154)

Drug: Mechanism of action in glaucoma

Apraclonidine/Brimonidine Stimulate: post-synaptic alpha 2 receptors and result in decreased aqueous production

Latanoprost: Increase uveoscleral outflow

Miotics (Pilocarpine): Increase trabecular outflow

Beta blockers (Timolol/betaxolol): Decrease aqueous production

Carbonic anhydrase inhibitors (acetazolamide): Decrease aqueous secretion.

3. Ans. (b) Bradycardia (Ref: KDT 6/e p104)

Cholinomimetic drug will cause bradycardia as an adverse effect and thus cannot be used for its treatment.

4. Ans. (a) Organophosphate poisoning (Ref: Katzung 12/e p110)

These are characteristic features of anti-cholinesterase (organophosphate and carbamate) poisoning.

Features of Organophosphate poisoning:

- **Muscarinic symptoms:** Pin point pupil, salivation, lacrimation, urination, defecation, gastrointestinal distress, vomiting, bronchospasm, bradycardia
- **Nicotinic symptoms:** Fasciculations and fibrillations of muscle, tachycardia, tachypnea
- **CNS symptoms:** Tremors, giddiness, ataxia, coma
- **Red tears:** Due to accumulation of porphyrin in the lacrimal glands

5. Ans. (d) Apraclonidine (Ref: Drug Facts and Comparisons 2006/2257)

Apraclonidine is a sympathomimetic agent used in open angle glaucoma. It decreases aqueous secretion. It can result in upper lid retraction as an adverse effect. It can also result in ocular allergy (less likely with brimonidine). Both apraclonidine and brimonidine can cause CNS depression and apnea in neonates and are contra-indicated in children less than 2 years of age.

6. Ans. (d) Pharmacological block (Ref: Goodman and Gilman 12/e p1777)

Looking at the options one by one:

- **Diabetic 3rd nerve palsy:** Third nerve palsy due to any reason will result in mydriasis (because oculomotor nerve supplies constrictor pupillae). However, as only nerve supply is destroyed but the receptors remain intact, so it will respond to pilocarpine (1%) and thus miosis will occur.
- **Adie's tonic pupil:** It manifests as denervation supersensitivity. Normal pupil responds to 1% Pilocarpine but does not contract with highly diluted solution like 0.05-0.1%. However, in Adie's pupil due to supersensitivity of receptors, even this diluted solution may also result in constriction.
- **Uncal herniation:** It results in pressure on third cranial nerve and presents as dilated pupil but it will respond to Pilocarpine as the receptors are intact.
- **Pharmacological block:** Drugs like atropine block the muscarinic receptors present on the pupil. As the receptors cannot work, even high doses of Pilocarpine cannot produce miosis.

7. Ans. (b) Postganglionic sympathetic from cervical sympathetic chain (Ref: Ganong 23/e p261, 265)

Constrictor pupillae (circular muscle of iris) is supplied by postganglionic parasympathetic fibres from Edinger Westphal nucleus whereas dilator pupillae (radial muscle of iris) is supplied by sympathetic fibres of cervical sympathetic chain.

8. Ans (b) Trochlear (Ref: Katzung 11/e p78)

Parasympathetic cranial nerves are III (oculomotor), VII (facial), IX (glossopharyngeal) and X (vagus).

9. **Ans. (a) Timolol** (Ref: KDT 6/e p139)

Timolol is a non-selective beta blocker and can precipitate acute attacks of asthma in a susceptible individual via blockade of β_2 receptors. Betaxolol is a cardioselective beta blocker and is less likely to cause this adverse effect.

10. **Ans. (b) Clozapine** (Ref: Katzung 10/e p461; KDT 6/e p426)

Friends, this seems to be another blunder from paper-setter. According to us, the question should contain 'EXCEPT' in the stem.

Three drugs given in the options i.e. clozapine, fluphenazine and paroxetine have anti-cholinergic properties and should be avoided in angle closure glaucoma. Therefore, if the question was correctly framed as '*all should be avoided in glaucoma except*', the answer would have been pilocarpine.

But, if we have to choose the answer for the question as such, we will go with clozapine, as it has maximum anti-cholinergic properties.

11. **Ans. (c) Cholinergic** (Ref: Katzung 10/e p76; KDT 6/e p93)

- Autonomic ganglia (both sympathetic as well as parasympathetic) release ACh that stimulates the N_N nicotinic receptors on the post-ganglionic fibres.

12. **Ans. (b) VI** (Ref: Katzung 10/e p75; KDT 6/e p89)

- Parasympathetic system is craniosacral in outflow. Cranial part involves III (oculomotor), VII (facial), IX (glossopharyngeal) and X (vagus) nerves whereas sacral portion includes S2 to S4.

13. **Ans. (b) Nor-adrenaline** (Ref: Katzung 10/e p76; KDT 6/e p116)

- Neurotransmitter secreted at end organ effectors of sympathetic system is mostly nor-adrenaline (except in sweat glands and hair follicle, where it is acetylcholine) whereas it is acetylcholine at parasympathetic system.

14. **Ans. (d) Metoprolol** (Ref: Katzung 10/e p103, 152; KDT 6/e p144-147)

- Metoprolol is a beta blocker with local anaesthetic activity. Such beta blockers are not indicated in glaucoma.
- Apraclonidine (alpha 2 agonist), timolol (beta blocker without local anaesthetic activity) and pilocarpine (directly acting miotic) are used in glaucoma.

15. **Ans. (b) Brimonidine** (Ref: Goodman & Gilman 12/e p1788; KDT 6/e p146-147)

- Apraclonidine and brimonidine can cross blood brain barrier and may result in CNS depression and apnea in neonates. These are therefore contra-indicated in children less than 2 years.

16. **Ans. (d) Reactivation of AChE enzyme** (Ref: Katzung 10/e p116; KDT 6/e p105)

- Pralidoxime and diacetylmonoxime are cholinesterase regenerator compounds used for organophosphate poisoning.

17. **Ans. (a) Edrophonium** (Ref: KDT 6/e p104)

Myasthenia gravis can be differentiated from cholinergic crisis with the help of a short acting anticholinesterase agent, edrophonium. It improves the symptoms in myasthenia gravis whereas worsens the condition in cases of cholinergic crisis. Neostigmine is used for the treatment of myasthenia.

18. **Ans. (a) Hemicholinium prevents the release of acetylcholine from the storage vesicles; (b) Botulinum toxin increase the ACh release; (d) Vesamicol inhibit the uptake of choline** (Ref: KDT 6/e p94)

- Hemicholinium blocks choline uptake (*the rate limiting step in ACh synthesis*).
- Vesamicol block the transport of ACh into the synaptic vesicles.
- Botulinum toxin inhibits the release of acetylcholine.
- Acetylcholine esterase is inhibited by organophosphates and carbamates.
- Pralidoxime reactivates ACh.

19. **Ans. (a) It is a quaternary ammonium compound; (e) It possess agonistic action on N_M receptors** (Ref: KDT 6/e p101-102; Lee 12/e p217)

- Neostigmine is a reversible cholinesterase inhibitor. It is a quaternary ammonium compound. (lipid insoluble agent), so it does not cross blood-brain-barrier.
- It is partly hydrolyzed by serum cholinesterase and partly excreted unchanged by the kidneys.
- It possesses some agonistic action on N_M receptors.

20. **Ans. (b) Rise in blood pressure** (Ref: KDT 6/e p97)

Stimulation of muscarinic (M_3) receptors decreases BP whereas parasympathetic system stimulation has no effect on BP because blood vessels contain M_3 receptors but no parasympathetic supply.

21. **Ans. (d) Cycloplegia** (Ref: KDT 6/e p97)

Pilocarpine is a directly acting cholinergic drug. It causes miosis and cyclospasm (not cycloplegia). It can increase all secretions of the body.

22. **Ans. (c) It has additional direct agonistic action on nicotinic receptors at muscle end plate** (Ref: KDT 6/e p103)
Neostigmine is a quaternary ammonium derivative and is lipid insoluble. Its absorption from GIT and penetration in the brain and cornea is much less than physostigmine. It produces additional action on N_M receptors.
23. **Ans. (b) It is longer acting** (Ref: KDT 7/e p108)
 - Pyridostigmine acts for 3-6 hours as compared to 0.5-2 hour duration of action of neostigmine.
 - It is less potent than neostigmine.
 - Rest of the properties are similar to neostigmine.
24. **Ans. (a) Shorter duration of action** (Ref: KDT 6/e p101)
25. **Ans. (d) α_2 Receptors** (Ref: KDT 6/e p146)
Stimulation of α_2 receptors located on ciliary epithelium reduces *secretion* of aqueous humor.
26. **Ans. (a) Strong local anaesthetic activity** (Ref: KDT 6/e p144)
Timolol and betaxolol are the preferred β -blockers for the treatment of glaucoma because they lack local anaesthetic activity. Drugs possessing this property increase the risk of corneal ulcers.
27. **Ans. (b) Betaxolol** (Ref: KDT 6/e p145)
Betaxolol is a cardioselective β -blocker useful in glaucoma. It is longer acting than timolol. Another non-selective β -blocker used topically for the treatment of glaucoma is levobunolol.
28. **Ans. (b) Cycloplegia** (Ref: KDT 6/e p93)
Botulinum toxin interferes with the release of ACh and thus acts as a parasympatholytic agent. Bronchospasm and diarrhoea are the symptoms of muscarinic stimulation whereas muscle spasms may be seen on nicotinic stimulation. Cholinergic drugs cause cyclospasm whereas anticholinergics result in cycloplegia.
29. **Ans. (c) Pilocarpine** (Ref: KDT 6/e p98)
Pilocarpine is a directly acting and physostigmine is an indirectly acting cholinomimetic useful for glaucoma.
30. **Ans. (a) Atropine** (Ref: KDT 6/e p104)
31. **Ans. (c) Organophosphate poisoning** (Ref: KDT 6/e p104, 105)
All the symptoms are of anticholinesterase poisoning except raised blood pressure and heart rate. At high doses, ACh can stimulate N_N and N_M receptors. These symptoms may occur due to the nicotinic actions of ACh.
32. **Ans. (c) Muscle paralysis** (Ref: KDT 6/e p104, 105)
Atropine is a non-selective antagonist at muscarinic receptors. It can penetrate blood brain barrier and reverse the muscarinic action in the CNS. It can also reverse hypertension and bronchoconstriction caused due to stimulation of muscarinic receptors. However, muscle paralysis is due to Nicotinic (N_N) action on which it has no activity.
33. **Ans. (d) Postural hypotension** (Ref: KDT 6/e p115)
Postural hypotension is due to blockade of sympathetic system. Ganglion blockers inhibit the transmission through both sympathetic as well as parasympathetic ganglia whereas muscarinic blockers inhibit only parasympathetic activity.
34. **Ans. (b) Diarrhea** (Ref: KDT 6/e p101)
Neostigmine and pyridostigmine are reversible cholinesterase inhibitors that can cause cholinergic adverse effects like diarrhoea and increased secretions.
35. **Ans. (d) It interferes with the action of acetyl cholinesterase** (Ref: Katzung 11/e p105)
Neostigmine acts by inhibiting the enzyme acetylcholinesterase. This enzyme is involved in degradation of ACh, consequently neostigmine increases the synaptic level of ACh. Muscle weakness can be improved by stimulation of N_M receptors at muscle end plate due to increased ACh.
36. **Ans. (c) Cause muscles to relax and be unable to contract** (Ref: KDT 6/e p340)
Drugs competing with ACh at neuromuscular junction are competitive or non-depolarizing neuromuscular blockers. These drugs are used as muscle relaxants. In contrast to depolarizing muscle relaxants, these do not cause initial fasciculations.
37. **Ans. (d) Memantine** (Ref: KDT 6/e p472, 473)
 - Donepezil, rivastigmine, galantamine and tacrine are cholinergic (due to inhibition of cholinesterase enzyme) drugs useful for Alzheimer's disease.
 - Memantine is an NMDA blocker, used for Alzheimer's disease.
38. **Ans. (d) Quarternary structure** (Ref: KDT 6/e p101)
Quarternary ammonium compounds are water soluble and thus cannot cross blood brain barrier. Neostigmine is a quarternary derivative whereas physostigmine is a tertiary amine.

39. **Ans. (b) Inhibition of nor-epinephrine release from adrenergic nerve endings** (Ref: Goodman & Gilman 11/e p184-185; KDT 6/e p96)

- Most of the blood vessels contain cholinergic M_3 receptors but no parasympathetic nerve supply.
- Exogenously administered ACh can stimulate M_3 receptors and result in vasodilation.
- Stimulation of M_3 receptors increases the production of NO (endothelium derived relaxing factor; EDRF) that causes smooth muscle relaxation resulting in vasodilation.
- Vasodilation also may arise indirectly due to inhibition of NA release from nerve endings by ACh.
- If endothelium is damaged, ACh can stimulate receptors on vascular smooth muscle cells resulting in vasoconstriction.

40. **Ans. (d) Therapy with pralidoxime should ideally be monitored by measuring blood cholinesterase levels.** (Ref: KDT 6/e p105, Drug facts and comparisons 2010/599)

- Pralidoxime is ACh esterase reactivator used for organophosphate poisoning.
- Blood cholinesterase levels can be used to monitor therapy, however RBC cholinesterase levels better reflect ACh esterase activity than serum or plasma levels because *with chronic exposure to organophosphates, serum levels may return to normal but RBC levels remain depressed.*
- Chlorinated pesticides like DDT are CNS stimulants and their overdose is treated by diazepam like drugs. Pralidoxime has no role in their treatment.
- Nerve gases used in warfare act by inhibiting acetyl cholinesterase. Atropine and oximes are used for their treatment.
- When atropine and pralidoxime are used together, the signs of atropinization may occur earlier than might be expected when atropine is used alone.

41. **Ans. (a) Tacrine** (Ref: KDT 6/e p104, 472, 473)

Because of hepatotoxicity, and requirement of frequent dosing, tacrine is less often used than other agents.

42. **Ans. (b) Esteratic site of AChEs** (Ref: KDT 6/e p99-100)

- The active region of Acetylcholinesterase (AChE) has two sites i.e. an anionic site and an esteratic site. Anticholinesterase poisoning like Organophosphate compounds binds to esteratic site of AChE.

43. **Ans. (b) Edrophonium** (Ref: KDT 6/e p104)

- Drug used in ameliorative test (**tensilon test**) for myasthenia gravis is *edrophonium*. It is a cholinergic drug and can be used for diagnosis of myasthenia gravis *because of its short duration of action (10 – 30 min.)*

44. **Ans. (d) Is a competitive antagonist of acetylcholine** (Ref: KDT 6/e p106)

Atropine acts as an antagonist at muscarinic receptors. It has no activity on nicotinic receptors and do not interfere with the release of ACh.

45. **Ans. (c) Malathion Poisoning** (Ref: KDT 6/e p105)

- Pralidoxime is cholinesterase reactivator useful for organophosphate (malathion, parathion) poisoning.

46. **Ans. (b) Opiates** (Ref: KDT 6/e p102, 456)

Causes of Pin-Point Pupil

- Opioids Poisoning
- Organophosphate Poisoning
- Carbamate Poisoning
- Carbolic acid Poisoning
- Pontine Hemorrhage

47. **Ans. (c) Neostigmine** (Ref: KDT 6/e p103)

48. **Ans. (a) Pralidoxime** (Ref: Katzung 11/e p121)

49. **Ans. (b) Carbamate poisoning** (Ref: Katzung 11/e p106-107)

50. **Ans. (c) Rapidly destroyed in the body** (Ref: Katzung 11/e p97)

51. **Ans. (c) Acetylcholine** (Ref: KDT 6/e p91)

52. **Ans. (a) Edrophonium** (Ref: KDT 6/e p101)

53. **Ans. (c) Physostigmine** (Ref: KDT 6/e p101)

54. **Ans. (a) Physostigmine** (Ref: KDT 6/e p102)

55. Ans. (c) **Brimonidine** (Ref: KDT 6/e p146)
 56. Ans. (a) **Physostigmine** (Ref: KDT 6/e p101)
 57. Ans. (b) **Betaxolol** (Ref: KDT 6/e p145)
 58. Ans. (b) **Parathion** (Ref: KDT 6/e p105)
 59. Ans. (c) **Decreasing breakdown of acetylcholine** (Ref: KDT 6/e p101)
 60. Ans. (c) **Edrophonium** (Ref: KDT 6/e p105, Katzung 11/e p104)

Physostigmine, neostigmine and pyridostigmine are carbamates by chemical nature, they bind to both esteritic as well as anionic site whereas edrophonium is an alcohol and binds to anionic site only.

61. Ans. (a) **Aminoglycosides** (Ref: KDT 6/e p722)

Aminoglycosides can result in neuromuscular blockade that can aggravate myasthenia gravis.

62. Ans. (b) **Neuromuscular junction** (Ref: Katzung 11/e p98)

Bethanechol acts on muscarinic receptors only whereas physostigmine increases ACh, thus can stimulate both muscarinic and nicotinic receptors. Neuromuscular junction contains N_M receptors, thus will be affected by physostigmine but not by bethanechol.

63. Ans. (a) **Pralidoxime** (Ref: KDT 7/e p111)

Oximes are ineffective in carbamate poisoning. Rather, these can worsen the poisoning due to weak anticholinesterase activity of its own.

64. Ans. (b) **Glycopyrrolate** (Ref: KDT 7/e p116)

- Glycopyrrolate is a quaternary ammonium compounds and is thus water soluble and unable to penetrate BBB.

65. Ans. (b) **Prolongs A-V conduction** (Ref: Katzung, 11/e p113-123)

- Muscarinic antagonists will produce actions opposite to parasympathetic system, thus it will decrease gastric as well as respiratory secretions.
- Action of ACh through muscarinic receptors is to increase the AV conduction, thus resulting in bradycardia. Antagonist will thus result in opposite effect i.e. shorten the AV conduction.
- ACh via muscarinic receptors cause contraction of sphincter pupillae muscle and result in miosis. Muscarinic antagonists will have opposite effect i.e. mydriasis. However, this mydriasis is a passive effect due to relaxation of constrictor pupillae. These agents themselves do not cause contraction of radial muscle of iris; however, they stop the counteracting effect of sphincter pupillae and allow the radial muscle to do its work.

Therefore, although both (b) and (d) can be the answers, if only one option need to be chosen, We will definitely go with answer as (b).

66. Ans (b) **Darifenacin**, (c) **Oxybutynin** and (d) **Flavoxate** (Ref: Campbell-Walsh. Urology, 9/e p2102, Goodman and Gilman, 11/e p231-232, CMDT 2010/71)

Most likely, this question has typographic mistake and they have forgotten to write EXCEPT in the question, because anticholinergic drugs are indicated for overactive bladder and darifenacin, solifenacin, oxybutynin, flavoxate, tolterodine and fesoterodine are commonly used for this condition. So, if except is in the option, then answer would obviously be duloxetine.

67. Ans (a) **Atropine** (Ref: Modi's Medical Jurisprudence and Toxicology. 23rd, 2005/92, 403, 429-430, Goodman and Gilman 12/e p234-235)

These are the characteristic features of anti-cholinergic overdose.

68. Ans (a) **Anticholinergic** (Ref: Katzung 11/e p122)

69. Ans. (b) **Scopolamine hydrochloride** (Ref: J Psychiatry and Law 1993;3: 447-471)

Controlled administration of intravenous hypnotics to obtain information from subjects who are unable or unwilling to provide it otherwise, is known as Narcoanalysis or Narcosynthesis.

Drugs used for narcoanalysis are:

- Ethanol
- Scopolamine

- Temazepam
- Barbiturates like Thiopentone and Amobarbital

These drugs are also known as truth drug or truth serum.

- Phenobarbitone is not used, rather amobarbital is used for narcoanalysis.

70. **Ans. (d) Duloxetine** (Ref: *Principles of Pharmacology*, 1/e p157, 159; KDT 6/e p111)

- Anticholinergic drugs decrease the motility of urinary tract and thus may result in urinary retention (therefore contra-indicated in BHP).
- *Dicyclomine, flavoxate and oxybutynin* are useful for the treatment of urinary incontinence due to detrusor instability (urge incontinence)
- *Tolterodine, darifenacin and solifenacin* are selective M_3 antagonists that are also useful for urinary incontinence.
- Duloxetine is an SSRI used for the treatment of depression

71. **Ans. (a) Closure of Ca^{++} channels at the presynaptic membrane** (Ref: *Katzung* 10/e p90; KDT 6/e p93)

Botulinum toxin acts by inhibiting the calcium mediated exocytosis of ACh from the vesicles in the synapse.

72. **Ans. (b) Inhibiting release of acetylcholine** (Ref: *Katzung* 10/e p78; KDT 6/e p93)

73. **Ans. (c) Urinary retention** (Ref: *Katzung* 10/e p117; KDT 6/e p113)

- Ipratropium and tiotropium are antimuscarinic drugs used for treatment of bronchial asthma and COPD by inhalational route.
- Antimuscarinic drugs are contra-indicated (relative) in patients with
 - Glaucoma especially angle closure glaucoma
 - History of BHP (urinary retention)

74. **Ans. (b) Ipratropium** (Ref: *Katzung* 10/e p115; KDT 6/e p110-111)

- Ipratropium is an anticholinergic drug which is used for the treatment of COPD and bronchial asthma.

75. **Ans. (a) Atropine** (Ref: KDT 6/e p98)

- Treatment of choice for rapid onset type of mushroom poisoning is atropine.

76. **Ans. (c) Neostigmine** (Ref: KDT 6/e p104)

- Cholinergic drugs increase GI motility. Neostigmine is an inhibitor of the enzyme AChE (which is responsible for the breakdown of ACh). It thus acts like a cholinergic agent.
- Glycopyrrolate and atropine are anticholinergic drugs; thus reduce GI motility. Fentanyl is an opioid and can cause constipation.

77. **Ans. (b) Glycopyrrolate** (Ref: *Morgan's Anaesthesia* 3/e p210, 211; KDT 6/e p109, 110)

- All of these drugs possess anticholinergic properties.
- Glycopyrrolate cannot cross blood brain barrier, therefore does not produce central action.
- Atropine sulphate can cross blood brain barrier whereas atropine methonitrate is a quaternary ammonium compound and is devoid of central action.

78. **Ans. (d) Mydriasis** (Ref: *Katzung* 11/e p117)

- Atropine is an anticholinergic drug. It causes increased heart rate.
- Atropine causes mydriasis and decreased sweating.
- No consistent or marked effect on BP, though hypotension may occur due to histamine-release and direct vasodilator action (at high dose); tachycardia and vasomotor centre stimulation tend to rise BP.

79. **Ans. (d) Blockade of muscarinic auto-receptors on vagal nerve endings** (Ref: KDT 6/e p107)

Atropine is a non-selective antagonist of M_1 , M_2 and M_3 muscarinic receptors. M_2 cholinergic receptors are responsible for bradycardia and blockade of these receptors can result in tachycardia. Atropine initially acts on presynaptic M_1 receptors (normally decrease the release of ACh) and result in greater release of ACh which is responsible for bradycardia. Later on, blockade of M_2 receptors will lead to tachycardia.

80. **Ans. (a) Exerts depressant effect on the CNS at relatively low doses** (Ref: KDT 6/e p109)

Hyoscine is a CNS depressant and can be used as truth serum (to induce twilight sleep). Atropine at low doses stimulates the brain whereas inhibits it at very high concentration.

81. **Ans. (a) Glycopyrrolate** (Ref: KDT 6/e p110)

Glycopyrrolate is used to reduce the secretions (to prevent reflex bronchospasm) during anaesthesia. It is mainly used as pre-anaesthetic medication.

82. **Ans. (b) Physostigmine** (Ref: KDT 6/e p113, 114)
Being tertiary amine, physostigmine can reverse CNS manifestations of belladonna (source of atropine) poisoning. It is therefore, preferred as an antidote for this type of poisoning.
83. **Ans. (d) Hyperthermia** (Ref: KDT 6/e p113)
Atropa belladonna contains anticholinergic principles like atropine and hyoscine. Atropine is contra-indicated in children due to the risk of hyperthermia.
84. **Ans. (c) Reversible antagonist at muscarinic receptors** (Ref: KDT 6/e p109)
85. **Ans. (a) Hypertension** (Ref: KDT 6/e p112, 113)
86. **Ans. (a) Eye** (Ref: KDT 6/e p111)
87. **Ans. (b) Tropicamide** (Ref: Katzung 11/e p124)
Atropine is longest acting (5-6 days) whereas tropicamide is the shortest acting (15-60 min) mydriatic.
88. **Ans. (c) Muscarinic receptor inhibition** (Ref: KDT 6/e p111)
 - Oxybutynin is a synthetic anticholinergic agent.
89. **Ans. (a) Increase bowel sound** (Ref: KDT 6/e p107)
 - Atropine is an anticholinergic drug. It decreases bowel sounds.
90. **Ans. (c) Excessive salivation** (Ref: KDT 6/e p113)
Atropine is an *anticholinergic drug*. Its toxicity causes:
- Dry mouth (and not excessive salivation)
 - Hot skin
 - Dilated pupil and photophobia
 - Excitement
 - Flushing of skin
 - Hypotension → cardiovascular collapse
 - Convulsions and coma
91. **Ans. (a) Hyoscine** (Ref: KDT 6/e p113)
Hyoscine is used for the prophylaxis of motion sickness whereas other drugs listed in the question are used for the treatment of vomiting.
92. **Ans. (d) Increased bowel sounds** (Ref: KDT 6/e p107)
Atropine is an anticholinergic drug. It will decrease GI motility. Atropine flushing is seen in overdose, the exact mechanism of which is not known.
93. **Ans. (a) Mydriasis is required without cycloplegia** (Ref: KDT 6/e p127)
94. **Ans. (d) Physostigmine** (Ref: KDT 6/e p104)
95. **Ans. (d) Tropicamide** (Ref: KDT 6/e p111)
96. **Ans. (d) Pirenzepine** (Ref: KDT 6/e p111)
97. **Ans. (d) Amphetamine** (Ref: KDT 6/e p126)
98. **Ans. (d) Phenylephrine** (Ref: KDT 6/e p130)
99. **Ans. (b) Inhibition of sweating** (Ref: KDT 6/e p108)
100. **Ans. (a) Muscarinic** (Ref: KDT 6/e p111)
101. **Ans. (d) Noradrenaline** (Ref: KDT 7/e p130)
 - Dobutamine is selective beta 1 agonist, fenoldopam is selective D1 agonist whereas phenylephrine acts only on alpha1. NA can act on alpha1, alpha2 and beta1 receptors
102. **Ans. (c) Obstructive sleep apnea** (Ref: www.fda.gov; KDT 6/e p470-471)
 - Modafinil is a sympathomimetic drug and is alpha and beta agonist in brain. The drug also acts upon several other receptors. It has brain activating properties and is the drug of choice for narcolepsy.
 - Modafinil can also be used for sleep disorders in shift workers.
 - Recently, FDA has approved modafinil as an adjunctive treatment for obstructive sleep apnea. Remember, **continuous positive airway pressure (cPAP) is the treatment of choice for this disorder**. Modafinil is approved only as adjunctive treatment.

103. Ans. (c) Phenylephrine (Ref: Harrison /18/e p377-378)

Alpha blockers are used in erectile dysfunction not alpha agonists (phenylephrine).

Drugs useful in the management of erectile dysfunction (ED)

- Phosphodiesterase inhibitors
 - Sildenafil
 - Vardenafil
 - Tadalafil
 - Udenafil
- PGE₁ analog – Alprostadil
- Aviptadil

104. Ans. (a) Dobutamine decreases peripheral resistance (Ref: Harrison 18/e p1913)

Dobutamine acts by activating β_1 receptors and may decrease the peripheral resistance by its minor effect on β_2 receptors. It has no effect on dopamine D₁ or D₂ receptors.

- Dobutamine is a direct-acting inotropic agent whose primary activity results from stimulation of the β receptors of the heart while producing comparatively mild chronotropic, hypertensive, arrhythmogenic, and vasodilative effects. It does not cause the release of endogenous norepinephrine, as does dopamine. In animal studies, dobutamine produces less increase in heart rate and less decrease in peripheral vascular resistance for a given inotropic effect than does isoproterenol.
- Systemic vascular resistance is usually decreased with administration of dobutamine. Occasionally, minimum vasoconstriction has been observed. Similarly coronary blood flow may be increased with dobutamine.

105. Ans. (b) 1 : 1000 for inhalational route (Ref: Drug Facts and Comparisons, 2010/837)

For inhalational route, adrenaline is used in a concentration of 1:100 for treatment of bronchial asthma by nebulizer.

106. Ans. (b) As a vasodilator in treating coronary artery stenosis during angio procedures (Ref: CMDT-2010/1434-1435)

Tolazoline and phentolamine are alpha receptor blockers, therefore produce vasodilation.

107. Ans. (b) Salmeterol (Ref: KDT 6/e p216, 217, 218 & 5/e p200)

Salmeterol is a long acting β_2 agonist whereas albuterol (salbutamol), pirbuterol and orciprenaline are short acting agents.

108. Ans. (b) Dobutamine (Ref: Harrison 17/e p1399-1400)

- Pharmacological stress testing is done in individuals who are not able to exercise.
- It is done by infusion of **dobutamine** to increase myocardial oxygen demand.

109. Ans. (a) Ephedrine (Ref: Current Diagnosis And Treatment-obstetrics And Gynecology, 2008)

Vasopressors act by stimulating alpha adrenergic receptors. This vasoconstriction can lead to fetal hypoxia by reducing uteroplacental perfusion. Vasopressors acting predominantly by alpha receptors can also increase uterine tone and further aggravate the fetal hypoxia. Phenylephrine, methoxamine and mephentermine are all alpha agonists and can cause this side effect so not preferred in pregnant female.

Ephedrine on the other hand possess beta adrenergic activity also and result in less vasospasm (due to beta 2 mediated vasodilation) and is considered as the vasopressor of choice in pregnant females especially for the treatment of hypotensive complication of regional anaesthesia.

110. Ans. (a) Stimulation of lipolysis (Ref: Katzung 10/e p86; KDT 6/e p119)

Lipolysis is mediated by β_3 receptors whereas other actions are done by stimulation of β_2 receptors.

111. Ans. (a) Hypertensive emergencies (Ref: Katzung 10/e p133, 174)

- Fenoldopam is a D₁ agonist useful for i.v. treatment of hypertensive emergencies.

112. Ans. (b) Conversion of tyrosine to dopa (Ref: Katzung 10/e p78; KDT 6/e p116-117)

- Rate limiting enzyme in norepinephrine synthesis is tyrosine hydroxylase that catalyses the conversion of tyrosine to dopa. In ACh synthesis, rate limiting step is uptake of choline by the neurons.

113. Ans. (d) Hypokalemia (Ref: KDT 6/e p124 and Principles of pharmacology by HL Sharma and KK Sharma 2007/168)

- β_2 agonists cause a brief spell of hyperkalemia followed by hypokalemia.
- These do not cause hypoglycemia. However, β_2 blockers delays the recovery from hypoglycemia.

114. Ans. (b) Hypoglycemia (Ref: KDT 6/e p124)

- β_2 agonists are the inhaled bronchodilators used for the management of bronchial asthma.
- Tremor is the dose related adverse effect of these drugs.

- Brief hyperkalemia followed by hypokalemia is an important adverse effect of these agents.
- β_2 agonists do not cause hypoglycemia.

115. Ans. (d) Erectile dysfunction (Ref: KDT 6/e p129, 130)

- Erection of penis requires increased blood supply by means of vasodilatation. This can be produced by α -blockers and not by agonists. Other drugs for erectile dysfunction are phosphodiesterase inhibitors like sildenafil and tadalafil.
- Sympathomimetic agents are positive inotropic agents and can be used for the treatment of acute decompensated heart failure. Dopamine and dobutamine are particularly suited for this purpose.
- These agents can be used for the treatment of hypotension (dopamine) as well as hypertension (clonidine).

116. Ans. (a) IV noradrenaline increases systolic and diastolic BP and causes tachycardia (Ref: Katzung 10/e p132)

Noradrenaline increases blood pressure (both systolic and diastolic) which lead to reflex activation of baroreceptors resulting in bradycardia. Adrenaline increases systolic BP and cause tachycardia. It has negligible effect on diastolic BP. However both rise and fall have been noted. For details, see text.

117. Ans. (b) Dobutamine (Ref: Principles of pharmacology by HL Sharma and KK Sharma 2007/172)

- Dopamine, adrenaline and noradrenaline are endogenous catecholamines.
- Isoprenaline, dipivefrin, dobutamine, ibopamine, dopexamine and fenoldopam are the exogenous (synthetic) catecholamines.

118. Ans. (b) Methyl dopa (Ref: KDT 6/e p547)

Methyl dopa itself is not an α_2 agonist but it is converted to an active metabolite α -methyl norepinephrine which possesses α_2 agonistic action. All other drugs listed in the question are α_2 agonists for the treatment of hypertension.

119. Ans. (c) Benign hyperplasia of prostate (Ref: KDT 6/e p146)

α_2 agonists like apraclonidine and brimonidine are useful for the treatment of glaucoma. Clonidine is also used for the management of hypertension. Dexmedetomidine is a centrally acting α_2 agonist indicated for sedation of initially intubated and mechanically ventilated patients.

120. Ans. (a) β_1 receptors in heart stimulate its contractions; (c) β_2 -receptors are present in smooth muscles (Ref: KDT 6/e p123)

121. Ans. (d) Indirect sympathomimetics involved (Ref: KDT 6/e p68; Goodman Gilman's 11/e p31,162, 170)

- Tachyphylaxis (Tachy-fast; phylaxis-tolerance) is the rapid development of tolerance.
- Mechanism of tachyphylaxis is incompletely understood and thought to be due to depletion of neurotransmitter in the vesicle.
- Tachyphylaxis is usually seen with indirect acting sympathomimetics, e.g. tyramine, ephedrine, amphetamine etc.

122. Ans. (c) Intra-muscular adrenaline hydrochloride (Ref: KDT 6/e p129)

123. Ans. (b) Ephedrine (Ref: Goodman & Gilman 11/e p239)

Catecholamines are the drugs having dihydroxybenzene nucleus in its structure. Adrenaline, isoprenaline and dopamine contain this structure.

124. Ans. (a) Adrenaline (Ref: KDT 6/e p123)

Vasomotor reversal of dale is seen with adrenaline. When this drug is infused quickly, initially there is rise in blood pressure (due to stimulation of α receptors) followed by prolonged fall (β_2 action). α -blocking drugs inhibit the initial rise and only fall in blood pressure is recorded. This is known as vasomotor reversal. Nor-adrenaline has no β_2 activity and isoprenaline lacks α activity, therefore cannot demonstrate this phenomenon.

125. Ans. (a) Dopamine (Ref: KDT 6/e p126)

Dopamine has concentration dependent effects on various receptors. When infused at a rate of less than $2 \mu\text{g/kg/min.}$, it stimulates only dopamine receptors (resulting in renal vasodilation). At $2-10 \mu\text{g/kg/min.}$ infusion rate, it stimulates β_2 receptors also and at a rate greater than $10 \mu\text{g/kg/min.}$ it causes vasoconstriction due to stimulation of α -receptors.

126. Ans. (c) Secondary shock (Ref: KDT 6/e p129)

Sympathomimetic drugs are indicated in all types of shock except secondary shock. In this condition, there is reflex vasoconstriction. Alpha blockers are useful in this type of shock.

127. Ans. (c) Do not block any effect of injected adrenaline (Ref: KDT 6/e p132, 133)

Adrenergic neuron blocking drugs like guanethidine inhibits the release of nor-adrenaline from the neuron. These drugs

have no effect on α or β -receptors. Therefore, these may inhibit the effect of sympathetic nerve stimulation but will have no effect on exogenous adrenaline action.

128. Ans. (b) Dilatation of pupil (Ref: KDT 6/e p143)

Stimulation of α -receptors cause mydriasis whereas tachycardia and vasodilation are due to activation of β -adrenergic receptors.

129. Ans. (a) Acetylcholine (Ref: KDT 6/e p107)

Whenever blood pressure increases there is reflex stimulation of baroreceptors. These release ACh and depresses the heart.

130. Ans. (b) Asthma (Ref: KDT 6/e p127)

Beta-2 agonists are useful in premature uterine contractions to delay labour and not for delayed labor. Beta blockers are used in the treatment of angina.

131. Ans. (d) Phenylephrine (Ref: KDT 6/e p127)

- Nor-adrenaline decreases the heart rate due to reflex stimulation of baroreceptors. These reflexes are lost in a transplanted heart. However, by its β action, it can produce tachycardia.
- Phenylephrine is a selective α_1 agonist. It has no direct effect on the heart but produces bradycardia due to reflex stimulation of baro-receptors. These reflexes are lost in a transplanted heart. Therefore, it produces no effect on heart.

132. Ans. (a) Cocaine (Ref: KDT 6/e p117)

It is a local anaesthetic agent (acts by inhibiting Na^+ channel in the axonal membrane) that also possesses indirect sympathomimetic activity.

133. Ans. (a) Increase heart rate (Ref: KDT 6/e p123)

For explanation see text.

134. Ans. (b) Dobutamine (Ref: KDT 6/e p126)

135. Ans. (c) Patient's tumor secreting almost pure adrenaline and no noradrenaline (See below)

Urinary excretion of metanephrines in excess suggests the secretion of mainly adrenaline by the tumor (metanephrine is a metabolite of adrenaline and nor-metanephrine is a degradation product of nor-adrenaline). Adrenaline acts on α -receptors to cause increase in blood pressure (220/160 mmHg in this case) and on β_1 receptors to cause tachycardia (160/min. in this patient). However, it also possesses β_2 action that is responsible for vasodilation. This action is suppressed in the presence of strong α -action. On giving α -blockers like phentolamine, this β_2 -action is unmasked leading to profound hypotension (36/0 mm Hg in this patient). This phenomenon is known as vasomotor reversal of Dale.

136. Ans. (a) Renal vasodilatory effect (Ref: Katzung 11/e p137)

Dopamine acts on D_1 , β_1 and α_1 receptors. Stimulation of D_1 receptors cause renal vasodilation, which is useful clinically to improve renal perfusion in shock with oligouria.

137. Ans. (c) Ephedrine (Ref: KDT 6/e p123)

- Ephedrine acts directly as well as indirectly through release of nor-adrenaline. Latter increases systolic (β_1) as well as diastolic (α_1 action) blood pressure. This is due to lack of β_2 mediated vasodilation.
- Adrenaline transiently increase diastolic BP which later on decreases due to its β_2 stimulatory action.

138. Ans. (a) The usual dose is 0.5-1 mg by i.m. route (Ref: KDT 6/e p129)

- Adrenaline 0.5 ml of 1 : 1000 solution (i.e., 0.5 mg) by i.m. route is drug of choice for anaphylactic shock. It can also be used by s.c. route
- If not responding, it can be repeated after 5 minutes (not 2-4 hours). In desperate circumstances i.v. route can be used but it must be diluted 10 times (i.e., 1 : 10000 concentration is used), therefore same solution cannot be utilized. However, in rare circumstances, i.v. adrenaline can result in cerebral hemorrhage due to uncontrolled rise in blood pressure.

139. Ans. (d) 1-2 $\mu\text{g/kg/min}$ (Ref: Harrison 17th/1453)

Dose of Dopamine	Effects
1-2 micro gm/kg/min	Renal vasodilation (Renal dose)
2-10 micro gm/kg/min	Stimulates β_1 receptors of heart
> 10 μ gm/kg/min	Stimulates peripheral α receptor s leading to vasoconstriction

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140. Ans. (a) 120 seconds (Ref: Lawrence 9/e p453)

Dobutamine is an inotropic drug which has onset of action = 1-2 min.
 Peak action = 1-10 min.
 Duration of action = < 10 min.
 Half life = 2 min.

141. Ans. (c) Sedation (Ref: KDT 6/e p217)

- Side effects of salbutamol :
 1. Palpitation
 2. Muscle tremors
 3. Throat irritation
 4. Nervousness
 5. Ankle edema

142. Ans. (b) Subcutaneous adrenaline (Ref: KDT 6/e p130)

143. Ans. (c) Reuptake (Ref: KDT 6/e p117)

Endogenous adrenaline action is terminated mainly by reuptake whereas exogenous agent is metabolized by COMT and MAO.

144. Ans. (b) Anaphylactic shock (Ref: KDT 6/e p129)

- Epinephrine is the agent of choice for the treatment of anaphylactic shock. It increases BP by α action and causes bronchodilation by β_2 action.
- For bronchial asthma, selective β_2 agonists like salbutamol are preferred.
- For glaucoma, a prodrug of epinephrine, dipivefrine is useful (as adrenaline cannot cross corneal membrane).
- Treatment for PVD is α blockers.

145. Ans. (b) COMT (Ref: KDT 6/e p117)

Endogenous adrenaline action is terminated mainly by reuptake whereas exogenous agent is metabolized by COMT and MAO.

146. Ans. (a) α_1 receptors are usually presynaptic (Ref: KDT 6/e p119)

Presynaptic sympathetic receptors are usually α_2 . Other statements are true.

147. Ans. (a) Dopamine (Ref: KDT 6/e p126)

148. Ans. (b) Yohimbine (Ref: KDT 6/e p119)

149. Ans. (a) Adrenaline (Ref: KDT 6/e p123)

150. Ans. (a) VMA (Ref: KDT 6/e p117)

151. Ans. (a) α_2 (Ref: KDT 6/e p547)

152. Ans. (a) Epinephrine (Ref: KDT 6/e p124)

153. Ans. (b) β_2 selectivity (Ref: KDT 6/e p217)

154. Ans. (b) Diastolic (Ref: KDT 6/e p123)

155. Ans. (a) Tremors (Ref: KDT 6/e p217)

156. Ans. (b) ADHD (attention deficit hyperkinetic disorder) (Ref: KDT 6/e p470)

157. Ans. (a) Methylation (Ref: KDT 6/e p116)

158. Ans. (a) Agonist of D_1 and D_2 receptors (Ref: KDT 6/e p126)

159. Ans. (a) Adenyl cyclase (Ref: KDT 6/e p48)

160. Ans. (a) α blocker (Ref: KDT 6/e p123)

161. Ans. (a) Reserpine (Ref: KDT 6/e p549)

162. Ans. (d) Gastrointestinal sphincter contraction (Ref: KDT 6/e p119)

163. Ans. (a) Isoprenaline (Ref: KK Sharma 1/e p172)

164. Ans. (c) Can Produce CNS stimulation (Ref: KDT 6/e p546)

165. Ans. (d) All of the above (Ref: KDT 6/e p546-547)

166. Ans. (a) Ephedrine (Ref: Katzung 11/e p134)
167. Ans. (b) Cardiac output (Ref: KDT 6/e p126)
168. Ans. (b) Urine output (Ref: KDT 6/e p126)
169. Ans. (c) Decrease in the production of aqueous humor (Ref: Goodman and Gilman 12/e p1787)
Beta-blockers decrease the formation of aqueous humor and thus decrease intra-ocular pressure.
Goal of treatment in glaucoma is to prevent progressive optic nerve damage with minimum side effects.
170. Ans (c) Lupus Erythematosus (Ref: KDT 6/e p135-136)
Prazosin is a selective α_1 blocker and can be used for treatment of pheochromocytoma, peripheral vascular disease, benign hyperplasia of prostate and hypertension. It is the drug of choice for scorpion sting.
171. Ans. (d) Carvedilol (Ref: KDT 6/e p140)
• Carvedilol has additional α blocking activity.
172. Ans. (d) Propanolol (Ref: Goodman & Gilman 11/e p286)
173. Ans. (c) Sotalol (Ref: KDT 6/e p140)
Lipid insoluble β -blockers like sotalol, atenolol, nadolol etc are excreted by the kidney and should be avoided in renal failure. Beta blockers contraindicated in renal failure are:
- A-Atenolol
N-Nadolol
S-Sotalol
174. Ans. (a) Carvedilol (Ref: Goodman & Gilman 11/e p285, 286; KDT 6/e p143)
Third generation β -blockers possess additional vasodilator activity apart from their α -blocking action. Carvedilol and labetalol block α receptors also and cause vasodilation.
175. Ans. (b) It is most effective in new onset decompensated heart failure (Ref: KDT 6/e p142, 143)
- Beta blockers are *absolutely contraindicated* in decompensated (*acute*) heart failure.
 - In compensated heart failure, these agents should be initiated at very low doses and the dose should be increased gradually.
 - If used in this manner, long term use of β -blockers can decrease the mortality in CHF patients.
 - *Carvedilol* is the most commonly used beta blocker in CHF due to its antioxidant and antimitogenic property.
176. Ans. (c) Carvedilol has alpha agonistic and selective β_1 blocking action (Ref: KDT 6/e p143)
• Labetalol and carvedilol are blockers of both α as well as β -receptors.
• Esmolol is the shortest acting and nadolol is the longest acting β -blocker.
• Atenolol is not lipid soluble. It is excreted by the kidney. These agents are longer acting than lipid soluble β -blockers like metoprolol.
177. Ans. (a) Labetalol; (b) Carvedilol (Ref: KDT 6/e p143)
178. Ans. (e) It can cause bradycardia (Ref: KDT 6/e p142)
• Esmolol is an **ultra short acting cardioselective β -blocker** devoid of partial agonistic or membrane stabilizing effect. It is **used in terminating supraventricular tachycardia**, episodic atrial fibrillation or flutter, arrhythmia during anaesthesia, to reduce BP and HR during cardiac surgery and early treatment of MI.
• β -blocker are contra-indicated in decompensated heart failure.
179. Ans. (a) Asthma, (b) Heart block (Ref: KDT 6/e p139)
Beta blockers are contra-indicated in
- A - Asthma
 - B - Block (Heart block)
 - C - CHF (Decompensated)
 - D - Diabetes mellitus
180. Ans. (a) Atropine; (c) Glucagon (e) Calcium chloride (Ref: Washington Manual 31/e p573)
• Treatment of β -blocker poisoning :

- Establish an i.v. line before any other therapy is undertaken.
- Gastric lavage is done if patient is seen within one hour of therapy.
- To treat hypotension, start i.v. saline, **I.V. glucagon is the drug of first choice in β -blocker poisoning**. Adrenaline and nor-adrenaline are less effective for the treatment of β -blocker poisoning because β -receptors are already occupied. Glucagon increases cardiac contractility by increasing cAMP through its action on glucagon receptors.
- Calcium chloride may also be used.

181. Ans. (b) Asthma; (c) Depression; (e) Hypotension (Ref: KDT 6/e p139)

182. Ans. (a) α_1 blocker; (b) β_1 blocker; (c) β_2 blocker; (d) Antioxidant; (e) Used in hypertension (Ref: KDT 6/e p143-144)

- Carvedilol is a $\beta_1 + \beta_2 + \alpha_1$ adrenoceptor blocker with $\alpha : \beta$ blocking property of 1 : 9.
- It has *antioxidant* property.
- It is used in hypertension and *angina*.
- It is used as *cardioprotective in CHF*.

183. Ans. (b) It has no intrinsic sympathomimetic activity; (d) It is a cardioselective β -blocker; (e) It can precipitate heart failure (Ref: KDT 6/e p141)

184. Ans. (a) It is a cardioselective β -blocker; (e) It has negative inotropic activity (Ref: KDT 6/e p141)

- Esmolol is an **ultrashort acting** β -blocker ($t_{1/2} < 10$ min.)
- It is inactivated by esterases in blood.
- β -blocker decreases heart rate and force of contraction (negative inotropic action).
- Beta blockers can precipitate or aggravate CHF.
- Selective beta 1 blocker and are less likely to cause bronchoconstriction, thus do not increase airway resistance.

185. Ans. (b) Oxprenolol (c) Pindolol (Ref: Katzung 11/e p146)

186. Ans. All (Ref: KDT 6/e p140)

- Cardioselective drugs are more potent in blocking cardiac (β_1) than β_2 receptors. However, selectivity is only relative and is lost at higher doses. Their features are :

- Lower propensity to cause bronchoconstriction.
- *Less interference with carbohydrate metabolism* and safer in DM, however warning symptoms of hypoglycaemia are blocked.
- *Less chances of precipitating Raynaud's phenomenon.*
- *No deleterious effect on blood lipid profile.*
- Ineffective in suppressing essential tremor.
- *Less liable to impair exercise capacity.*

187. Ans. (a) Is a β_1 selective blocker (Ref: KDT 6/e p145)

Betaxolol is less likely to induce bronchospasm than timolol.

188. Ans. (b) Ergotamine (Ref: KDT 6/e p168)

Ergot alkaloids are the α -blockers that can cause vasoconstriction.

189. Ans. (a) Terazosin (Ref: KDT 6/e p134)

Selective α_1 blockers provide faster and greater symptomatic relief to the patients of BHP, but do not affect the disease progression. 5 α reductase inhibitors like finasteride slow the disease progression but the beneficial effects are delayed (takes about 6 months).

190. Ans. (c) Acebutolol (Ref: KDT 6/e p140)

191. Ans. (c) Short term stressful situations (Ref: KDT 6/e p143)

Propranolol is used for controlling the performance anxiety, major manifestations of which are due to increased sympathetic activity (tachycardia, palpitations etc.).

192. Ans. (c) It is less likely to cause bradycardia (Ref: KDT 6/e p141)

- Metoprolol is a cardio-selective β -locker and thus is safer than non-selective blockers (like propranolol) in diabetics, asthmatics and the patients of peripheral vascular disease (e.g. Raynaud's disease). Due to lack of β_2 -blocking action, it cannot suppress muscle tremors. Potential to cause bradycardia is similar to non-selective β -blockers. Drugs possessing ISA (like pindolol) are less likely to cause bradycardia.

193. Ans. (d) Contraction of the radial smooth muscle in the iris (Ref: KDT 6/e p123)

- Smooth muscle of iris contains α receptors whereas heart, bronchus and uterus possess β -adrenergic receptors.

194. Ans. (b) Partial atrioventricular block (Ref: KDT 6/e p142, 143)

Beta blockers are contra-indicated in heart block because these can convert partial AV block to complete AV block. These agents are the drugs of choice for HOCM.

195. Ans. (b) Heart failure exacerbation from β -blockers (Ref: KDT 6/e p142)

Beta blockers are contra-indicated in acute CHF because these can exacerbate the heart failure. Bronchoconstriction and impairment of blood glucose response is seen with β -blockers. These agents also decrease intraocular pressure and are used for the treatment of glaucoma.

196. Ans. (d) Timolol lacks the local anaesthetic effects of propanolol (Ref: KDT 6/e p140, 141, 144, 145)

- Metoprolol is a cardioselective (β_1 selective) blocker and not β_2 selective.
- Esmolol is the shortest acting β -blocker and is useful for acute treatment.
- Nadolol is a non-selective β -blocker. It blocks both β_1 as well as β_2 receptors.
- Propanolol possesses maximum local anaesthetic activity whereas timolol lacks this property.
- For more details, see text.

197. Ans. (d) Nebivolol (Ref: KDT 6/e p137)

198. Ans. (a) Pindolol (Ref: KDT 6/e p141)

Drugs possessing ISA are useful in this situation.

199. Ans. (d) Timolol (Ref: Katzung 11/e p157)

200. Ans. (d) Prazosin (Ref: Harrison 17/e p2752)

Prazosin is used for treatment of scorpion sting.

201. Ans. (a) Hypothyroidism (Ref: KDT 6/e p142, 143)

- Beta blockers are used to treat hyperthyroidism (not hypothyroidism).
- These are the only drugs that offer prophylactic benefits in a patient of varices who has never bled.

202. Ans. (b) Variant angina (Ref: KDT 6/e p139)

- Propanolol worsens variant angina, due to unopposed α receptor mediated coronary constriction.
- For indications of β -blockers, refer to text.

203. Ans. (b) Parkinsonian tremor (Ref: KDT 6/e p143)

Propanolol is useful in the management of tremor due to overdose of sympathomimetic agents (β_2 mediated). Metoprolol as well as propanolol are effective in *essential or familial tremor* (β_1 mediated). β -blockers are ineffective in intention tremor and rest (parkinsonian) tremors.

204. Ans. (c) COPD (Ref: KDT 6/e p139)

Timolol is a non-selective β -blocker. It can prevent β_2 mediated bronchodilation and thus worsen the condition in patients of bronchial asthma and COPD.

205. Ans. (b) Partial heart block (Ref: KDT 6/e p 139, 142)

β -blockers are contraindicated in partial or complete heart block as they cause bradycardia.

206. Ans. (c) Butoxamine (Ref: Katzung 11/e p160)

207. Ans. (c) Masks the hypoglycemic symptoms (Ref: CMDT 2010/402)

208. Ans. (a) Esmolol (Ref: KDT 6/e p141)

209. Ans. (b) Propanolol (Ref: KDT 6/e p125)

210. Ans. (c) Tamsulosin (Ref: KDT 6/e p135)

211. Ans. (b) β Blocker (Ref: KDT 6/e p145)

212. Ans. (d) All (Ref: KDT 6/e p139)

213. Ans. (a) Carvedilol (Ref: KDT 6/e p143)

214. Ans. (a) Propanolol (Ref: Katzung 11/e p 162)

215. Ans. (a) Esmolol is mainly metabolized in liver (Ref: KDT 6/e p141)

216. Ans. (a) α_{1A} (Ref: KDT 6/e p135)

217. Ans. (d) Pindolol (Ref: KDT 6/e p141)

218. Ans. (b) Phenoxybenzamine (Ref: KDT 6/e p133)
219. Ans. (c) Hydrolysis by blood esterase (Ref: KDT 6/e p141)
220. Ans. (d) All of above (Ref: KDT 6/e p139)
221. Ans. (d) Phenoxybenzamine binding to alpha adrenergic receptors (Ref: Katzung 10/e p16; KDT 6/e p133)
- Phenoxybenzamine is an irreversible (covalent) antagonist at alpha receptors. All other drugs mentioned are reversibly interacting with their receptors.

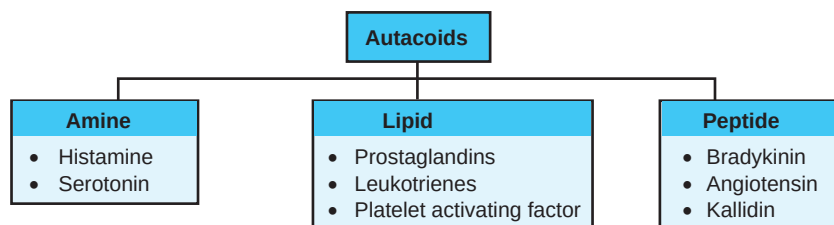
ANSWERS OF RECENT QUESTIONS ASKED BY NATIONAL BOARD

- Ans (a) Atenolol (Ref: KDT 7th/40)
- Ans (a) Causes increase in GI Ischemia (Ref: KDT 7th/134)
Dopamine causes vasodilation in renal and splanchnic vessels by stimulating D₁ receptors.
- Ans. (a) Acute CHF (Ref: KDT 6/e p142)
- Ans. (a) Adrenaline (Ref: KDT 6/e p122)
- Ans. (c) Neostigmine (Ref: KDT 6/e p104)
- Ans. (a) Adrenaline (Ref: KDT 6/e p130)
- Ans. (b) Carbaryl (Ref: KDT 6/e p105)
- Ans. (c) Pindolol (Ref: KDT 6/e p140)
- Ans. (d) Absence of pulmonary secretions (Ref: emedicine.medscape.com)
- Ans. (a) Atropine (Ref: KDT 7/e p118)
- Ans. (b) Alpha 2 (Ref: KDT 7/e p565)
- Ans. (b) Adjuvant pharmacotherapy for BMI > 30 kg/m² (Ref: CMDT 2014/1215)
NIH Clinical obesity guidelines recommend
 - Lifestyle modification for all
 - Surgery for patients with:
 - BMI >40 kg/m²
 - BMI >35 kg/m² with obesity related co-morbidities
 - Pharmacotherapy for patients with:
 - BMI >30 kg/m²
 - BMI >27 kg/m² with obesity-related risk factors.
- Ans. (b) Fludrocortisone (Ref: CMDT 2014/941)
- Ans. (a) Atropine (Ref: KDT 7/e p146)
 - Dopamine, adrenaline and isoprenaline act by stimulating β₁ receptors in heart. As patient has β-blocker overdose, these are likely to be ineffective
 - Atropine can increase heart rate in this person by blocking parasympathetic action on heart.
- Ans. (c) Yohimbine (Ref: KDT 7/e p140)
- Ans. (a) Mucous and pharyngeal secretions (Ref: KDT 7/e p113-115)
- Ans. (c) Bradycardia (Ref: KDT 7/e p114)
- Ans. (d) Intramuscular (Ref: KDT 7/e p138)
- Ans. (a) Tamsulosin (Ref: KDT 7/e p142)
- Ans. (a) Tamsulosin (Ref: KDT 7/e p142)
- Ans. (b) Shorter acting than edrophonium (Ref: KDT 7/e p105-109)
- Ans. (a) Glaucoma (Ref: KDT 7/e p121)

23. Ans. (b) Prazosin (Ref: KDT 7/e p142)
24. Ans. (d) All of the above (Ref: KDT 7/e p147)
25. Ans. (c) Inhibits Ach release (Ref: KDT 7/e p100)
26. Ans. (b) Carbaryl (Ref: KDT 7/e p111)
27. Ans. (a) Produce no miosis (Ref: KDT 7/e p153)
28. Ans. (c) Betaxolol (Ref: KDT 7/e p153)
29. Ans. (a) Bronchial smooth muscle (Ref: KDT 7/e p102)
30. Ans. (d) Partial AV block (Ref: KDT 7/e p147, 149-150)
31. Ans. (c) To prevent over dosage and discourage opioid dependence (Ref: KDT 7/e p686)
32. Ans. (a) Atenolol (Ref: KDT 7/e p148)
33. Ans. (b) Tropicamide (Ref: KDT 7/e p119)
34. Ans. (d) Naltrexone (Ref: KDT 7/e p110-111)
35. Ans. (c) Organophosphorous poisoning (Ref: KDT 7/e p110, 111)
36. Ans. (a) Phentolamine (Ref: KDT 7/e p141)
37. Ans. (c) Presynaptic blockade (Ref: KDT 7/e p99)
38. Ans. (b) Bronchoconstriction (Ref: KDT 7/e p114, 115)
39. Ans. (c) Nasal blockage (Ref: KDT 7/e p146-147)
40. Ans. (b) Carvedilol (Ref: KDT 7/e p151)
41. Ans. (b) Adrenaline (Ref: KDT 7/e p138)
42. Ans. (d) Pralidoxime (Ref: KDT 7/e p111)
43. Ans. (c) Timolol eye drops (Ref: CMDT 2014/175)
44. Ans. (c) Hypothermia (Ref: KDT 7/e p120)
Atropine poisoning is associated with hyperthermia (not hypothermia)
45. Ans. (d) Tyrosine (Ref: KDT 7/e p128)
46. Ans. (b) Atropine (Ref: KDT 7/e p121)
47. Ans. (c) Increasing aqueous humor outflow (Ref: KDT 7/e p156-157)
48. Ans. (d) Sympathetic cholinergic (Ref: KDT 7/e p93)
49. Ans. (d) Greater than 10 µg/kg/min (Ref: KDT 7/e p134)
50. Ans. (b) IV atropine (Ref: KDT 7/e p120)
51. Ans. (a) Timolol maleate (Ref: KDT 7/e p153)
52. Ans. (c) Metoprolol (Ref: KDT 7/e p147)
53. Ans. (c) Beta 1 (Ref: KDT 7/e p130)
54. Ans. (a) Clonidine (Ref: KDT 7/e p127)
55. Ans. (a) A-V block (Ref: KDT 7/e p147)
56. Ans. (b) Ephedrine (Ref: KDT 7/e p134)

- 57. Ans. (d) **Phenylephrine** (Ref: KDT 7/e p135)
- 58. Ans. (b) **Naloxone** (Ref: KDT 7/e p111)
- 59. Ans. (b) **Obesity** (Ref: KDT 7/e p137)
- 60. Ans. (d) **Glaucoma** (Ref: KDT 7/e p121)
- 61. Ans. (b) **Tachycardia** (Ref: KDT 7/e p103)
- 62. Ans. (d) **Trimethaphan** (Ref: KDT 7/e p123)
- 63. Ans. (d) **Methylphenidate** (Ref: KDT 7/e p139)
- 64. Ans. (d) **Myasthenic ptosis** (Ref: KDT 7/e p110)

These are the substances produced by wide variety of cells that act locally at the site of production. Autacoids are classified as



HISTAMINE

Histamine is *synthesized from histidine* and is stored within the storage granules of mast cells. It acts mainly on H_1 and H_2 receptors. Recently H_3 (presynaptic) and H_4 receptors have also been isolated.

Histamine is synthesized from histidine

ACTIONS

- It causes dilation of small blood vessels and can result in *flushing and hypotension*. Fall in blood pressure is mediated by both H_1 (early; by release of NO) as well as H_2 (delayed and persistent; direct action on smooth muscles of blood vessels) receptors.
- It *increases capillary permeability and result in edema* through stimulation of H_1 receptors.
- Intradermal injection may result in *triple response* consisting of red reaction (due to vasodilation), wheal (exudation of fluid due to increased permeability) and flare (spreading redness due to axon reflex). It is primarily an H_1 response.
- H_1 receptor stimulation has *negative dromotropic (decreases AV conduction)* effect whereas H_2 stimulation *increases the force of contraction* of isolated heart. Effect on intact heart is not prominent.
- Histamine is a powerful contractor of visceral smooth muscles through H_1 receptors and results in *bronchoconstriction and abdominal cramps*.
- Histamine *increases gastric secretion* by stimulation of H_2 receptors.
- It stimulates nerve endings and may result in *pruritis and pain*.
- Histamine synthesized within the brain *stimulates reticular activating system and maintains wakefulness* (through H_1 receptors). **H_3 receptors** are pre-synaptic in location and inhibit the release of histamine. Inverse agonist or antagonist of these receptors may increase histamine leading to wakefulness. **Pitolisant (tiprolisant)** is such a drug approved for **Narcolepsy**.
- It serves as a *mediator of inflammation and immediate type of hypersensitivity reactions*
 - ❖ **Betahistine** is an oral histamine analogue used to *control vertigo* in Meniere's disease
 - ❖ Some **basic drugs** like *d-tubocurarine, morphine, atropine, vancomycin and polymyxin B etc.* may result in histamine release.
- **H_4 receptors** are present in hematopoietic cells like eosinophils, basophils and mast cells. These promote chemotaxis. Antagonists of these receptors are being developed for allergic conditions.

Histamine induced fall in blood pressure is mediated by both H_1 (early) as well as H_2 (delayed and persistent) receptors.

Intradermal injection of histamine may result in *triple response* consisting of

- Red reaction (due to vasodilation).
- Wheal (exudation of fluid due to increased permeability)
- Flare (spreading redness due to axon reflex).

H_1 Anti-Histaminics

These drugs act as competitive antagonists at H_1 receptors. These may be classified into first generation and second generation compounds on the basis of CNS penetration and anticholinergic properties.



First generation anti-histaminics are *contraindicated in persons requiring constant attention*.



Tiprolisant is H₃ inverse agonist used for **Narcolepsy**



Uses of H₁ blockers (First Generation) based on anticholinergic properties

Possess	- Parkinsonism
Anti	- Acute muscular dystonia
Cholinergic	- Common cold
Properties	- Prophylaxis of motion sickness



Doxepin is a tricyclic antidepressant having most potent H₁ blocking action (800 times more potent than diphenhydramine).



Terfenadine and **Astemizole** result in polymorphic ventricular tachycardia (**Torsades de pointes**) manifested as prolongation of QTc interval.

(A) FIRST GENERATION ANTI-HISTAMINICS

These drugs *can penetrate blood brain barrier* and thus result in sedation and psychomotor impairment. Therefore, these drugs are *contraindicated in persons requiring constant attention* (like truck drivers, machinery operators and swimmers).

Another property of first generation compounds is the presence of *anticholinergic activity*. This property is responsible for their wide spectrum of uses and more adverse effects than second generation compounds. First generation drugs may be classified as:

Highly sedating	Moderately sedating	Mildly sedating
Diphenhydramine	Pheniramine	Chlorpheniramine
Dimenhydrinate	Cyproheptadine	Mepyramine
Promethazine	Meclizine	Cyclizine
Hydroxyzine	Bucizine	Clemastine
Doxepin	Cinnarizine	

Uses

Based on H ₁ blocking action	Based on anticholinergic properties	Other uses
1. Allergic conditions like <i>itching, urticaria, hay fever</i> etc. 2. <i>Insect bite, ivy poisoning</i> and to prevent the adverse effects due to histamine releasers.	1. <i>Common cold</i> (to control rhinorrhoea) 2. <i>Motion sickness</i> (as prophylactic agents) 3. <i>Parkinsonism</i> (promethazine may be used) 4. <i>Acute muscular dystonia</i>	1. Antihistaminics are drug of choice for <i>idiopathic pruritis</i> 2. Cinnarizine is useful in <i>vertigo</i> .

Adverse Effects

Major adverse effects of first generation agents are *sedation, psychomotor impairment and anticholinergic effects* (dryness of mouth, blurred vision, urinary retention, constipation etc.)

(B) SECOND GENERATION ANTI-HISTAMINICS

These drugs have little CNS penetration (do not cause sedation) and do not possess anticholinergic activity. Some drugs like cetirizine and azelastine possess additional anti-allergic mechanisms. These drugs *lack sedation* (can be used in truck drivers) and *anticholinergic adverse effects* but their use is also restricted to antiallergic effects.

IMPORTANT DRUGS

- **Terfenadine** is the fastest acting antihistaminic drug. In overdose, it blocks cardiac delayed rectifier K⁺ channels and may result in polymorphic ventricular tachycardia (torsades de' pointes) manifested as prolongation of QTc interval. Use of this drug with microsomal enzyme inhibitors like ketoconazole, erythromycin, clarithromycin and itraconazole increases the risk of this arrhythmia. Terfenadine is metabolized to an active metabolite "**fexofenadine**" (available as a separate drug) that lacks K⁺ channel blocking property.
- Astemizole is slowest and longest acting agent and possesses arrhythmogenic property similar to terfenadine. Therefore, it should not be administered with ketoconazole, erythromycin, clarithromycin and itraconazole.
- **Loratidine** is another *long acting* second generation antihistaminic and is metabolized to **desloratidine** (available as a separate drug).
- **Cetirizine** is an active metabolite of a first generation antihistaminic drug, hydroxyzine.

All second generation antihistaminics are metabolized to active products except cetirizine and mizolastine. It possesses additional anti-allergic mechanisms like inhibition of release of cytotoxic mediators from platelets and inhibition of chemotaxis. Some persons acquire sedative effects with cetirizine. *Levocetirizine* is l-isomer of cetirizine that is more potent and less sedative.

- *Azelastine* possesses *maximum topical activity* and can be given by nasal spray for allergic rhinitis.
- *Mizolastine, ebastine, levocabastine, rupatidine, acrivastine* and *olopatadine* are other second generation antihistaminic agents.
- **Olopatadine** is a recently approved topical H_1 -antihistaminic used as nasal spray for seasonal allergic rhinitis.
- **Alcaftadine** is approved as ophthalmic solution for allergic conjunctivitis.

Some authorities describe the term 3rd generation antihistaminics for the active enantiomer (like levo-cetirizine) or metabolite (e.g. desloratidine and fexofenadine) of 2nd generation drugs.

SEROTONIN

5-hydroxytryptamine (serotonin) is synthesized from tryptophan. It is produced by hydroxylation followed by decarboxylation of tryptophan; steps similar to catecholamine synthesis. It is similarly stored in the vesicles and its action is terminated by reuptake. It acts by activation of several serotonin receptors ($5-HT_1$ - $5-HT_7$ receptors).

Triphasic response of serotonin

- Early sharp fall (due to Bezold Jarisch reflex)
- Then brief rise (due to vasoconstriction)
- Followed by prolonged fall (due to arteriolar dilation)

ACTIONS

- On i.v. injection, it produces *triphasic response on blood pressure*. Early sharp fall (due to Bezold Jarisch reflex), then brief rise (due to vasoconstriction) followed by prolonged fall (due to arteriolar dilation) in blood pressure is seen.
- Serotonin is a powerful stimulator of smooth muscles. It *increases peristalsis and constricts bronchi*.

It has *gastroprotective action* by decreasing acid secretion and increasing mucus production.

$5-HT$ is involved in *regulation of sleep, cognition, behaviour and mood*.

Serotonin increases *platelet aggregation*.

Receptors

$5-HT_1$		$5-HT_{2A/2C}$	$5-HT_3$	$5-HT_4$
$5-HT_{1A}$	$5-HT_{1B/1D}$			
Presynaptic autoreceptor	Cause constriction of cranial vessels	Responsible for most of the direct actions of serotonin	Inotropic receptor (all others $5-HT$ receptors are G-protein coupled receptors)	Present in GIT Responsible for the increase in peristalsis
Modulates the release of serotonin		Ketanserin and ritanserin (antagonists) are useful as antihypertensive agents	Mediates most of the reflex and indirect actions of serotonin	
Partial agonist of this receptor (<i>buspirone, isapirone, gepirone</i>) are useful as anxiety drugs	Agonists at this receptor (<i>sumatriptan, naratriptan</i>) are useful for the treatment of acute migraine attacks	Clozapine and risperidone are atypical antipsychotic agents that act through antagonistic activity at this receptor.	Antagonists like <i>ondansetron, granisetron</i> and <i>tropisetron</i> are the agents of choice for chemotherapy induced vomiting	Agonists (<i>cisapride, mosapride, renzapride, tegaserod</i>) are useful in the treatment of gastroesophageal reflux disease

NON-SELECTIVE DRUGS

- **Cyproheptadine**: It blocks $5-HT_{2A}$, H_1 and muscarinic receptors. It increases appetite and can be used in children to *promote weight gain*.
- **Methysergide**: It is a $5-HT_{2A/2C}$ antagonist and a $5-HT_1$ agonist. It is indicated for the *prophylaxis of migraine attacks* but prolonged use can result in *pulmonary, endocardial and retroperitoneal fibrosis*.
- **LSD**: It is an ergot derivative and a *powerful hallucinogen*. It acts as an agonist at several serotonin receptors including $5-HT_{1A}$, $5-HT_{2A/2C}$ and $5-HT_{5-7}$ receptors.

Ergot derivatives can cause dry gangrene of hand and feet and coronary vasospasm.

Sumatriptan is the drug of choice for aborting acute attack of migraine.

Frovatriptan is the longest acting and rizatriptan is the fastest acting 5HT_{1B/1D} agonist.

Both triptans and ergot alkaloids can cause **coronary vasospasm** and are contraindicated in ischemic heart disease.

Triptans and ergotamine should not be administered within 24 hours of each other.

Propanolol is the most commonly used drug for prophylaxis of migraine attacks.

ERGOT ALKALOIDS

These are derived from a fungus *Claviceps purpurea*. Important compounds are *ergotamine*, *ergometrine* (ergonovine), *ergotoxine*, *bromocriptine*, *dihydroergotamine* and *methysergide*. These drugs possess partial agonistic and antagonistic effect at 5HT, α and dopaminergic receptors. **These drugs are only α blockers that can cause vasoconstriction** due to their partial agonistic activity on α and 5HT₂ receptors (maximum with ergotamine). **Hydrogenation of the compound decreases α agonistic activity but increases the α blocking potential.** Therefore dihydroergotamine has very little vasoconstricting activity. Ergot derivatives can cause dry gangrene of hand and feet as well as coronary vasospasm.

- **Ergotamine and dihydroergotamine** are used for the treatment of acute attack of migraine. These are contraindicated in patients with ischemic heart disease (due to their propensity to cause coronary vasospasm).
- **Dihydroergotoxine** (codeergocrine) is useful for the treatment of dementia.
- **Bromocriptine** is useful in Parkinsonism, hyperprolactinemia and acromegaly.
- **Methysergide** is useful for the prophylaxis of migraine attacks.

Migraine

It is unilateral pulsatile headache due to dilation and inflammation of the affected cerebral vessels. Mild and moderate attacks are usually controlled by NSAIDs whereas severe attacks require ergot alkaloids or triptans for termination.

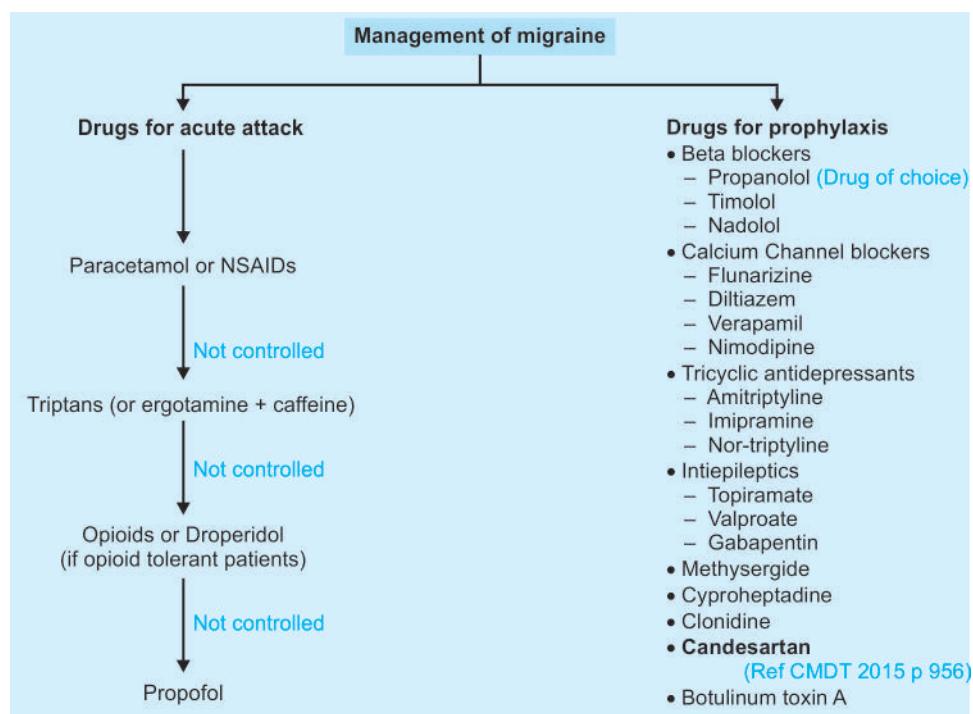
- **Ergotamine (oral/sublingual) or dihydroergotamine** (parenteral) can be used to abort acute attack of migraine. **Caffeine** enhances the absorption of ergotamine and is a powerful vasoconstrictor. It is usually combined with ergotamine. These drugs however, increase the nausea and vomiting during migraine attack.
- **Sumatriptan (subcutaneous)** is the drug of choice for aborting acute attack of migraine. It acts as a selective agonist at 5 HT_{1B/1D} receptors. It also suppresses the vomiting of migraine. It is a short acting drug and has low oral bioavailability. *Frovatriptan* is the longest acting and *rizatriptan* is the fastest acting congener. Other drugs useful are *zolmitriptan*, *eletriptan*, *naratriptan* and *almotriptan*. All of these drugs can cause **coronary vasospasm** and are contraindicated in ischemic heart disease. Triptans are also contra-indicated in patients with hypertension, epilepsy, pregnancy, liver and renal impairment. Triptans and ergotamine should not be administered within 24 hours of each other.
- Pharmacokinetic properties of triptans:

	Maximum	Minimum
• Oral bioavailability	Naratriptan	Sumatriptan
• Duration of action	Frovatriptan	Sumatriptan
• Onset of action	Rizatriptan (Fastest)	Frovatriptan (slowest)
• Plasma protein binding	Eletriptan	Sumatriptan

- For patients with history of CAD, triptans or ergotamine are contra-indicated, therefore opioids like intranasal butorphanol should be used for acute severe migraine.
- Prophylaxis of migraine is required if the attacks are frequent (>2-3 per month). The drugs useful for prophylaxis are:

- ❖ **Propanolol is the most commonly used drug** for prophylaxis of migraine attacks. Timolol, atenolol, metoprolol and nadolol can also be used but the drugs with ISA (e.g. pindolol) are ineffective.

- ❖ Calcium channel blockers like **flunarizine** (also blocks Na^+ channels) is also effective
- ❖ **Methysergide, cyproheptadine** and TCAs like amitriptyline can also be used.
- ❖ **Clonidine** can be used orally for the prophylaxis of migraine attacks.
- ❖ **Topiramate** (anticonvulsant drug) has recently been approved for prophylaxis of migraine. Valproate and gabapentin also possess some prophylactic activity.
- ❖ **Onabotulinum toxin A** has recently been approved for prophylaxis when headaches occur for more than 14 days per month. It is given every 12 weeks as multiple injections around the head and neck to try to dull future headache symptoms.



PROSTAGLANDINS

Prostaglandins and thromboxanes are synthesized from arachidonic acid (obtained from membrane phospholipids due to the action of phospholipase A_2 ; rate limiting enzyme) with the help of enzyme cyclooxygenase (COX).

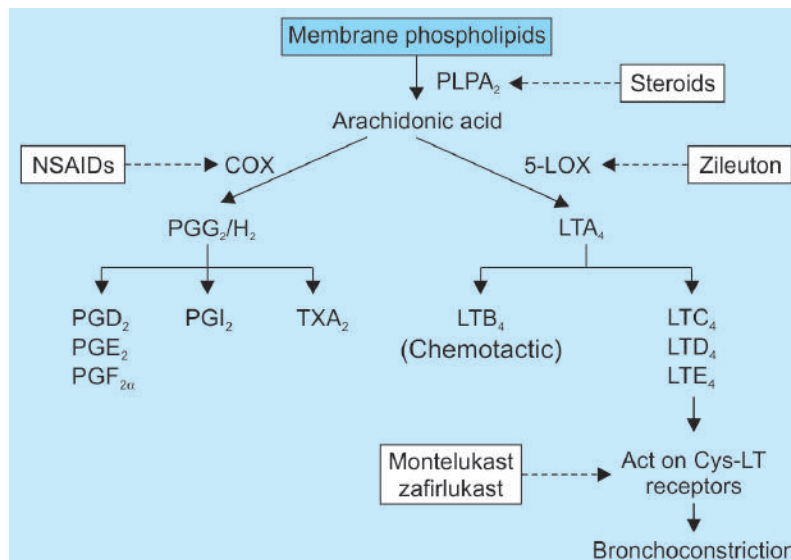


Phospholipase A_2 is rate limiting enzyme in synthesis of prostaglandins.

COX-1	COX-2	COX-3
• Constitutive (Always present in Cells) • Serves house-keeping function e.g. gastro-protection	• Inducible (Synthesis Simulated by endotoxins and other inflammatory mediators) • Participates in inflammation • Constitutive in brain, endothelium and kidney • Pro-carcinogenic due to inhibitory activity on apoptosis, stimulation of cell migration and invasiveness.	• Recently isolated from cerebral cortex • Involved in pain perception and fever • Not involved in inflammation • Paracetamol targets COX-3

COX acts on arachidonic acid to produce cyclic endoperoxides ($\text{PGG}_2/\text{PGH}_2$) in all cells. Further fate of these compounds depends on the presence of different enzymes in the cells. Platelets contain thromboxane synthetase and results in the production of TXA_2 whereas vascular endothelium contains prostacyclin synthase and thus produces PGI_2 . Various cells contain enzyme

isomerase and can convert cyclic endoperoxides to PGD_2 , PGE_2 and $\text{PGF}_{2\alpha}$. **Corticosteroids** inhibit the enzyme phospholipase A_2 by inducing the production of lipocortins (Now known as annexins). **NSAIDs** decrease PG and TX production by inhibiting COX.



Actions

CNS

PGE_1 and PGE_2 are pyrogenic and cause fever. NSAIDs act as antipyretic agents by inhibiting these PGs.

PERIPHERAL NERVE ENDINGS

PGE_2 and PGI_2 sensitize pain receptors to various mediators. NSAIDs act as analgesics by decreasing the synthesis of PGs.

CVS

- PGE_2 and PGI_2 are vasodilators whereas $\text{PGF}_{2\alpha}$ and TXA_2 are vasoconstrictor agents. *Epoprostenol* (PGI_2) and *treprostinil* (longer acting PGI_2 analogue) can be used for the treatment of pulmonary hypertension.
- PGE_2 increases capillary permeability.
- PGE_2 and PGI_2 keeps ductus arteriosus patent. In some congenital heart diseases (like transposition of great vessels), it becomes essential to **keep ductus arteriosus patent** before surgery. For this indication, *alprostadil* (PGE_1) and *epoprostenol* (PGI_2) can be given intravenously. If ductus arteriosus fails to close (**patent ductus arteriosus**) at birth, NSAIDs like aspirin and indomethacin are given to close it.

PLATELETS

- PGI_2 inhibits platelet aggregation whereas TXA_2 is a potent aggregator of platelets. Non-selective COX inhibitors inhibit the generation of both of these compounds. TXA_2 is synthesized in platelets and its synthesis cannot be resumed, once it is inhibited by NSAIDs (because platelets lack nuclei) whereas synthesis of PGI_2 resumes after sometime (endothelial cells can synthesize new COX). Net result of this process is inhibition of TXA_2 synthesis and *platelet anti-aggregation*.
- *Low dose aspirin* can be used as an *antiplatelet* drug for the prophylaxis of MI and stroke.
- *Epoprostenol* (PGI_2) can be used as an *anti-aggregatory* drug in dialysis and cardiopulmo-



Alprostadil is used to keep ductus arteriosus patent before surgery whereas NSAIDs like aspirin and indomethacin are used for treatment of. **Patent ductus arteriosus**

nary bypass. It can also be used for storage of platelets for transfusion.

M

PGI₂ Inhibits platelet aggregation whereas **TXA₂** is a potent aggregator of platelets.

UTERUS

- PGE₂ and PGF_{2α} are powerful uterine stimulants (contractor). *Dinoprostone (PGE₂) intravaginally and carboprost (PGF_{2α}) intraamniotic injection can be used for inducing mid trimester abortion. Misoprostol (PGE₁) along with methotrexate or mifepristone is used for induction of abortion in first few weeks of pregnancy.*
- PGE₂ causes softening of cervix (cervical ripening) during labour. *Dinoprostone or misoprostol intravaginally are employed for cervical ripening during labour.*
- *Carboprost (PGF_{2α}) can be used to control post partum hemorrhage (contraction of uterus leads to compression of blood vessels resulting in decreased bleeding).*
- PGs are responsible for pain during menstruation (*dysmenorrhoea*) and NSAIDs like *mefenamic acid* are useful for relieving this pain.
- Use of *misoprostol in pregnancy* is associated with *moebius synrome* (abnormal development of cranial nerves; most commonly VI and VII).

BRONCHUS

- PGI₂ and PGE₂ are bronchodilators and TXA₂ and PGF_{2α} are bronchoconstrictor agents.
- *Aerosolized PGE₂ has been used effectively to abort acute attacks of asthma.*
- COX inhibitors like aspirin cause more production of LTs (because due to enzyme inhibition arachidonic acid now produces only LTs). *Aspirin can result in precipitation of asthma attacks* because LTs are the main bronchoconstricting mediators in human asthma.



Recently it has been found that *aspirin acetylated COX-2 enzyme can convert arachidonic acid to 15-HETE (15-hydroxyeicosatetraenoic acid)*. In WBCs, 15-HETE is converted to epi-lipoxins (15-epi-LXA₄ or 15-epi-LXB₄). These are called **aspirin-triggered lipoxins** and have **powerful bronchoconstrictor** action. This finding can explain induction of asthma with aspirin but not by other COX-inhibitors.

GIT

- PGE₂ and PGI₂ decrease acid secretion and increase mucus production and mucosal blood flow. All these factors decrease the chances of peptic ulcer. NSAIDs on long term use can precipitate PUD due to inhibition of PG synthesis.
- *Misoprostol is the most specific drug for the treatment of peptic ulcer due to chronic NSAID use.* [Remember, the drug of choice is proton pump inhibitors]
- PGE₂ and PGF_{2α} cause *diarrhea and colicky pain* in the abdomen. These symptoms are important side effects of these drugs.
- PG seems to play some role in colonic cancer. *Regular use of aspirin or celecoxib decreases the risk of colonic polyps and cancers.*



Misoprostol is the most specific drug whereas proton pump inhibitors are drugs of choice for the treatment of peptic ulcer due to chronic NSAID use.

KIDNEY

- PGE₂ and PGI₂ cause *renal vasodilation, natriuresis* and increased water clearance due to inhibition of the action of ADH. These agents also *facilitate renin release*.
- Loop diuretics act partly by increasing the stimulation of COX; therefore NSAIDs *attenuate the diuretic action* of these drugs.
- **Bartter syndrome** is characterized by *excess PGs leading to hyperreninemia, excess aldosterone and the resultant hypokalemia and alkalosis*. **Indomethacin** is used for treatment of this syndrome.

MALE REPRODUCTIVE SYSTEM

PGE₂ and PGI₂ increases sperm motility and enhances penile erection. *Alprostadil can be used to treat erectile dysfunction.*

EYE

PGF_{2α} decreases intraocular pressure **by increasing the uveoscleral outflow**. Latanoprost (PGF_{2α}) is being used as eye drops for glaucoma. *Bimatoprost, travaprost and unoprostone are new prostaglandin analogues for this indication.*

Use of misoprostol in pregnancy is associated with Moebius syndrome

LEUKOTRIENES

These are synthesized from arachidonic acid with the help of the enzyme, 5-lipoxygenase. This enzyme must associate with **5-lipoxygenase activating protein (FLAP)** for leukotriene synthesis. First step is the production of LTA_4 that is converted either to LTB_4 or to cysteinyl leukotrienes (LTC_4 , D_4 and E_4). LTC_4 and LTD_4 are also known as **slow reacting substance of anaphylaxis (SRS-A)** due to their powerful bronchoconstricting action. LTB_4 is a powerful chemotactic agent and is an important mediator of all types of inflammation.

Action of LTs can be inhibited by:

- Corticosteroids (decrease the production of LTs by inhibiting phospholipase A_2)
- Lipoxygenase inhibitors (zileuton)
- LT receptor antagonists (zafirlukast, montelukast, iralukast)

PLATELET ACTIVATING FACTOR (PAF)

Lyso-PAF is produced by the action of phospholipase A_2 on cell membranes (phospholipase A_2 is also involved in the production of arachidonic acid). This substance is converted to **PAF** by acetylation. PAF is an important mediator of inflammation and allergy. It is the **most potent agent known to cause increase in the capillary permeability**.

Drugs affecting PAF are:

- Glucocorticoids decrease the production of PAF by inhibiting phospholipase A_2
- Apafant and lexipafant are PAF antagonists that are being investigated for the treatment of acute pancreatitis.

THROMBOXANE A_2

Drugs affecting TXA_2 are:

- COX inhibitors like **aspirin** decrease the synthesis of TXA_2
- **Daltroban** and **sultroban** are TXA_2 receptor antagonists.
- **Dazoxiben** inhibits the enzyme thromboxane synthetase.

NON STEROIDAL ANTI INFLAMMATORY DRUGS (NSAIDS)

NSAIDs act by inhibiting COX enzyme and thus prostaglandin synthesis. These drugs act as antipyretic, analgesic and anti-inflammatory agents. Prostaglandins play a protective role in the stomach and non-selective COX inhibitors can cause GI toxicity (peptic ulcer) on long term use.

Classification

- Non selective COX inhibitors (inhibit both COX 1 and COX 2)
- Preferential COX 2 inhibitors (inhibitory activity on COX 2 is greater than COX 1)
- Selective COX 2 inhibitors

NON SELECTIVE COX INHIBITORS

(a) Paracetamol (Acetaminophen)

It **does not possess anti-inflammatory activity** because it is ineffective in the presence of peroxides generated at the site of inflammation. Other explanation offered is **selective COX 3 inhibition** in the brain. It produces **very little GI toxicity** and can be administered in patients intolerant to other NSAIDs. It is metabolized to N-acetyl paraaminobenzo quinoneimine (NAPQ) by microsomal enzymes. This metabolite has high affinity for sulfhydryl groups and can combine with the enzymes and other biomolecules resulting in **hepatotoxicity**.

Normally acetaminophen is a safe drug because glutathione (contain sulfhydryl group due

PGF_{2α} decreases intraocular pressure **by increasing the uveoscleral outflow**.

Licofelone is combined COX-LOX inhibitor that is being investigated as a **disease modifying anti-osteoarthritis drug (DMAOAD)**.

to presence of sulfur containing amino acid, cysteine) produced by the liver combines with NAPQ to detoxify it. However chronic alcoholics are predisposed to toxicity because: Glutathione production decreases due to liver disease.

- Alcohol is a powerful inducer of microsomal enzymes. It increases the production of NAPQ from acetaminophen resulting in toxicity.

Paracetamol acts by inhibiting COX-3 in brain

Acetaminophen toxicity can be decreased by providing sulfhydryl donors like *N-acetylcysteine* (antidote of choice). Acetaminophen overdose constitutes medical emergency and 90% of patients will develop severe liver damage, if plasma concentration is **greater than 300 µg/ml at 4 hours or 45 µg/ml at 15 hours after ingestion**. Gastric lavage (with activated charcoal) should be done to prevent further absorption but it is **ineffective after 4 hours** of ingestion.

N-acetylcysteine is antidote of choice for paracetamol poisoning.

(b) Salicylates

Aspirin is the only **irreversible inhibitor** of COX enzyme (other salicylates are reversible inhibitors). Apart from antipyretic, analgesic and anti inflammatory effects, aspirin has several other indications.

- At low doses (40-325 mg)**, it acts as an *antiplatelet drug* and is useful in the prophylaxis of myocardial infarction and stroke. It acts by inhibiting cyclooxygenase enzyme and thus decreasing the synthesis of TXA₂ (platelet aggregator). However it also inhibits PGI₂ (anti-aggregatory) synthesis. Net effect is to decrease TXA₂ synthesis because:

- ❖ TXA₂ is synthesized by *platelets* and these are *exposed to aspirin in the portal circulation*. Here, it acetylates COX enzyme and irreversibly inhibits the generation of TXA₂. Very little aspirin reaches the systemic circulation to inhibit PGI₂ synthesis.
- ❖ *Platelets lack nuclei* and cannot synthesize new COX enzyme once it is inhibited whereas endothelium can regenerate COX enzyme to produce PGI₂. Net effect is thus inhibition of TXA₂ generation.

- Aspirin and indomethacin are useful for the closure of ductus arteriosus in children with **PDA** (Alprostadil is used to keep it patent).
- Aspirin is used to **inhibit niacin induced flushing** (it is PG mediated).
- It is also useful in *dysmenorrhoea and pre-eclampsia*.
- COX-2 inhibitory action is responsible for *decreased incidence of colorectal carcinoma* in patients on long term aspirin therapy.

Paracetamol (acetaminophen) has no anti-inflammatory activity and **Nimesulide and nefopam** do not act by decreasing PG synthesis

Adverse Effects

- Salicylates can cause **dose dependent effects on acid base balance**. Respiratory alkalosis occurs first characterized by *headache, vertigo, tinnitus, vomiting and hyperventilation* (salicylism). Excessive metabolic compensation can result in **metabolic acidosis** manifested as loss of vision, hyperpyrexia, vasomotor collapse, dehydration, convulsions and coma. Chances of metabolic acidosis are **more in infants** because early symptoms like tinnitus and vertigo are frequently missed. *Salicylate poisoning is treated by supportive measures, gastric lavage, correction of metabolic acidosis and urinary alkalinization to increase the excretion.*
- Aspirin can **prolong bleeding time** and should be used cautiously with anticoagulants.
- At therapeutic doses, it can cause hyperuricemia** by decreasing the excretion of uric acid. It, therefore, should not be used in patients with gout. It also decreases the uricosuric action of probenecid. At high doses (>5 g/d), it increases the excretion of uric acid, but such high doses are not tolerated.
- Aspirin is **contraindicated in children (<12 yrs old)** due to **increased risk of Reye's syndrome**.

Aspirin is the only **irreversible inhibitor** of COX enzyme

At low doses (40-325 mg), it acts as an *antiplatelet drug*.

Aspirin is contraindicated in children (<12 yrs old) due to increased risk of **Reye's syndrome**.

Sulindac and **nabumetone** are *prodrugs*.

Ketorolac is the *only NSAID* that can be used *i.v.*

Piroxicam and **tenoxicam** are *longest acting NSAIDs* due to *enterohepatic cycling*.

Rofecoxib and **valdecoxib** were *withdrawn* due to *increased risk of thrombotic disorders like myocardial infarction*.

(c) Other Non-selective COX Inhibitors

- **Indomethacin** inhibits $PLPA_2$ and possesses immunosuppressive properties apart from its COX inhibitory action. It causes more GI upset than other NSAIDs. It is implicated in causing *headache* (analgesic causing pain) and *sedation*. Treatment with *indomethacin*, combined with *potassium repletion* and *spironolactone* is associated with *improvement* in the symptoms and biochemical derangements of *Bartter's syndrome*.
- **Phenylbutazone** causes agranulocytosis due to bone marrow suppression.
- Propionic acid derivatives include **ibuprofen**, **ketoprofen** and **flurbiprofen**. Ketoprofen possesses additional lysosomal stabilizing action and flurbiprofen can be used topically as eye drops. Ibuprofen has been cleared for paediatric patients.
- **Naproxen** and **oxaprozin** are long acting drugs that also inhibit leucocyte migration.
- **Mefenamic acid** also possesses PG receptor antagonistic and $PLPA_2$ inhibitory activity. It is very useful in dysmenorrhoea.
- **Phenacetin** (prodrug of paracetamol) is implicated in causing analgesic nephropathy.
- **Ketorolac** is the only NSAID that can be used *i.v.* It is also available as eye drops. Course longer than 5 days is not recommended.
- **Piroxicam** and **tenoxicam** are longest acting NSAIDs due to enterohepatic cycling. **Oxaprozin** is another very long acting NSAID.
- **Apazone** possess potent uricosuric activity. It is indicated in conditions, in which other NSAIDs have failed.

PREFERENTIAL COX-2 INHIBITORS

These drugs have more inhibitory action on COX-2 than COX-1. Drugs included in this group are **nimesulide** (*potential of causing hepatotoxicity*), meloxicam, **nabumetone** (*prodrug*), etodolac and diclofenac. *All NSAIDs are acidic in nature except nabumetone*. Relatively less GI toxicity is experienced with the use of these drugs.

SELECTIVE COX-2 INHIBITORS

These drugs have advantage of **very little GI toxicity**. However renal toxicity is similar and **chances of thrombosis** (acute MI and stroke) are **increased on prolonged use**. *Rofecoxib and valdecoxib were withdrawn due to increased risk of thrombotic disorders like myocardial infarction*.

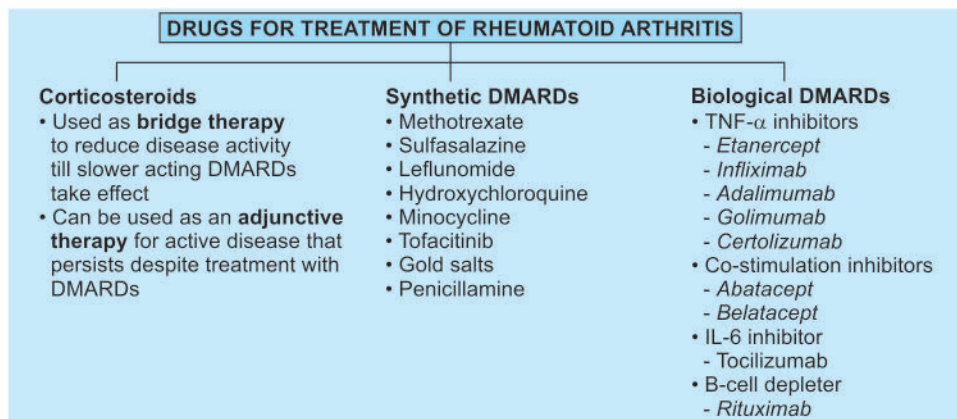
- Celecoxib, rofecoxib and valdecoxib are sulfonamide derivatives, thus can cause rash and hypersensitivity.
- **Etoricoxib** is *longest acting coxib* and monitoring of hepatic function is must during its use.
- **Lumiracoxib** is a newer COX 2 inhibitor that has *more activity in the acidic medium*
- **Parecoxib** is a prodrug of valdecoxib that can be administered parenterally.

Note:

- All NSAIDs are weak acids *except nabumetone*.
- All NSAIDs are racemic mixtures except naproxen (present as single enantiomer) and diclofenac (have no chiral center).
- Nephrotoxicity and hepatotoxicity may occur with any NSAID.
- All NSAIDs are almost equally efficacious except
 - Tolmetin is not effective in gout.
 - Aspirin is less effective for ankylosing spondylitis.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune multisystem disease. *NSAIDs are used to provide symptomatic relief but exert no effect on the progression of the disease.* Disease modifying anti rheumatoid drugs (DMARDs) slow the progression of disease but act slowly (takes 6 weeks to 6 months).



A. Corticosteroids

Low-dose corticosteroids can be used as a bridge therapy (until DMARDs start to work) or as adjunctive therapy (with DMARDs) in rheumatoid arthritis

B. Synthetic DMARDs

1. Methotrexate

It is **first choice DMARD** and is used at much lower doses (7.5 mg weekly) than required in cancer chemotherapy (30 mg daily).

Adverse effects of methotrexate

- Gastric irritation and stomatitis (most common)
- Pancytopenia
- Hepatotoxicity with fibrosis and cirrhosis **Risk factors are:**
 - ❖ Chronic hepatitis
 - ❖ Heavy alcohol consumption
 - ❖ Diabetes mellitus
 - ❖ Obesity
 - ❖ Kidney disease
- Interstitial pneumonitis (Hypersensitivity reaction)
- Teratogenicity
- Increased risk of B-cell lymphomas
- Amoxicillin and probenecid increase risk of methotrexate toxicity

2. Sulfasalazine

It is metabolized to *sulfapyridine* and *5-aminosalicylic acid*. Former is the active moiety in RA and latter is useful for ulcerative colitis. It is used in patients when methotrexate is contraindicated.

3. Leflunomide

It is a **prodrug** (converted in the body to an active metabolite) that **inhibits the enzyme dihydro orotate dehydrogenase**. This enzyme is required for pyrimidine synthesis and thus growth of B cells is arrested by leflunomide. *Cholestyramine decreases its toxicity by enhancing its clearance.* It is *faster acting* (action is manifested in 4 weeks as compared to 3 months with

Methotrexate is first choice DMARD

Leflunomide is a prodrug (converted in the body to an active metabolite) that inhibits the enzyme dihydro orotate dehydrogenase.

Teriflunomide is dihydro-orotate dehydrogenase inhibitor (like leflunomide). It is indicated for relapsing-remitting multiple sclerosis.



Hydroxychloroquine is the safest DMARD in pregnancy.

other DMARDs) *alternative to methotrexate*.

4. Chloroquine and hydroxychloroquine

These antimalarial drugs are also useful as DMARDs. Hydroxychloroquine is preferred over chloroquine due to less chances of retinal damage by the former.

5. Minocycline

It is reserved for early mild cases and works better during the first year of RA. Mechanism of action is not clear but it has anti-inflammatory property including the ability to inhibit collagenase. Most common adverse effect of minocycline is dizziness.

6. Tofacitinib

It is an inhibitor of Janus kinase 3. Tofacitinib is approved for severe RA refractory to methotrexate. It is effective orally. Like TNF- α inhibitors, screening of patients for latent TB must be done prior to receiving the drug.



Tofacitinib is an inhibitor of Janus kinase 3 and is approved for severe rheumatoid arthritis refractory to methotrexate. It can be given orally.

7. Old drugs

Gold and D-penicillamine are highly efficacious DMARDs but are rarely used now due to severe toxic reactions. Gold salts can be used orally (auranofin) as well as intramuscularly (aurothiomalate). *Dermatitis is the most common adverse effect seen with gold salts*. These can also result in kidney and liver damage, peripheral neuropathy, pulmonary fibrosis, encephalopathy and bone marrow depression.

C. Biological DMARDs

1. TNF- α blocking agents

TNF- α plays a major role in the joint destruction in patients with RA. Five drugs **etanercept** (s.c.), **adalimumab** (s.c.), **infliximab** (i.v.), **golimumab** (s.c.) and **certolizumab** (s.c.) act as DMARDs by blocking the action of TNF- α . These drugs can cause *activation of latent tuberculosis*. **Infliximab** is also indicated in *Crohn's disease, psoriatic arthritis, Wegener's granulomatosis and sarcoidosis*.

TNF- α blockers in Rheumatoid arthritis

Drug	Dose	Route	Frequency
Infliximab	3–10 mg/kg	Intravenous	0,2,6,10,14 weeks, then every 8 weeks
Etanercept	50 mg	Subcutaneous	Weekly
Adalimumab	40 mg	Subcutaneous	Once in 2 weeks
Golimumab	50 mg	Subcutaneous	Monthly
Certolizumab	200-400 mg	Subcutaneous	Every 2-4 weeks

2. Co-stimulation inhibitors

Abatacept and **belatacept** act by inhibiting CD80 and CD86 co-stimulatory molecules on antigen presenting cells. Interaction of these with CD 28 on T-cells is necessary for T-Cell activation. These are indicated for RA resistant to combination of methotrexate and TNF- α inhibitors.



Abatacept is a co-stimulation inhibitor indicated for severe refractory rheumatoid arthritis.

3. Tocilizumab

It is a monoclonal antibody against IL-6. It is approved for RA in combination with methotrexate.

4. Rituximab

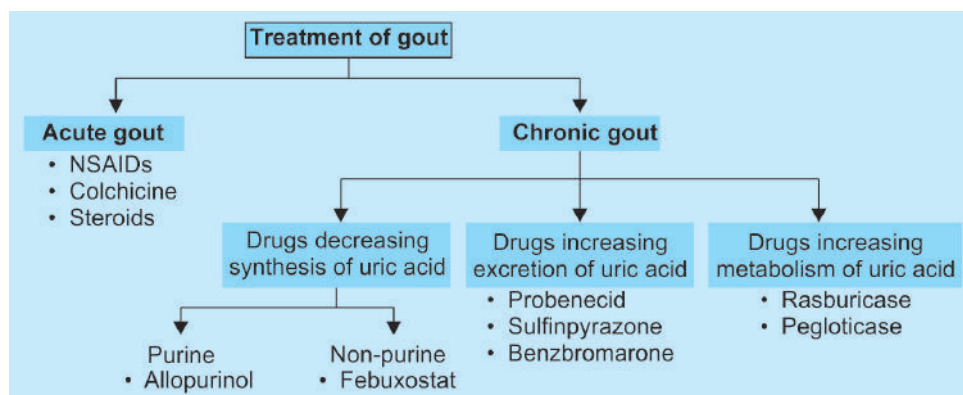
It is a monoclonal antibody that depletes B-cells and is used for RA in combination with methotrexate

Disease Modifying Anti-Osteoarthritis Drugs (DMAOAD)

Osteoarthritis is treated by NSAIDs but these do not arrest the disease progression or joint destruction. Recently two compounds; **Diacerin (IL-1 antagonist)** and **Licofelone (combined COX-LOX inhibitor)** have been developed to slow the progression of the disease.

Gout

It is a disease characterized by elevated serum uric acid level. Uric acid has low water solubility and gets precipitated in the joints, kidney and subcutaneous tissues. Secondary hyperuricemia may result due to excessive production (breakdown of proteins and nucleic acids during cancer chemotherapy) or decreased excretion (due to the use of thiazides, loop diuretics, ethambutol, clofibrate etc.) of uric acid.



ACUTE GOUT

It is manifested as severe inflammation of joints (due to precipitation of uric acid crystals)

- **NSAIDs** like indomethacin are *drug of choice* due to better tolerability. **Aspirin is not used** as it may cause hyperuricemia. **Tolmetin is not effective.**
- **Colchicine** is *more effective and faster acting* than NSAIDs but is used rarely due to its high toxicity. It acts by inhibiting granulocyte migration into the inflamed joint. It causes *metaphase arrest* (other drugs causing metaphase arrest are *vinca alkaloids, ixabepilone and taxanes*). Most common and dose limiting toxicity is *diarrhea*. It can also cause *kidney damage, myopathy and bone marrow depression*.
- Two indications for daily colchicine are:
 - ❖ To prevent further attacks
 - ❖ Along with urate-lowering therapy to suppress attacks precipitated by abrupt changes in serum uric acid
- Intra-articular corticosteroids can be used in the refractory cases.
- IL-1 inhibitors like **anakinara**, **canakinumab** and **rilonacept** have efficacy for management of acute gout but are not FDA-approved for this indication (Ref. - CMDT-2015, pg 814)

CHRONIC GOUT

Strategies to decrease uric acid in the serum are to *decrease the synthesis or to increase the excretion and metabolism*.

NSAIDs like indomethacin are drug of choice for acute gout

Colchicine is *more effective and faster acting* than NSAIDs

Uses of Colchicine

U – Uric acid raised [Prophylaxis of recurrent attacks of gouty arthritis]
C – Cirrhosis
M – Mediterranean fever [Acute]
S – Sarcoid arthritis

Dose of 6-Mercaptopurine and azathioprine should be decreased when given with allopurinol.

Drugs decreasing uric acid synthesis are contra-indicated in acute gout

Plenty of fluids and urinary alkalinizers should be given with probenecid to prevent precipitation of uric acid crystals in the kidney tubules.

Makes
 Xanthine
 Oxidase
 STATic
 FebuXOSTAT

M

Recombinant
Bird's
Uricase
Ras b uricase

Drugs Decreasing Synthesis

Allopurinol (hypoxanthine analog) and recently approved drug, **febuxostat** (a non-purine drug) decrease the production of uric acid by *inhibiting the enzyme xanthine oxidase*. Allopurinol is metabolized by the same enzyme to alloxanthine which is a long acting inhibitor of xanthine oxidase. These are indicated as **drug of choice for chronic gout** in the inter-critical period (between two acute attacks) and also with anticancer drugs (to decrease secondary hyperuricemia). 6-Mercaptopurine and *azathioprine* are metabolized by xanthine oxidase; therefore *dose of these drugs should be decreased* when given with allopurinol. *Allopurinol is also used as an adjuvant to sodium stibogluconate in the treatment of kala azar*. **It is contra-indicated in acute gout** because uric acid has inhibitory effect on release of cytokines and allopurinol may aggravate the inflammation by reducing uric acid.

- Most frequent adverse effect with xanthine oxidase inhibitors is precipitation of acute attack of gout.
- There is strong association between HLA-B*5801 and allopurinol hypersensitivity
- Combined use of allopurinol and ampicillin causes a drug rash in 20% of patients.
- Allopurinol requires dose adjustment in renal failure whereas febuxostat can be administered without dose adjustment.
- Febuxostat can result in abnormal liver function tests

Drugs Increasing Excretion

Probenecid, sulfinpyrazone and benzbromarone acts as competitive inhibitors of reabsorption of uric acid in proximal tubules. Plenty of fluids and urinary alkalinizers should be given concurrently to prevent precipitation of uric acid crystals in the kidney tubules. These drugs are *ineffective in the presence of renal damage*. Probenecid is also used along with penicillins to decrease their renal excretion.

- **Uricosuric drugs should not be used if**
 - ❖ Creatinine clearance is <50ml/min.
 - ❖ History of nephrolithiasis (uric acid or calcium stones)
 - ❖ Evidence of overproduction of uric acid (> 800 mg of uric acid in a 24-hour urine collection)

Drugs Increasing Metabolism

Urate oxidase (uricase) metabolizes insoluble uric acid to soluble allantoin in the birds. This enzyme is absent in humans. *Recombinant urate oxidase is now available as rasburicase*. **Pegloticase** is another similiar drug that is pegylated to increase duration of action. Pegloticase and rasburicase are administered by i.v. route and are indicated only in patients with chronic gout refractory to other treatments.

DRUG OF CHOICE	
Condition	Drug of choice
• Migraine	
– Acute-mild to moderate	NSAIDs
– Acute-severe	Sumatriptan
– Prophylaxis	Propanolol
• Abortion < 7 weeks	Mifepristone + misoprostol
• Induction of labour	Oxytocin
• Post-partum hemorrhage	Oxytocin
• Cervical priming	Misoprostol
• NSAID-induced peptic ulcer	Proton pump inhibitors
• Open angle glaucoma	Latanoprost
• To maintain patency of ductus arteriosus	Alprostadil
• Treatment of patent ductus arteriosus (PDA)	Indomethacin
• Bartter syndrome	Indomethacin
• Pulmonary hypertension	Oral diltiazem or amlodipine or nifedipine
• Erectile dysfunction	Sildenafil
• Rheumatoid arthritis	
– Pain relief	NSAIDs
– Bridge therapy	Corticosteroids
– DMARD	Methotrexate
• Flushing due to nicotinic acid	Aspirin
• Prophylaxis of MI and stroke	Aspirin
• Acetaminophen (Paracetamol) poisoning	N-Acetyl cysteine
• Anaphylactic shock	Adrenaline
• Acute mediterranean fever	Colchicine
• Cancer chemotherapy induced vomiting	5HT ₃ antagonists like ondansetron
• Cisplatin induced vomiting	
– Early	Ondansetron
– Delayed	Aprepitant
• Gout	
– Acute	NSAIDs except aspirin
– Refractory acute	Colchicine
– Chronic	Allopurinol
– Chronic (in patient allergic to allopurinol)	Febuxostat
• Hyperuricemia secondary to anticancer drugs	Allopurinol

MULTIPLE CHOICE QUESTIONS

HISTAMINE AND SEROTONIN

- Which is not a 2nd generation anti-histaminic agent? *(AIIMS Nov 2012)*
 - Cetirizine
 - Cyclizine
 - Loratidine
 - Fexofenadine
- A peptide that causes increased capillary permeability and edema is? *(AI 2012)*
 - Histamine
 - Angiotensin II
 - Bradykinin
 - Renin
- Ergometrine is commonly used for: *(MPPG 2003)*
 - Post Partum Hemorrhage
 - To shorten 2nd stage of labour
 - Dysmenorrhea
 - Toxemia of pregnancy
- A highway truck driver has profuse rhinorrhoea and sneezing. Which amongst the following drugs would you prescribe him? *(AI 2002)*
 - Pheniramine
 - Promethazine
 - Dimenhydrinate
 - Cetirizine
- Which of the following is NOT a second generation antihistaminic? *(AIIMS, May 2008, AIIMS Nov 2006)*
 - Cyclizine
 - Fexofenadine
 - Loratidine
 - Acrivastine
- The H_3 receptor agonist exhibits all of the following actions EXCEPT: *(AIIMS Nov, 2002)*
 - Inhibition of H_1 receptor induced wakefulness
 - Increase in H_1 mediated gastrin secretion
 - Inhibition of H_1 mediated bronchoconstriction
 - Negative chronotropic effect on atria
- Second generation anti-histaminics used in allergic rhinitis are: *(PGI June, 2003)*
 - Azelastine
 - Fexofenadine
 - Chlorpheniramine maleate
 - Desloratidine
 - Promethazine
- All of the following actions of histamine are mediated through H_1 receptors EXCEPT:
 - Release of EDRF from vascular endothelium resulting in vasodilation
 - Direct action on vascular smooth muscle causing vasodilation
 - Bronchoconstriction
 - Release of catecholamines from adrenal medulla
- Which of the following drugs can cause hypotension by release of histamine from mast cells?
 - Aspirin
 - Procaine
 - Morphine
 - Sulfadiazine
- All of the following antihistaminic agents lack anticholinergic property EXCEPT:
 - Promethazine
 - Astemizole
 - Levo-cetirizine
 - Loratidine
- The drug possessing antagonistic action at histamine, serotonin and muscarinic receptors is:
 - Promethazine
 - Terfenadine
 - Cyproheptadine
 - Hydroxyzine
- Mr. Surya Kant was prescribed a first generation H_1 antihistaminic drug. He should be advised to avoid:
 - Driving motor vehicles
 - Consuming processed cheese
 - Strenuous physical exertion
 - All of the above
- All of the following statements are TRUE about second generation antihistaminic agents EXCEPT:
 - These do not impair psychomotor performance
 - These possess high anti-motion sickness activity
 - These lack anticholinergic actions
 - These may possess additional antiallergic mechanisms
- This antihistaminic drug can cause cardiac arrhythmia at high dose by blocking cardiac K^+ channels. It is most likely to be:
 - Levo-cetirizine
 - Fexofenadine
 - Astemizole
 - Loratidine

15. Anti-vertigo drug which modulates calcium channels and has prominent labyrinthine suppressant property is:
 - (a) Cyproheptadine
 - (b) Cinnarizine
 - (c) Clemastine
 - (d) Cetirizine
16. Ketoconazole should not be given to a patient being treated with astemizole because:
 - (a) Ketoconazole induces the metabolism of astemizole
 - (b) Dangerous ventricular arrhythmias can occur
 - (c) Astemizole inhibits the metabolism of ketoconazole
 - (d) Astemizole antagonizes the antifungal action of ketoconazole
17. True statement about fexofenadine is:
 - (a) It undergoes high first pass metabolism in liver
 - (b) Terfenadine is an active metabolite of this drug
 - (c) It does not block cardiac K^+ channels
 - (d) It has high affinity for central H_1 receptors
18. H_1 antihistaminic having best topical activity is:
 - (a) Loratidine
 - (b) Cetirizine
 - (c) Astemizole
 - (d) Azelastine
19. All 5-HT receptors are heptahelical serpentine receptors EXCEPT:
 - (a) $5-HT_1$
 - (b) $5-HT_2$
 - (c) $5-HT_3$
 - (d) $5-HT_4$
20. Which of the following serotonergic receptors is an autoreceptor?
 - (a) $5-HT_{1A}$
 - (b) $5-HT_{1B/1D}$
 - (c) $5-HT_{2A}$
 - (d) $5-HT_3$
21. Most important receptor involved in chemotherapy induced vomiting is:
 - (a) Histamine H_1 receptor
 - (b) Serotonin $5-HT_3$ receptor
 - (c) Dopamine D_2 receptor
 - (d) Opioid μ receptor
22. Selective $5-HT_4$ agonist useful in gastroesophageal reflux disease and lacking arrhythmogenic property is:
 - (a) Buspirone
 - (b) Sumatriptan
 - (c) Cisapride
 - (d) Tegaserod
23. Which of the following can reverse one or more smooth muscle effects of circulating histamine in humans?
 - (a) Granisetron
 - (b) Adrenaline
 - (c) Ranitidine
 - (d) Sumatriptan
24. H_1 antihistaminics afford benefit in a number of conditions. All of the following conditions are benefited by antagonism of histamine EXCEPT:
 - (a) Dermographism
 - (b) Insect bite
 - (c) Common cold
 - (d) Seasonal hay fever
25. Two antihistaminics terfenadine and astemizole were withdrawn from the market following the occurrence of cardiac arrhythmias when they were present in high levels in the blood. These effects were explained by the fact:
 - (a) Use of these drugs by addicts
 - (b) Genetic predisposition to metabolize succinylcholine slowly
 - (c) Concurrent treatment with phenobarbital
 - (d) Treatment of these patients with erythromycin, a macrolide antibiotic
26. The non sedative antihistamines are all EXCEPT one:

(Karnataka 2009 DPG 2003, Karnataka 2007)

 - (a) Fexofenadine
 - (b) Desloratidine
 - (c) Levocetirizine
 - (d) Cinnarizine
27. Ketanserin is:

(DPG 1999)

 - (a) $5HT_{1B}$ antagonist
 - (b) $5HT_2$ antagonist
 - (c) $5HT_{1A}$ agonist
 - (d) $5HT_{1D}$ antagonist
28. The long acting classical H_1 antihistaminic include which of the following?

(TN 2004)

 - (a) Chlorpheniramine
 - (b) Astemizole
 - (c) Cetirizine
 - (d) Clemastine
29. Which of the following drugs, if given with terfenadine, can cause ventricular arrhythmias?

(MH 2002)

 - (a) Ketoconazole
 - (b) Griseofulvin
 - (c) Ampicillin
 - (d) Sparfloxacin
30. One of the following is not a 5-HT receptor antagonist:

(MP 2009)

 - (a) Ketanserin
 - (b) Lanreotide
 - (c) Methysergide
 - (d) Tropisetron
31. Antihistaminic used in motion sickness is:

(Kolkata 2008)

 - (a) Cetirizine
 - (b) Meclizine
 - (c) Diphenhydramine
 - (d) Fexofenadine
32. Ondansetron is a potent:

(Karnataka 2001)

 - (a) Antiemetic
 - (b) Anxiolytic

- (c) Analgesic
- (d) Antidepressant

33. Fexofenadine is metabolic product of: (Karnataka 2000)

- (a) Loratidine
- (b) Astemizole
- (c) Cetirizine
- (d) Terfenadine

34. Cisapride is useful in: (Karnataka 2000)

- (a) Gastroesophageal reflux disease
- (b) Gastrointestinal spasm
- (c) Carcinoid syndrome
- (d) Gastrointestinal hypermotility

35. Histamine blocker in stomach act through:

- (a) Decreasing cAMP in stomach (Bihar 2004)
- (b) Increasing cAMP in stomach
- (c) Increasing IP3 in stomach
- (d) Decreasing IP3 in stomach

ERGOT ALKALOIDS AND MIGRAINE

36. After taking some drug for acute attack of migraine, a patient developed nausea and vomiting. He also developed tingling and numbness in the tip of the finger that also turned blue. Which of the following is the most likely drug implicated in causing the above findings?

- (a) Dihydroergotamine (AI 2012)
- (b) Sumatriptan
- (c) Aspirin
- (d) Butorphanol

37. Drugs used in prophylaxis of migraine are all except? (AI 2010)

- (a) Propranolol
- (b) Flunarizine
- (c) Topiramate
- (d) Levetiracetam

38. All of the following can be used for prophylaxis of migraine except: (AI 2010)

- (a) Sumatriptan
- (b) Valproate
- (c) Propranolol
- (d) Topiramate

39. Drugs used for prophylaxis of migraine is/are:

- (a) Flunarizine (PGI Dec. 2004)
- (b) Cinnarizine
- (c) Beta blocker
- (d) Sodium valproate
- (e) Carbamazepine

40. Which of the following is most useful for reversing severe ergot induced vasospasm?

- (a) Ergotamine
- (b) Methysergide
- (c) Nitroprusside
- (d) Phenoxybenzamine

41. Selective 5-HT_{1B/1D} receptor agonist useful in acute migraine is:

- (a) Buspirone
- (b) Ondansetron
- (c) Frovatriptan
- (d) Ketanserin

42. Which of the following adverse effects is characteristically associated with methysergide?

- (a) Pulmonary hypertension
- (b) Retroperitoneal fibrosis
- (c) Hepatotoxicity
- (d) Ischemic heart disease

43. Dihydroergotamine differs from ergotamine in the following respect:

- (a) It is a more potent oxytocic
- (b) It has antiemetic property
- (c) It has high oral bioavailability
- (d) It is more potent α adrenergic blocker and less potent vasoconstrictor

44. Ergot alkaloid commonly used to prevent post-partum hemorrhage is:

- (a) Methyl ergometrine
- (b) Ergotamine
- (c) Dihydroergotamine
- (d) Dihydroergotoxine

45. Choose the CORRECT statement about sumatriptan:

- (a) It activates 5-HT_{1A} receptors
- (b) It tends to suppress both pain and vomiting in migraine
- (c) It does not carry risk of precipitating coronary vasospasm
- (d) It is combined with ergotamine for the treatment of severe migraine

46. Which of the following drugs is used for the prophylaxis of migraine but not for angina pectoris?

- (a) Verapamil
- (b) Diltiazem
- (c) Flunarizine
- (d) Amlodipine

47. Drugs used in migraine prophylaxis are all except:

- (a) Flunarizine (DPG 2010, DNB 2007, Kolkata 2005)
- (b) Propranolol
- (c) Cyproheptadine
- (d) Sumatriptan

48. Sumatriptan is used in:

- (a) Mania (DPG 2000)
- (b) Depression
- (c) Schizophrenia
- (d) Migraine

49. **Sumatriptan is:** (DPG 1999, TN 2004, MH-2007)
 (a) 5HT_{1D} antagonist
 (b) 5HT_{1A} agonist
 (c) 5HT_{1D} agonist
 (d) 5HT_{1A} antagonist
50. **Drug of choice in acute severe migraine is:** (IIP 2008, Jharkhand 2005)
 (a) Ergotamine
 (b) Sumatriptan
 (c) Dihydroergotamine
 (d) Propranol
51. **Methyl ergometrine is used in the prophylaxis of** (TN 2000)
 (a) Migraine
 (b) Postpartum hemorrhage
 (c) PIH
 (d) None of the above
52. **Which one of the following is true about sumatriptan?** (TN 2005)
 (a) Antagonist of serotonin
 (b) Interacts with alpha and beta adrenergic receptors
 (c) Has antimigraine activity
 (d) Can be used in a patient with ischaemic heart disease
- (c) Prothrombin time
 (d) Activated partial thromboplastin time:
58. **Misoprostol is a:** (AI 2006)
 (a) Prostaglandin E₁ analogue
 (b) Prostaglandin E₂ analogue
 (c) Prostaglandin antagonist
 (d) Antiprogesterin
59. **All of the following are correct statements EXCEPT:**
 (a) PGs and leukotrienes are derived from arachidonic acid (AI 2001)
 (b) COX II is induced by cytokines at the site of inflammation
 (c) COX I is an inducible enzyme
 (d) Leukotrienes cause smooth muscle contraction
60. **Which NSAID undergoes enterohepatic circulation?** (AIIMS Nov 2006)
 (a) Phenylbutazone
 (b) Aspirin
 (c) Ibuprofen
 (d) Piroxicam
61. **A 20 yr old female weighing 55kg is admitted to the emergency department having consumed 10 g of paracetamol together with alcohol 6 hrs earlier. A serum paracetamol level is reported as 400 micrograms/ml. Which of the following is correct with respect to this?** (AIIMS Nov, 2004)
 (a) Gastric lavage is mandatory
 (b) Administration of activated charcoal
 (c) Abnormalities of the kidney function are likely to be present
 (d) Hepatotoxicity is likely to occur
62. **Prostaglandins have effects on a variety of tissues. The different prostaglandins may have different effects. Which of the following statements is NOT correct?** (AIIMS Nov, 2002)
 (a) The human arteriolar smooth muscle is relaxed by PGE₂ and PGI₂ whereas TXA₂ and PGF_{2α} cause vasoconstriction
 (b) PGE₁ and PGI₂ inhibit platelet aggregation whereas TXA₂ facilitate aggregation
 (c) PGE₂ has marked oxytocic action while PGF_{2α} has tocolytic action
 (d) PGE₂ is a bronchodilator whereas PGF_{2α} is a bronchoconstrictor
63. **Therapeutic uses of prostaglandin E₁ include all of the following EXCEPT:** (AIIMS Nov, 2002)
 (a) Medical termination of pregnancy
 (b) Impotence
 (c) Primary pulmonary hypertension
 (d) Maintenance of patent ductus arteriosus
64. **True statements about TXA₂ is:** (PGI Dec. 2007)
 (a) It is formed in platelets
 (b) It is formed from PGG₂/H₂
 (c) It is prothrombotic
 (d) It is having platelet anti-aggregatory activity
 (e) Aspirin can inhibit its production

■ EICOSANOIDS AND NSAIDS

53. **Which of the following statements is NOT TRUE about NSAIDs?** (AIIMS May, 2005)
 (a) Acetyl salicylic acid is an irreversible inhibitor of COX enzyme.
 (b) Acetylsalicylic acid reduces in vivo synthesis of prostaglandins.
 (c) Its clearance is independent of plasma concentration
 (d) Antiplatelet effect of low dose aspirin is related to pre-systemic COX inhibition
54. **The therapeutic efficacy of antihypertensive drugs is blunted by NSAIDs because they:** (DPG-2011)
 (a) Cause sodium excretion
 (b) Increase the clearance of antihypertensive drugs
 (c) Decrease the absorption of antihypertensive drugs
 (d) Decrease the synthesis of vascular prostacyclin
55. **Aspirin should be used with caution in the following groups of patients because of which of the following reason:** (DPG-2011)
 (a) In diabetics because it can cause hyperglycemia
 (b) In children with viral disease, because of the risk of acute renal failure
 (c) In gout, because it can increase serum uric acid
 (d) In pregnancy, because of high risk of teratogenicity
56. **Aspirin inhibits which of the following enzymes?** (DPG 2009)
 (a) Lipoprotein lipase
 (b) Lipoxigenase
 (c) Cyclooxygenase
 (d) Phospholipase D
57. **A patient on aspirin will have increase in:** (AI 2007)
 (a) Bleeding time
 (b) Clotting time

65. True statements regarding aspirin toxicity are: (PGI June, 2006)
- Tinnitus is an early symptom
 - 10-30 g causes poisoning
 - Hyperthermia, tachypnea are early complications
 - Cause thrombocytopenic purpura
 - Children can tolerate much higher dose than adults
66. COX pathway is inhibited by: (PGI June, 2002)
- Aspirin
 - Indomethacin
 - Betamethasone
 - Calcitonin
 - Diclofenac
67. Which of the following is/are cyclo-oxygenase inhibitors: (AP 2003, PGI June, 2001)
- Aspirin
 - Prednisolone
 - Indomethacin
 - Betamethasone
 - Rofecoxib
68. A relatively newer agent 'latanoprost' is now being used. Which of the following statements is true regarding this agent?
- It is PGF_{2α} derivative used in glaucoma
 - It is selective α₁ blocker used in benign hypertrophy of prostate
 - It is a 5α reductase inhibitor used to reduce the size of enlarged prostate gland
 - It is a PGE₂ analogue used intravaginally for cervical priming
69. All of the following are indications for eicosanoids or their inhibitors EXCEPT:
- Abortion
 - Essential hypertension
 - Patent ductus arteriosus
 - Transposition of the great arteries
70. Which of the following drugs inhibit platelet cyclooxygenase reversibly?
- Alprostadil
 - Aspirin
 - Ibuprofen
 - Prednisolone
71. Which of the following is a component of slow reacting substance of anaphylaxis (SRS-A)?
- LTC₄
 - LTB₄
 - Misoprostol
 - Prostacyclin
72. Which of the following drugs reduces the activity of phospholipase A₂?
- Alprostadil
 - Aspirin
 - Ibuprofen
 - Prednisolone
73. The chief advantage of ketorolac over aspirin is that the former:
- Can be combined more safely with an opioid such as codeine.
 - Does not prolong bleeding time.
 - Is available in a parenteral formulation that can be used intramuscularly or intravenously.
 - Is less likely to cause acute renal failure in patients with pre-existing renal impairment.
74. Which of the following patient characteristics is a possible reason for the use of celecoxib in the treatment of arthritis?
- History of severe rash after treatment with a sulfonamide antibiotic
 - History of gout
 - History of peptic ulcer disease
 - History of type 2 DM
75. Irreversible inhibitor of cyclooxygenase is:
- Aspirin
 - Phenylbutazone
 - Indomethacin
 - Piroxicam
76. Prostaglandin E₂ analogs can be used for all of the following conditions EXCEPT:
- Treatment of patent ductus arteriosus
 - Treatment of bronchial asthma
 - Cervical priming
 - Treatment of NSAID induced peptic ulcer
77. Aspirin in low doses produces long lasting inhibition of platelet cyclooxygenase because:
- Platelet contain low quantity of COX
 - Platelets cannot synthesize fresh COX molecules
 - Platelets bind aspirin with high affinity
 - Platelet COX is inducible
78. Zafirlukast acts by blocking the action of:
- Prostacyclin
 - Platelet activating factor
 - Leukotriene B₄
 - Leukotriene C₄/D₄
79. NSAID lacking anti-inflammatory action is:
- Paracetamol
 - Ibuprofen
 - Diclofenac sodium
 - Celecoxib
80. True statement about cyclooxygenase -2 is:
- It is not inhibited by indomethacin
 - It is inducible
 - It generates cytoprotective prostaglandins in gastric mucosa
 - It is found only in fetal tissues

81. All of the following effects are produced by inhibitors of prostaglandin synthesis EXCEPT:
 - (a) Prolongation of bleeding time
 - (b) Prolongation of prothrombin time
 - (c) Prolongation of labour
 - (d) Gastric mucosal damage
82. All of the following actions of aspirin are mediated by inhibition of prostaglandin synthesis EXCEPT:
 - (a) Analgesia
 - (b) Closure of patent ductus arteriosus
 - (c) Hyperventilation
 - (d) Bleeding tendency
83. Use of aspirin in a diabetic patient can result in:
 - (a) Hyperglycemia
 - (b) Hypoglycemia
 - (c) Ketoacidosis
 - (d) Alkalosis
84. The plasma half life of aspirin:
 - (a) Is independent of dose
 - (b) Is longer for anti-inflammatory doses compared to that for analgesic dose
 - (c) Is shorter for anti-inflammatory doses compared to that for analgesic dose
 - (d) Can be increased by alkalinizing the urine
85. TRUE statement about aspirin is:
 - (a) In an afebrile patient acute overdose of aspirin produces hypothermia
 - (b) Aspirin suppresses flushing associated with large dose of nicotinic acid
 - (c) Aspirin therapy prevents granulomatous lesions and cardiac complications of acute rheumatic fever
 - (d) Long term aspirin therapy increases the risk of developing colon cancer
86. Which of the following actions of aspirin is manifested at the lowest dose?
 - (a) Analgesic
 - (b) Antipyretic
 - (c) Anti-inflammatory
 - (d) Antiplatelet aggregatory
87. Phenylbutazone use as an NSAID is restricted because:
 - (a) It has lower anti-inflammatory efficacy than other NSAIDs
 - (b) It has potential to cause agranulocytosis
 - (c) It has weak analgesic action
 - (d) It alters the protein binding and metabolism of many drugs
88. Analgesic that itself can cause headache as a side effect is:
 - (a) Indomethacin
 - (b) Mephenamic acid
 - (c) Piroxicam
 - (d) Aspirin
89. A truck driver presented to the hospital with a minor soft tissue injury. Which of the following NSAID should not be prescribed to him?
 - (a) Celecoxib
 - (b) Indomethacin
 - (c) Naproxen
 - (d) Diclofenac sodium
90. Rofecoxib as compared to indomethacin is:
 - (a) Less likely to cause gastric ulcer and their complications
 - (b) Likely to be more effective in rheumatoid arthritis
 - (c) Not likely to produce renal complications
 - (d) All of the above
91. NSAID proposed to be acting via inhibition of COX-3 is:
 - (a) Nimesulide
 - (b) Paracetamol
 - (c) Ketorolac
 - (d) Rofecoxib
92. Which of the following NSAIDs has been approved for use in children?
 - (a) Indomethacin
 - (b) Ibuprofen
 - (c) Ketorolac
 - (d) Piroxicam
93. Among NSAIDs aspirin is unique because it:
 - (a) Irreversibly inhibits its target enzyme
 - (b) Reduces the risk of colon cancer
 - (c) Reduces fever
 - (d) Selectively inhibits COX-2 enzyme
94. Aspirin is used in the prophylaxis of myocardial infarction because it results in:
 - (a) Inhibition of thromboxane synthetase
 - (b) Inhibition of cyclooxygenase
 - (c) Decreased serum lipids
 - (d) Coronary steal phenomenon
95. Mechanism of action of aspirin in MI is:
 - (a) Inhibition of thromboxane synthesis
 - (b) Inhibition of cyclooxygenase
 - (c) Decreased serum lipids
 - (d) Thrombolytic action
96. A patient comes to you complaining that whenever he takes aspirin for headache, he develops severe shortness of breath. Which of the following may be partly responsible for this effect?
 - (a) Leukotrienes
 - (b) Prostaglandin E
 - (c) Thromboxane A₂
 - (d) Prostacyclin
97. A 3 year old child presented to OPD with the symptoms of influenza. Aspirin is contraindicated in this patient because of increased risk of:
 - (a) Gastric bleeding
 - (b) Thrombocytopenia

- (c) Fanconi syndrome
(d) Reye's syndrome
98. A college student is brought to emergency after taking an overdose of a non-prescription drug. The patient is confused and lethargic. He has been hyperventilating and dehydrated. Arterial blood gas analysis demonstrates metabolic acidosis. In the management of this patient, which is NOT likely to be of any therapeutic value?
(a) Alkalinization of urine
(b) Correction of metabolic acidosis
(c) Gastric lavage
(d) Treatment with acetyl cysteine
99. Individuals with alcoholic cirrhosis of liver may develop severe hepatotoxicity after doses of acetaminophen that are not toxic to individuals with normal liver function. This increased sensitivity to acetaminophen's toxicity is due to:
(a) Decrease availability of acetaldehyde dehydrogenase
(b) Decreased hepatocellular stores of glutathione
(c) Decreased activity of Cytochrome P450 enzymes
(d) Increased liver blood flow
100. A new born was diagnosed as having a congenital abnormality that resulted in transposition of great vessels. While preparing the infant for surgery, the medical team needed to keep the ducts arteriosus open. They did this by infusing:
(a) Cortisol
(b) Indomethacin
(c) Alprostadil
(d) Tacrolimus
101. The antidote of choice in paracetamol poisoning is:
(a) Flumazenil (Karnataka 2009)
(b) Sodium bicarbonate
(c) N-acetylcysteine
(d) Methylene Blue
102. Prostaglandin useful for the prevention of duodenal ulcer is:
(a) Dinoprost (DPG 2002)
(b) Misoprostol
(c) Alprostadil
(d) Carboprost
103. Prostaglandin inhibiting action of aspirin is useful in the treatment of all of the following conditions, EXCEPT:
(a) Analgesia and antipyresis (DPG 2001)
(b) Closure of ductus arteriosus
(c) Uricosuria
(d) Antiinflammatory and anti platelet aggregation
104. Which of the following drugs inhibit an enzyme in the prostaglandin synthesis?
(a) Aminocaproic acid (DPG 2000)
(b) Aspirin
(c) Aprotinin
(d) Alteplase
105. Misoprostol, a prostaglandin analogue is useful as:
(a) Uterine relaxant (DPG 2000)
(b) Anti-ulcer
(c) Bronchodilator
(d) Vasodilator
106. Drug commonly causing analgesic nephropathy is:
(a) Aspirin (DPG 1999)
(b) Ibuprofen
(c) Phenacetin
(d) Phenylbutazone
107. Which one of the following is aspirin?
(a) Methyl salicylate (MPPG 2007, 2004)
(b) Para-aminobenzoic acid
(c) Para-aminosalicylic acid
(d) Acetyl salicylic acid
108. True about COX-2 are all EXCEPT: (MPPG 2001)
(a) It is constitutionally expressed on some cell surfaces
(b) Activation of COX-2 leads to ulceroprotective effect on gastric mucosa
(c) Induced at the site of inflammation
(d) It is utilized in generation of eicosanoids with a ring structure
109. Which of the following is non opioid analgesic and does not inhibit prostaglandin synthesis? (UP 2007)
(a) Nefopam
(b) Tenoxicam
(c) Ketorolac
(d) Piroxicam
110. All are true about Reye's Syndrome Except: (UP 2008)
(a) Hepatic encephalopathy
(b) Seen with ampicillin therapy
(c) Fever and rash
(d) Viral associated
111. Ibuprofen acts on: (UP 2005)
(a) Lipoxygenase pathway
(b) Cyclooxygenase pathway
(c) Kinin system
(d) Serotonin system
112. Which of the following prostaglandin analogues is used in glaucoma? (UP 2006)
(a) Misoprostol
(b) Latanoprost
(c) Enprostil
(d) Rioprostil
113. Cyclooxygenase enzyme is not inhibited by: (RJ 2000)
(a) Aspirin
(b) Warfarin
(c) Phenylbutazone
(d) Diclofenac

114. Which prostaglandin helps in cervical ripening?
(a) PGI₂ (RJ 2007)
(b) PGF₂
(c) PGE₂
(d) PGD₂
115. Development of hepatic central lobular necrosis secondary to acetaminophen overdose can be prevented effectively by which of the following if given within a few hours after ingestion?
(a) N-acetylcysteine (RJ 2007)
(b) Dimercaprol
(c) Sodium nitrite
(d) Amyl nitrite
116. For pain control in a patient having history of G I bleeding, which of the following is given?
(a) Nimesulide (Jharkhand 2004, 2005)
(b) Ibuprofen
(c) Rofecoxib
(d) Pentazocin
117. Rofecoxib was withdrawn due to:
(a) Ischemic heart disease (Bihar 2005)
(b) Renal complication
(c) Liver adenoma
(d) Gastric ulcer
118. Which of the following statements is true of ketorolac?
(a) Has potent anti-inflammatory activity (Karnataka 2007)
(b) Its analgesic efficacy is equal to morphine in postoperative pain
(c) Is used as preanaesthetic analgesic
(d) It interacts with opioid receptor
119. Use of aspirin in children with viral disease is associated with:
(a) Metabolic acidosis (DPG 1999)
(b) Reye's syndrome
(c) Renal tubular acidosis
(d) Fixed drug eruption
- RHEUMATOID ARTHRITIS AND GOUT**
120. Which of the following drugs cause oligospermia?
(a) Leflunomide (AIIMS May 2010)
(b) D-Penicillamine
(c) Methotrexate
(d) Sulfasalazine
121. Allopurinol prevents conversion of:
(a) Hypoxanthine to xanthine (PGI June, 2004)
(b) Xanthine to hypoxanthine
(c) Hypoxanthine to I.M.P.
(d) Xanthine to uric acid
122. Long term use of aspirin in rheumatoid arthritis is limited by its propensity to cause:
(a) Metabolic acidosis
(b) Hypersensitivity reactions
(c) Gastric mucosal damage
(d) Salicylism
123. Which of the following disease modifying anti-rheumatoid drugs is a prodrug?
(a) Etanercept
(b) Nimesulide
(c) Sulfasalazine
(d) Colchicine
124. All of the following drugs can produce hyperuricemia EXCEPT:
(a) Ethambutol
(b) Pyrazinamide
(c) Sulfipyrazone
(d) Hydrochlorothiazide
125. Drug of choice for acute gout is:
(a) Colchicine
(b) Indomethacin
(c) Allopurinol
(d) Dexamethasone
126. Most common dose limiting adverse effect of colchicine is:
(a) Sedation
(b) Kidney damage
(c) Diarrhea
(d) Muscle paralysis
127. Which of the following drugs is useful in chronic gout but is NOT a uricosuric agent?
(a) Probenecid
(b) Phenylbutazone
(c) Sulfipyrazone
(d) Allopurinol
128. Allopurinol is useful in all of the following conditions EXCEPT:
(a) Cancer chemotherapy induced hyperuricemia
(b) Hydrochlorothiazide induced hyperuricemia
(c) Acute gouty arthritis
(d) Kala-azar
129. Rasburicase is a newer drug used in gout. It act by:
(a) Decreasing urate synthesis
(b) Increasing urate oxidation
(c) Decreasing intestinal absorption of uric acid
(d) Increasing renal excretion of uric acid
130. A drug that is effective for rheumatoid arthritis but is not appropriate for osteoarthritis is:
(a) Acetaminophen
(b) Infliximab
(c) Ketorolac
(d) Rofecoxib
131. A drug X is useful in the treatment of rheumatoid arthritis. It is available only in parenteral formulation and its mechanism of action is antagonism of tumor necrosis factor. Which of the following can be X?
(a) Cyclosporine
(b) Penicillamine

- (c) Phenylbutazone
- (d) Etanercept

132. A 45 year old male, Sonu presented to OPD with severe pain in the knee and shoulder joint. On examination and further investigations, a diagnosis of rheumatoid arthritis was made and the patient was started on methotrexate 15mg weekly. However, even after 6 months of using methotrexate, recurrent episodes of arthritis continued. The physician wanted to add another DMARD that inhibit the pyrimidine synthesis by inhibiting dihydroorotate dehydrogenase enzyme. Which of the following drug, physician is thinking about?

- (a) Sulfasalazine
- (b) Infliximab
- (c) Leflunomide
- (d) Abatacept

133. Which of the following is a DMARD? (DPG 2006)

- (a) Desferrioxamine
- (b) Penicillamine
- (c) Succimer
- (d) Dimercaprol

134. Which of the following increases uric acid excretion?

- (a) Allopurinol (DPG 2000)
- (b) Aspirin
- (c) Colchicine
- (d) Probenecid

135. Which of the following drugs is useful in acute attack of gout? (DPG 1998)

- (a) Furosemide
- (b) Sulfapyrazone
- (c) Allopurinol
- (d) Piroxicam

136. Allopurinol potentiates the action of:

- (a) Corticosteroids (Karnataka 2007, MPPG 2001)
- (b) Probenecid
- (c) 6-Mercaptopurine
- (d) Ampicillin

137. Probenecid interacts with: (MPPG 2001)

- (a) Streptomycin
- (b) Ampicillin
- (c) Vancomycin
- (d) Erythromycin

138. Drug useful for gout: (RJ 2002)

- (a) Pyrazinamide
- (b) Rifampicin
- (c) Allopurinol
- (d) Naloxone

139. Loading dose of leflunomide in rheumatoid arthritis is:

- (a) 20 mg (RJ 2005)
- (b) 10 mg
- (c) 100 mg
- (d) 400 mg

140. Allopurinol specifically inhibits:

- (a) Xanthine oxidase (MH PGM CET 2005) (MH 2000)
- (b) Arginase
- (c) Carbamoyl transferase
- (d) Urease

141. Leflunomide is used in the treatment of: (MH 2006)

- (a) Rheumatoid arthritis
- (b) Dermatomyositis
- (c) Bony metastasis
- (d) Postmenopausal osteoporosis

142. Which of the following disease modifying anti-rheumatic drugs (DMARDs) is the drug of first choice?

- (a) Methotrexate (MH 2006)
- (b) Gold compounds
- (c) D-penicillamine
- (d) Anakinra

143. The most common effect of colchicine which is dose limiting is: (TN 2002)

- (a) Diarrhea
- (b) Dyspepsia
- (c) Retinal damage
- (d) Loss of taste sensation

MISCELLANEOUS

144. Most common cause of Mobius syndrome is use of which of the following drug in pregnancy? (AI 2012)

- (a) Misoprostol
- (b) Thalidomide
- (c) Methotrexate
- (d) Dinoprostone

145. Which of the following agent is not used for treatment of erectile dysfunction? (AIIMS May 2008)

- (a) PGE₂
- (b) Vardenafil
- (c) Phenylephrine
- (d) Alprostadil

146. Which of the following drugs has covalent interaction with its target? (AIIMS Nov, 2005)

- (a) Aspirin
- (b) Penicillin
- (c) Nitric oxide
- (d) Bosentan

147. A 70 yr old man was administered penicillin i.v. Within 5 minutes, he developed generalized urticaria, swelling of lips, hypotension and bronchospasm. The first choice is to administer: (AIIMS Nov, 2002)

- (a) Chlorpheniramine inj
- (b) Epinephrine inj.
- (c) High dose hydrocortisone tablet
- (d) Nebulized salbutamol

148. Which of the following is used to treat severe pulmonary hypertension?
- Angiotensin I
 - Omapatrilat
 - Bosentan
 - Endothelin
149. The primary endogenous substrate for nitric oxide synthase (NOS) is:
- Citrulline
 - Arginine
 - Heme
 - Methionine
150. Raju, a 30-year-old male presents to the OPD with sudden onset pain, swelling and redness of the left first metatarsophalangeal joint. A needle aspirate of the joint shows needle-shaped, negatively birefringent crystals. The physician prescribed a drug for the patient, but he came back next day with nausea, vomiting and diarrhea after taking the medication. Which of the following is the most likely drug that was prescribed to this patient?
- Allopurinol
 - Colchicine
 - Steroids
 - Indomethacin
151. Nitric oxide produces its anti-aggregatory action by increasing the levels of *(AIIMS 2001) (PGI 2000) (MH 2006)*
- cAMP
 - cGMP
 - ADP
 - Phosphoinositol
152. Inhibitor of platelet aggregation includes *(AP 2004)*
- TXA₂
 - PGI₂
 - PGG₂
 - All of the above
153. Bosentan is a/an: *(RJ 2007)*
- Serotonin uptake inhibitor
 - Endothelin receptor antagonist
 - Leukotriene modifier
 - Phosphodiesterase inhibitor
2. Which enzyme is irreversibly inhibited by aspirin ?
- Lipoxygenase
 - Cyclooxygenase
 - Thromboxane synthase
 - Phospholipase
3. Which drug is not included in DMARDs:
- Chloroquine
 - Vincristine
 - Penicillamine
 - Leflunomide
4. Prostaglandins are used in all of the following conditions except:
- Cervical ripening
 - Post partum haemorrhage
 - Erectile dysfunction
 - Palliative treatment of patent ductus arteriosus
5. Allopurinol is used in the treatment of:
- Gout
 - Hypothyroidism
 - Hypertension
 - Hyperlipidemia
6. Irreversible inhibition of COX is done by:
- Aspirin
 - Nimesulide
 - Celecoxib
 - Naproxen
7. NSAID with least anti-inflammatory action is:
- Indomethacin
 - Paracetamol
 - Ketorolac
 - Ibuprofen
8. Which of the following is a 5HT₃ antagonist ?
- Cisapride
 - Ondansetron
 - Clozapine
 - Buspirone
9. Dinoprost is
- PG E₁
 - PG E₂
 - PGF_{2α}
 - PGI₂
10. H₁ antagonist has all the functions except:
- Antipruritic
 - Sedation
 - Decrease gastric acid secretion
 - Antivertigo
11. Prostaglandin derivatives are used in following conditions except:
- Cervical ripening
 - As an abortifacient
 - NSAID induced peptic ulcer
 - Patent ductus arteriosus

RECENT QUESTIONS ASKED BY NATIONAL BOARD

1. 5 HT₁ agonists are used as ?
- Anti anxiety drugs
 - Antipsychotic drugs
 - For GERD
 - For chemotherapy induced vomiting

12. Which of the following NSAID has good tissue penetrability with concentration in synovial fluid?
 - (a) Ketorolac
 - (b) Diclofenac sodium
 - (c) Sulindac
 - (d) Piroxicam
13. Best drug for chronic gout in patient with renal impairment is:
 - (a) Naproxen
 - (b) Probenecid
 - (c) Allopurinol
 - (d) Sulfinpyrazone
14. Alprostadil is not used for:
 - (a) Erectile dysfunction
 - (b) Pulmonary hypertension
 - (c) Patent ductus arteriosus
 - (d) Critical limb ischemia
15. Ergometrine is not used for initiation of labour because:
 - (a) Slow onset of action
 - (b) Fetal hypoxia
 - (c) Increases blood pressure
 - (d) Act on D2 receptors to cause vomiting
16. NSAID given in once daily dose is:
 - (a) Naproxen
 - (b) Ketorolac
 - (c) Piroxicam
 - (d) Paracetamol
17. Most commonly used drug for prophylaxis of migraine is:
 - (a) Sumatriptan
 - (b) Propranolol
 - (c) Valproate
 - (d) Flunarizine
18. All of the following drugs are reversible inhibitors of cyclo-oxygenase except:
 - (a) Diclofenac
 - (b) Ibuprofen
 - (c) Aspirin
 - (d) Indomethacin
19. Which of the following drug causes irreversible inhibition of cyclooxygenase?
 - (a) Naproxen
 - (b) Aspirin
 - (c) Indomethacin
 - (d) Acetaminophen
20. Latanoprost (PGE_2 alpha) is used in:
 - (a) Maintenance of ductus arteriosus
 - (b) Pulmonary hypertension
 - (c) Gastric mucosal protection
 - (d) Glaucoma
21. Misoprostol is an analogue of:
 - (a) PGE_1
 - (b) PGE_2
 - (c) PGF_2
 - (d) PGI_2
22. Which of the following drug is useful in prophylaxis of migraine?
 - (a) Propranolol
 - (b) Sumatriptan
 - (c) Domperidone
 - (d) Ergotamine
23. Drug of choice for treating anaphylaxis is:
 - (a) Adrenaline
 - (b) Corticosteroid
 - (c) Antihistaminic
 - (d) Sodium cromoglycate
24. Which of the following drug is useful in acute attack of migraine?
 - (a) Bromocriptine
 - (b) Cinnarizine
 - (c) Sumatriptan
 - (d) Ondansetron
25. Effects mediated by H_1 histamine receptor include:
 - (a) Inhibition of gastric acid secretion
 - (b) Induction of hepatic cytochrome P450 enzymes
 - (c) Maintenance of a wakeful state
 - (d) Vasoconstriction of arterioles
26. N-acetylcysteine reduces the severity of hepatic necrosis in toxicity due to:
 - (a) Isoniazid
 - (b) Acetaminophen
 - (c) Halothane
 - (d) Methyldopa
27. Which of the following H_1 blocker has high anti-cholinergic activity:
 - (a) Cetrizine
 - (b) Chlorpheniramine
 - (c) Fexofenadine
 - (d) Astemizole
28. The preferred antidote for paracetamol (acetaminophen) poisoning is:
 - (a) Activated charcoal
 - (b) N-acetyl cysteine
 - (c) Adrenaline
 - (d) Magnesium hydroxide gel
29. Allopurinol is a competitive inhibitor of:
 - (a) Uricase
 - (b) Xanthine oxidase
 - (c) Guanase
 - (d) Adenosine deaminase

30. A 15 year old boy was stung by a bee. He had difficulty in breathing and facial edema. What is the best treatment?
- IV Adrenaline
 - SC Adrenaline
 - IV Antihistamine
 - IV Hydrocortisone
31. All of the following are well known ototoxic drugs except:
- Aspirin
 - Acetaminophen
 - Aminoglycosides
 - Loop diuretics
32. Which one is a contraindication to the use of ergot derivatives:
- Migraine
 - Hyperprolactinemia
 - Obstructive vascular disease
 - Postpartum hemorrhage
33. Triptans used in migraine headaches are agonists at which receptor:
- 5HT_{ID/IB}
 - 5HT_{1A}
 - 5HT₃
 - 5HT_{2A}
34. Gout is a disorder associated with:
- Increase in lactic acid
 - Increase in uric acid
 - Increase in hippuric acid
 - Increase in glutamic acid
35. Which one of the following drug and active metabolite combination is incorrect:
- Hydroxyzine-Cetirizine
 - Terfenadine-Fexofenadine
 - Chlorpromazine-Promethazine
 - Loratidine-Desloratidine
36. The drug which blocks both H₁ and 5 HT₂ receptor is:
- Phenoxybenzamine
 - Cyproheptadine
 - Ritanserin
 - Ondansetron
37. Prostaglandins are synthesized from:
- Lignoceric acid
 - Nervonic acid
 - Arachidonic acid
 - Butyric acid
38. Which of the following actions are performed by prostacyclin PGI₂:
- Vasodilation and platelet aggregation
 - Vasodilation and inhibition of platelet aggregation
 - Vasoconstriction and platelet aggregation
 - Vasoconstriction and inhibition of platelet aggregation
39. All of the following are true about prostaglandin E₂ except:
- It is the principal prostaglandin synthesized in the stomach
 - Its biosynthesis is inhibited by aspirin
 - It stimulates gastric acid secretion
 - It causes dilatation of submucosa blood vessels
40. Serotonin can be synthesized from:
- Tryptophan
 - Tyrosine
 - Dopa
 - Epinephrine
41. Uricosuric drug among these is:
- Probenecid
 - Colchicine
 - Allopurinol
 - All of these
42. Allopurinol works on the basis of:
- Decreased excretion of uric acid
 - Decreased metabolism of uric acid
 - Increased excretion of uric acid
 - Decreased synthesis of uric acid
43. Latanoprost is used in treatment of:
- Induction of labor
 - Refractive
 - Glaucoma
 - Iridocyclitis

EXPLANATIONS

1. **Ans. (b) Cyclizine** (Ref: Goodman and Gilman 12/e p921,922)

Antihistaminics may be classified into first generation and second generation compounds on the basis of CNS penetration and anticholinergic properties. First Generation Anti-histaminics can penetrate blood brain barrier and possess additional anticholinergic properties which are lacking in second generation drugs. Cyclizine is a first generation whereas cetirizine, loratidine and fexofenadine are second generation drugs.

2. **Ans. (c) Bradykinin** (Ref: KDT 6/e p490, 491)

Although both histamine as well as bradykinin can cause edema and increase in permeability, histamine is an amine whereas bradykinin is a peptide.

3. **Ans. (a) Post partum hemorrhage** (Ref: KDT 6/e p322)

Obstetric indications of ergometrine (Ergonovine):

- To control and prevent Post partum hemorrhage. It is given at the time of delivery of anterior shoulder.
- After Caesarean Section/instrumental delivery – to prevent uterine atony.
- To ensure normal involution in multipara.

4. **Ans. (d) Cetirizine** (Ref: KDT 6/e p157)

It is a non-sedating second generation antihistaminic agent and is preferred for the patients requiring constant attention. It does not cause sedation or impairment of psychomotor function. Other drugs listed in the question are first generation antihistaminics.

5. **Ans. (a) Cyclizine** (Ref: KDT 6/e p156)

6. **Ans. (b) Increase in H_1 mediated gastrin release** (Ref: KDT 6/e p153)

H_3 receptors act as pre-synaptic receptors and decrease the release of histamine and other neurotransmitters. These antagonize H_1 mediated wakefulness and bronchoconstriction. These also decrease gastrin release and produce negative chronotropic effect. Inverse agonist of H_3 receptor (tiprolisant) is approved for Narcolepsy.

7. **Ans. (a) Azelastine; (b) Fexofenadine; (d) Desloratidine** (Ref: KDT 6/e p158-159)

Chlorpheniramine and promethazine are first generation anti-histaminics.

8. **Ans. (b) Direct action on vascular smooth muscle causing vasodilation** (Ref: KDT 6/e p153)

Both H_1 and H_2 receptors cause vasodilation. H_1 receptors are present in the endothelium and cause vasodilation by releasing NO. However, H_2 receptors are present on the smooth muscles and cause direct vasodilation.

9. **Ans. (c) Morphine** (Ref: KDT 6/e p155)

Basic drugs like morphine, d-TC and amphotericin B etc. act as histamine liberators and can cause acute reaction leading to itching and hypotension.

10. **Ans. (a) Promethazine** (Ref: KDT 6/e p158)

All the drugs listed in the question are second generation anti-histaminic agents except promethazine.

11. **Ans. (c) Cyproheptadine** (Ref: KDT 6/e p166)

12. **Ans. (a) Driving motor vehicles** (Ref: KDT 6/e p157)

First generation antihistaminic agents cause sedation and impairment of psychomotor function.

13. **Ans. (b) These possess high anti-motion sickness activity** (Ref: KDT 6/e p157)

Anti-motion sickness activity is related to anticholinergic property. This property is exhibited by first generation compounds whereas second generation antihistaminics lack this potential.

14. **Ans. (c) Astemizole** (Ref: KDT 6/e p158)

15. **Ans. (b) Cinnarizine** (Ref: KDT 6/e p160)

16. **Ans. (b) Dangerous ventricular arrhythmias can occur** (Ref: KDT 6/e p158)
Ketoconazole, erythromycin and clarithromycin are potent inhibitors of microsomal enzymes. Astemizole, terfenadine and cisapride are the drugs that can block cardiac K^+ channels at high concentration. If administered along with microsomal enzyme inhibitors, these drugs can result in torsades de pointes, a serious polymorphic ventricular tachycardia.
17. **Ans. (c) It does not block cardiac K^+ channels** (Ref: KDT 6/e p158)
Fexofenadine is an active metabolite of terfenadine. It lacks K^+ channel blocking property, therefore is devoid of arrhythmogenic potential. It is available as a separate second generation H_1 blocking agent.
18. **Ans. (d) Azelastine** (Ref: KDT 6/e p159)
19. **Ans. (c) $5-HT_3$** (Ref: KDT 6/e p163)
All serotonin receptors are G-protein coupled receptors except $5-HT_3$, which is an ionotropic receptor.
20. **Ans. (a) $5-HT_{1A}$** (Ref: KDT 6/e p163)
21. **Ans. (b) Serotonin $5-HT_3$ receptor** (Ref: KDT 6/e p163)
22. **Ans. (d) Tegaserod** (Ref: KDT 6/e p654)
Both cisapride and tegaserod are selective $5-HT_4$ agonists useful in the treatment of GERD. Cisapride possesses cardiac K^+ channel blocking activity and can lead to torsades de pointes. Tegaserod is devoid of this adverse effect. However, tegaserod has recently been withdrawn due to increased risk of MI and stroke.
23. **Ans. (b) Adrenaline** (Ref: KDT 6/e p129)
 - Adrenaline is a physiological antagonist of histamine. It reverses bronchoconstriction caused by histamine. Ranitidine is an H_2 antagonist that decreases gastric acid secretion but has no effect on smooth muscles.
24. **Ans. (c) Common cold** (Ref: KDT 6/e p160)
In this condition, excessive secretions (like rhinorrhoea) are due to cholinergic overactivity. First generation antihistaminics possess anticholinergic property and therefore are effective for common cold. On the other hand, second generation agents (lacking anticholinergic actions) are ineffective.
25. **Ans. (d) Treatment of these patients with erythromycin, a macrolide antibiotic** (Ref: KDT 6/e p158)
Astemizole and terfenadine are metabolized by microsomal enzymes. Erythromycin inhibits these enzymes and raises the plasma concentration of these drugs. At high levels, these agents block cardiac K^+ channels leading to arrhythmias.
26. **Ans. (d) Cinnarizine** (Ref: KDT 6/e p156)
27. **Ans. (b) $5HT_2$ antagonist** (Ref: KDT 6/e p167)
28. **Ans. (a) Chlorpheniramine** (Ref: KDT 6/e p156-157)
29. **Ans. (a) Ketoconazole** (Ref: KDT 6/e p763)
30. **Ans. (b) Lanreotide** (Ref: KDT 6/e p166-167)
Lanreotide is a somatostatin analog used in acromegaly.
31. **Ans. (c) Diphenhydramine** (Ref: Katzung 11/e p278)
Diphenhydramine and promethazine have maximum anti-cholinergic activity and maximum ability to cross the blood brain barrier and are thus most effective in motion sickness.
32. **Ans. (a) Antiemetic** (Ref: KDT 6/e p646)
33. **Ans. (d) Terfenadine** (Ref: KDT 6/e p158)
34. **Ans. (a) Gastroesophageal reflux disease** (Ref: KDT 6/e p645)
35. **Ans. (d) Decreasing IP_3 in stomach** (Ref: KDT 6/e p153)
36. **Ans. (a) Dihydroergotamine** (Katzung 11/e p289)
This is a classical sign of ergot induced vasoconstriction. Dihydroergotamine can be used for acute attack of migraine and can result in these symptoms. Due to their vasoconstricting potential, ergot alkaloids are contra-indicated in a patient with peripheral vascular disease. These may also lead to development of gangrene.
37. **Ans. (d) Levetiracetam** (Ref: Katzung 11/e p283)
Prophylaxis of migraine is required if the attacks are frequent (>2-3 per month). The drugs useful for prophylaxis are:
 - Propranolol is the most commonly used drug for prophylaxis of migraine attacks. Timolol, atenolol, metoprolol and nadolol can also be used but the drugs with ISA (e.g. pindolol) are ineffective.
 - Calcium channel blockers like flunarizine (also blocks Na^+ channels) is also effective

- Methysergide, cyproheptadine and TCAs like amitriptyline can also be used.
- Clonidine can be used orally for the prophylaxis of migraine attacks.
- Topiramate (anticonvulsant drug) has recently been approved for prophylaxis of migraine. Valproate and gabapentin also possess some prophylactic activity.

38. **Ans. (a) Sumatriptan** (Ref: Katzung 11/e p283)

'Sumatriptan is the drug of choice for acute severe migraine but it is not indicated for prophylaxis'

39. **Ans. (a) Flunarizine; (c) β blocker; (d) Sodium valproate** (Ref: KDT 6/e p169)

- For details see text.

40. **Ans. (c) Nitroprusside** (Ref: Goodman & Gilman 11/e p311)

This agent is a mixed dilator and is highly effective agent against ergot induced vasospasm. It is also the drug of choice for most of the hypertensive emergencies.

41. **Ans. (c) Frovatriptan** (Ref: KDT 6/e p171)

42. **Ans. (b) Retroperitoneal fibrosis** (Ref: KDT 6/e p166, 167)

43. **Ans. (d) It is more potent α blocker and less potent vasoconstrictor** (Ref: KDT 6/e p168)

Hydrogenation of ergot alkaloids decrease their vasoconstrictor action and increase the α -blocking activity.

44. **Ans. (a) Methylergometrine** (Ref: KDT 6/e p322)

Methylergometrine (methergin) is administered during delivery of anterior shoulder to prevent postpartum hemorrhage.

45. **Ans. (b) It tends to suppress both pain and vomiting in migraine** (Ref: KDT 6/e p171)

Sumatriptan decreases whereas ergotamine aggravates the vomiting of migraine. These two agents should not be administered concomitantly due to the risk of severe coronary spasm. Triptans act as agonists at $5HT_{1B/1D}$ receptors.

46. **Ans. (c) Flunarizine** (Ref: KDT 6/e p172)

47. **Ans. (d) Sumatriptan** (Ref: Harrison 17/e p102, CMDT-2010/874)

48. **Ans. (d) Migraine** (Ref: KDT 6/e p170, 171)

49. **Ans. (c) $5HT_{1D}$ agonist** (Ref: KDT 6/e p170, 171)

50. **Ans. (b) Sumatriptan** (Ref: KDT 6/e p171)

51. **Ans. (b) Postpartum hemorrhage** (Ref: KDT 6/e p322)

52. **Ans. (c) Has antimigraine activity** (Ref: KDT 6/e p171)

53. **Ans. (c) Its clearance is independent of plasma concentration** (Ref: KDT 6/e p185)

Acetylsalicylic acid (aspirin) is an irreversible inhibitor of COX enzyme. It results in the inhibition of PG and TX synthesis. At low doses (40-325 mg), it exerts antiplatelet action. This drug shows *saturation kinetics at high doses* i.e. kinetics changes from first order to zero order. Therefore at high dose, amount of drug excreted will be constant. That means clearance is not constant.

54. **Ans. (d) Decrease the synthesis of vascular prostacyclins** (Ref: KDT 6/e p708)

- PGE_2 and PGI_2 cause renal vasodilation, natriuresis and increased water clearance due to inhibition of the action of ADH.
- Loop diuretics act partly by increasing the stimulation of COX; therefore NSAIDs attenuate the diuretic action of these drugs.

55. **Ans. (c) In gout, because it can increase serum uric acid** (Ref: KDT 6/e p190)

- At therapeutic doses, Aspirin can cause hyperuricemia by decreasing the excretion of uric acid. It, therefore, should not be used in patients with gout. It also decreases the uricosuric action of probenecid. At high doses (>5 g/d), it increases the excretion of uric acid, but such high doses are not tolerated.
- Aspirin is contraindicated in children (<12 yrs old) due to increased risk of Reye's syndrome, which is a type of hepatic encephalopathy.
- It should be avoided in diabetics because of risk of hypoglycemia
- It should be avoided in pregnancy because it may be responsible for low birth weight babies, however, it does not cause congenital malformations.

56. **Ans. (c) Cyclooxygenase** (Ref: *Katzung 10/e p554; KDT 6/e p185*)
- Aspirin is an NSAID and acts by irreversible inhibition of cyclooxygenase enzyme that decreases the formation of prostaglandins.
57. **Ans. (a) Bleeding time** (Ref: *Harrison's 16/e p341 and KDT 6/e p609*)
- Antiplatelet drugs (like aspirin and clopidogrel) prolong the bleeding time.
 - Anticoagulant drugs prolong the clotting time.
 - Drugs interfering with intrinsic pathway (like heparin) prolong the aPTT.
 - Drugs interfering with extrinsic pathway (like warfarin) prolong the PT.
 - Thrombin time is prolonged in cases of afibrinogenemia and dysfibrinogenemia.
58. **Ans. (a) Prostaglandin E₁ analogue** (Ref: *KDT 6/e p181*)
- Natural prostaglandin in body is PGE₂ whereas misoprostol and alprostadil are synthetic PGs which are PGE₁ analogs.
59. **Ans. (c) COX-1 is an inducible enzyme** (Ref: *KDT 6/e p185*)
- COX-2 is inducible whereas COX-1 is a constitutional (house keeping) enzyme.
60. **Ans. (d) Piroxicam** (Ref: *KDT, 6/e p194*)
- Piroxicam is a long acting analgesic due to enterohepatic circulation. Single daily dose is usually sufficient.
61. **Ans. (d) Hepatotoxicity is likely to occur** (Ref: *KDT 6/e p198, 199*)
- Ingestion of 10g (ten gram) of paracetamol will result in acute poisoning. Chances of death and fulminant hepatic failure are high if the plasma levels are above the line joining 200 µg/ml at 4 hours and 30µg/ml at 15 hours. Gastric lavage and activated charcoal at 6 hours will not be effective because most of the drug would have been absorbed by this time.
62. **Ans. (c) PGE₂ has marked oxytocic action while PGF_{2α} has tocolytic action** (Ref: *KDT 6/e p181*)
- PGE₂ mainly causes softening of cervix and is utilized for cervical ripening whereas PGF_{2α} is an oxytocic agent and can be utilized for the induction of abortion.
63. **Ans. (c) Primary pulmonary hypertension** (Ref: *KDT 6/e p180, 182*)
- PGI₂ analogs (like epoprostenol and treprostinil) are used for treatment of pulmonary hypertension. PGE₁ analogs are used for first trimester abortion (misoprostol), impotence (alprostadil) and maintenance of the patency of ductus arteriosus (alprostadil).
64. **Ans. (a) It is formed in platelets; (b) It is formed from PGG₂/H₂; (c) It is prothrombotic; (e) Aspirin can inhibit its production** (Ref: *KDT 6/e p174*)
- TXA₂ is produced inside the platelets with the help of TXA₂ synthetase.
 - It is formed from cyclic endoperoxides (PGG₂/H₂) with the help of an enzyme, cyclooxygenase.
 - Aspirin inhibits its production by irreversible inhibition of cyclooxygenase enzyme.
 - TXA₂ causes aggregation of platelets, therefore is prothrombotic.
65. **Ans. (a) Tinnitus is an early symptom; (b) 10-30 g causes poisoning** (Ref: *KDT 6/e p189-190; Washington Manual of Medical Therapeutics, 31/e p586*)
- Symptoms of aspirin poisoning**
 - At anti-inflammatory dose (3-6 gm/day) produces the syndrome called Salicylism comprising of dizziness, tinnitus, vertigo, excitement, mental confusion, reversible impairment of hearing.
 - The dose has to be titrated to one which is just below that produces these symptoms, tinnitus is a good guide.
 - Metabolic acidosis, hyperthermia and acidotic breathing are seen in severe poisoning
 - Aspirin causes platelet dysfunction by inhibiting cyclooxygenase pathway.
 - Fatal dose in adult is 15-30 g but considerably lower in children.
66. **Ans. (a) Aspirin; (b) Indomethacin; (e) Diclofenac** (Ref: *KDT 6/e p187, 193, 195*)
- Aspirin inhibits COX irreversibly by acetylating one of its serine residues; return of COX activity depends on synthesis of fresh enzyme. Other NSAIDs like *indomethacin, diclofenac etc are competitive and reversible inhibitors of COX*, return of activity depends on their dissociation from the enzyme which is turn is governed by the pharmacokinetic characteristics of the compound.
 - Corticosteroids like betamethasone act by inhibiting phospholipase A₂.

67. **Ans. (a) Aspirin; (c) Indomethacin; (e) Rofecoxib** (Ref: KDT 6/e p184)
68. **Ans. (a) It is $\text{PGF}_{2\alpha}$ derivative used in glaucoma** (Ref: KDT 6/e p147)
69. **Ans. (b) Essential hypertension** (Ref: KDT 6/e p190, 191)
70. **Ans. (c) Ibuprofen** (Ref: KDT 6/e p185)
Alprostadil (PGE_1) and prednisolone do not inhibit COX enzyme whereas aspirin is an irreversible inhibitor of this enzyme.
71. **Ans. (a) LTC_4** (Ref: KDT 6/e p175)
 LTC_4 , D_4 and E_4 are known as slow reacting substance of anaphylaxis as these can cause bronchoconstriction.
72. **Ans. (d) Prednisolone** (Ref: KDT 6/e p279)
It is a powerful anti-inflammatory agent. It acts by inhibiting the synthesis of PG, TX and LT via the inhibition of phospholipase A_2 enzyme. However, its most important mechanism of anti-inflammatory action is the inhibition of chemotaxis.
73. **Ans. (c) Is available in a parenteral formulation that can be used intramuscularly or intravenously** (Ref: KDT 6/e p194, 195)
Ketorolac is the only NSAID that can be administered intravenously.
74. **Ans. (c) History of peptic ulcer disease** (Ref: KDT 6/e p197)
Non-selective COX inhibitors on long term use are associated with peptic ulcer disease. These should be avoided in the patients having history of PUD. Selective COX-2 inhibitors like celecoxib are safe in this regard.
75. **Ans. (a) Aspirin** (Ref: KDT 6/e p185)
76. **Ans. (a) Treatment of patent ductus arteriosus** (Ref: KDT 6/e p181, 191)
- PGE_2 analogues are used to maintain the patency of ductus arteriosus whereas aspirin or indomethacin are used for the treatment of PDA.
 - PGE_2 is a bronchodilator and can be used to treat bronchial asthma via inhalational route.
 - Cervical priming and NSAID induced PUD are other indications of this agent.
77. **Ans. (b) Platelet cannot synthesize fresh COX molecules** (Ref: KDT 6/e p185)
Aspirin in low doses irreversibly inhibits COX enzyme in platelets and the endothelium. Platelets lack nucleus and thus cannot regenerate COX whereas endothelium can synthesize fresh enzyme. Net effect of this process is the inhibition of platelet COX and thus, TXA_2 synthesis. Low TXA_2 level results in the anti-aggregation of platelets.
78. **Ans. (d) Leukotriene C_4/D_4** (Ref: KDT 6/e p222)
79. **Ans. (a) Paracetamol** (Ref: KDT 6/e p198)
80. **Ans. (b) It is inducible** (Ref: KDT 6/e p185)
COX-1 is a house-keeping enzyme that is responsible for the generation of gastroprotective PGs. COX-2 is an inducible enzyme whose production is markedly increased at inflammatory sites. Indomethacin is a non-selective inhibitor of both isoforms of COX.
81. **Ans. (b) Prolongation of prothrombin time** (Ref: KDT 6/e p186)
Prothrombin time is increased by the drugs interfering with the coagulation pathway (e.g. warfarin). As COX has no role in coagulation, inhibitors of PG synthesis do not prolong PT. However, bleeding time (BT) is prolonged by the drugs interfering with platelet function. Aspirin increases BT by acting as an antiplatelet agent.
82. **Ans. (c) Hyperventilation** (Ref: KDT 6/e p186, 188)
- All other actions are mediated via inhibition of PG synthesis whereas hyperventilation caused by aspirin is due to respiratory stimulation.
83. **Ans. (b) Hypoglycemia** (Ref: KDT 6/e p188)
84. **Ans. (b) Is longer for anti-inflammatory doses compared to that for analgesic dose** (Ref: KDT 6/e p189)
- Aspirin and other salicylates show saturation kinetics (zero order) and thus, their half life is not constant. Clearance at high doses (anti-inflammatory) is lesser than at low (analgesic) doses. Thus $t_{1/2}$ is more for anti-inflammatory dose than for analgesic dose.

85. **Ans. (b) Aspirin suppresses flushing associated with large dose of nicotinic acid** (Ref: KDT 6/e p191)
Nicotinic acid can cause flushing due to release of PGs. Premeditation with aspirin decreases this complication. Aspirin can cause hyperthermia in overdose. It decreases the risk of developing colon cancer.
86. **Ans. (d) Antiplatelet aggregatory** (Ref: KDT 6/e p191)
87. **Ans. (b) Its potential to cause agranulocytosis** (Ref: KDT 6/e p195)
88. **Ans. (a) Indomethacin** (Ref: KDT 6/e p195)
89. **Ans. (b) Indomethacin** (Ref: KDT 6/e p195)
Sedation caused by indomethacin can interfere with driving.
90. **Ans. (a) Less likely to cause gastric ulcer and their complications** (Ref: KDT 6/e p197)
Selective COX-2 inhibitors are less likely to cause GI complications like PUD. However as COX-2 is also present constitutively in the kidney, chances of renal complications are similar. These drugs have similar or less efficacy than non-selective COX inhibitors.
91. **Ans. (b) Paracetamol** (Ref: KDT 6/e p198)
92. **Ans. (b) Ibuprofen** (Ref: KDT 6/e p190, 193)
93. **Ans. (a) Irreversibly inhibits its target enzyme** (Ref: KDT 6/e p185)
94. **Ans. (b) Inhibition of cyclooxygenase** (Ref: KDT 6/e p191)
Aspirin acts as an antiplatelet drug in MI. It inhibits COX enzyme and thus reduces the synthesis of TXA₂. However it has no effect on the enzyme, thromboxane synthetase. Therefore, answer here is the inhibition of COX.
95. **Ans. (a) Inhibition of thromboxane synthesis** (Ref: KDT 6/e p191)
See the difference from the above question. Here in the question, it is written thromboxane synthesis and not synthetase. Aspirin inhibits TX synthesis via inhibiting COX and thus this is more specific explanation of its antiplatelet action.
96. **Ans. (a) Leukotrienes** (See below)
Aspirin inhibits COX enzyme and results in the diversion of AA pathway towards LT synthesis. As LTs are powerful bronchoconstrictor agents, these may result in the shortness of breath in patients who are susceptible. Aspirin acetylated COX starts producing lipoxins (known as aspirin triggered lipoxins) that also have bronchoconstrictor properties.
97. **Ans. (d) Reye's syndrome** (Ref: KDT 6/e p189)
Aspirin can increase the risk of Reye's syndrome, if used in children with viral diseases.
98. **Ans. (d) Treatment with acetylcysteine** (Ref: KDT 6/e p189, 190)
- This patient is a case of salicylate poisoning. Gastric lavage is done to remove unabsorbed poison. Metabolic acidosis must be corrected by sodium bicarbonate. Alkalinization of urine will increase the excretion of this weakly acidic drug. Treatment with acetylcysteine has no role in salicylate poisoning. It is the antidote of choice for paracetamol poisoning.
99. **Ans. (b) Decreased hepatocellular stores of glutathione** (Ref: KDT 6/e p198, 199)
Chronic alcohol intake results in liver dysfunction and decreased glutathione stores. Deficiency of this compound increases the toxicity of acetaminophen because NAPQ, a metabolite of this compound, can now react easily with sulfhydryl groups of the biomolecules. Alcohol also induces the enzymes responsible for conversion of acetaminophen to NAPQ.
100. **Ans. (c) Alprostadil** (Ref: KDT 6/e p182)
Prostaglandins (like alprostadil) are used to keep ductus arteriosus patent whereas aspirin or indomethacin are used for the treatment (closure) of PDA.
101. **Ans. (c) N-acetylcysteine** (Ref: KDT 6/e p199)
102. **Ans. (b) Misoprostol** (Ref: KDT 6/e p634)
103. **Ans. (c) Uricosuria** (Ref: KDT 6/e p188)

Inhibition of PG synthesis is responsible for analgesic, antipyretic, anti-inflammatory and antiplatelet actions of aspirin. This action is also utilized in the treatment of PDA. High doses of aspirin cause uricosuria whereas therapeutic doses result in hyperuricemia. These effects are unrelated to its action on PG synthesis.

104. Ans. (b) Aspirin (Ref: KDT 6/e p187)

105. Ans. (b) Anti-ulcer (Ref: KDT 6/e p632, 634)

106. Ans. (c) Phenacetin (Ref: KDT 6/e p198)

It is a prodrug of paracetamol and is commonly implicated in the causation of analgesic nephropathy.

107. Ans. (d) Acetyl salicylic acid (Ref: KDT 6/e p187)

108. Ans. (b) Activation of COX-2 leads to ulceroprotective effect on gastric mucosa (Ref: KDT 6/e p178, Katzung 9/e p582)

- COX-2 is constitutively active within kidney, endothelium and brain. Recommended doses of COX-2 inhibitors cause renal toxicities similar to those associated with other NSAIDs.
- COX-2 inhibitors have been shown to have less gastrointestinal side effects because COX-1 is mainly involved in protection from gastric ulcers.
- Constitutive COX-1 isoform tend to be house keeping in function while COX-2 is induced during inflammation.
- COX have role in synthesis of PG's from arachidonic acid, PGs have 20C fatty acids containing cyclopentane ring.
- Selective COX-2 inhibitors increase the risk of MI.

109. Ans. (a) Nefopam (Ref: KDT 6/e p199)

110. Ans. (b) Seen with ampicillin therapy (Ref: KDT 6/e p189)

111. Ans. (b) Cyclooxygenase pathway (Ref: Katzung 11/e p626-627)

112. Ans. (b) Latanoprost (Ref: Katzung 11/e p315)

113. Ans. (b) Warfarin (Ref: KDT 6/e p184-185)

114. Ans. (c) PGE₂ (Ref: KDT 6/e p181)

115. Ans. (a) N-acetylcysteine (Ref: KDT 6/e p199)

116. Ans. (c) Rofecoxib (Ref: KDT 6/e p200)

117. Ans. (a) Ischemic heart disease (Ref: KDT 6/e p197)

118. Ans. (b) Its analgesic efficacy is equal to morphine in post-operative pain (Ref: KDT 6/e p194)

- Ketorolac is an NSAID promoted for systemic use mainly as an analgesic, not as an anti-inflammatory drug (though it has typical NSAID properties).
- The drug does appear to have significant analgesic efficacy and has been used successfully to replace morphine in some situations involving mild to moderate postsurgical pain.

119. Ans. (b) Reye's syndrome (Ref: KDT 6/e p189)

120. Ans. (d) Sulfasalazine (Ref: Goodman and Gilman 12/e p1466)

Sulfasalazine can cause a reversible infertility in males owing to changes in sperm number and morphology.

121. Ans. (a) Hypoxanthine to xanthine; (d) Xanthine to uric acid (Ref: KDT 6/e p209)

Xanthine oxidase catalyses the conversion of hypoxanthine to xanthine as well as xanthine to uric acid. This enzyme is inhibited by allopurinol.

122. Ans. (c) Gastric mucosal damage (Ref: KDT 6/e p189)

123. Ans. (c) Sulfasalazine (Ref: KDT 6/e p203)

124. Ans. (c) Sulfipyrazone (Ref: KDT 6/e p205)

This drug is uricosuric agent and is used in the treatment of hyperuricemia.

125. **Ans. (b) Indomethacin** (Ref: KDT 6/e p206)
NSAIDs except aspirin are the agents of choice for the treatment of acute gout.
126. **Ans. (c) Diarrhea** (Ref: KDT 6/e p206)
127. **Ans. (d) Allopurinol** (Ref: KDT 6/e p205, 209)
128. **Ans. (c) Acute gouty arthritis** (Ref: KDT 6/e p209)
Allopurinol is contra-indicated in acute gout. Rarely it can be used in kala azar patients.
129. **Ans. (b) Increasing urate oxidation** (Ref: Goodman & Gilman 11/e p710)
Rasburicase and pegloticase are recombinant urate oxidase enzymes that convert insoluble uric acid to soluble allantoin.
130. **Ans. (b) Infliximab** (Ref: KDT 6/e p205)
It is a TNF- α antagonist that plays no role in osteoarthritis.
131. **Ans. (d) Etanercept** (Ref: KDT 6/e p205)
Infliximab and etanercept are TNF- α antagonists useful for the treatment of rheumatoid arthritis. These are administered by parenteral route. TNF- α antagonists can cause reactivation of latent tuberculosis.
132. **Ans. (c) Leflunomide** (Ref. : KK Sharma 2/e p378-379)
For details, see text.
133. **Ans. (b) Penicillamine** (Ref: KDT 6/e p204)
134. **Ans. (d) Probenecid** (Ref: KDT 6/e p207)
135. **Ans. (d) Piroxicam** (Ref: KDT 6/e p194, 206)
NSAIDs and colchicine are highly effective in acute attack of gout whereas allopurinol and sulfinpyrazone are used for chronic gout. Furosemide causes hyperuricemia and should be avoided in patients with gout.
136. **Ans. (c) 6-Mercaptopurine** (Ref: KDT 6/e p209)
Allopurinol inhibits xanthine oxidase, which metabolises 6-MP and azathioprine, so dose of 6-MP is reduced to $\frac{1}{4}$ - $\frac{1}{2}$ if used along with allopurinol.
137. **Ans. (b) Ampicillin** (Ref: KDT 6/e p209)

Interactions of Probenecid

- It competitively blocks active transport of organic acids at all sites especially renal tubules. It inhibits excretion of penicillin/ampicillin and increases its blood level.
- It also inhibits urinary excretion of cephalosporins, sulfonamides, methotrexate and indomethacin.
- It inhibits tubular secretion of nitrofurantoin.
- Salicylates, pyrazinamide and ethambutol inhibit uricosuric action of probenecid.
- It inhibits biliary excretion of rifampicin.

138. **Ans. (c) Allopurinol** (Ref: KDT 6/e p742)
139. **Ans. (c) 100 mg** (Ref: KDT 6/e p204)
140. **Ans. (a) Xanthine oxidase** (Ref: KDT 6/e p208)
141. **Ans. (a) Rheumatoid arthritis** (Ref: KDT 6/e p204)
142. **Ans. (a) Methotrexate** (Ref: KDT 6/e p203)
143. **Ans. (a) Diarrhea** (Ref: KDT 6/e p206)
144. **Ans. (a) Misoprostol** (Ref: Katzung 11/e p1029)

Mobius syndrome is extremely rare congenital condition characterized by facial paralysis and inability to move the laterally. It results due to paralysis of sixth and seventh cranial nerves. Important causes of this syndrome are:

- Birth trauma
- Use of misoprostol in mother during pregnancy

- Use of thalidomide in mother during pregnancy
- Use of cocaine in mother during pregnancy

145. **Ans. (c) Phenylephrine** (Ref: Harrison 17/e p299; KDT 6/e p295-296)

- Phenylephrine is an α -agonist and will cause vasoconstriction therefore not used in erectile dysfunction where vasodilation of penile vessels is required.
- Other drugs given in the option are used for this condition
- For further details, see chapter 19.

146. **Ans. (a) Aspirin** (Ref: KDT 6/e p185)

Covalent interaction means irreversible inhibition of the enzyme. Aspirin irreversibly acetylates the cox enzyme.

147. **Ans. (b) Epinephrine inj** (Ref: KDT 6/e p128)

Epinephrine (adrenaline) is the drug of choice for anaphylactic shock. It is given by s.c. or i.m. route in a concentration of 1:1000. Intravenous route is rarely used but at much lower (1:10,000) concentration.

148. **Ans. (c) Bosentan** (Ref: Katzung 10/e p287)

- Bosentan is a non-specific antagonist of endothelin receptors (both ET_A and ET_B). It is useful for the treatment of primary pulmonary hypertension.
- Omapatrilat is a vasopeptidase inhibitor used for the treatment of CHF.

149. **Ans. (b) Arginine** (See below)

- NOS normally metabolizes arginine to NO and citrulline.
Arginine $\rightarrow$ Citrulline + NO
- NO is a potent vasodilator that acts by increasing cGMP.

150. **Ans. (b). Colchicine** (Ref: KK Sharma 2/e p356)

This patient's acute onset pain and swelling of the right first metatarsophalangeal joint and joint aspirate showing needle-shaped negatively birefringent crystals indicate that he most likely has acute gouty arthritis. Colchicine is an effective anti-inflammatory agent in acute gouty arthritis but commonly result in nausea, vomiting, diarrhea and myopathy as adverse effects.

151. **Ans. (b) cGMP** (Ref: KDT 6/e p524)

152. **Ans. (b) PGI₂** (Ref: KDT 6/e p176)

153. **Ans. (b) Endothelin receptor antagonist** (Ref: Katzung 11/e p304)

ANSWERS OF RECENT QUESTIONS ASKED BY NATIONAL BOARD

1. **Ans (a) Anti anxiety drugs** (Ref: KDT 7th/174)
2. **Ans (b) Cyclooxygenase** (Ref: KDT 7th/195)
3. **Ans (b) Vincristine** (Ref: KDT 7th/210)
4. **Ans (d) Palliative treatment of patent ductus arteriosus** (Ref: KDT 7th/189-190)
5. **Ans (a) Gout** (Ref: KDT 7th/217)
6. **Ans (a) Aspirin** (Ref: KDT 7th/195)
7. **Ans (b) Paracetamol** (Ref: KDT 7th/206)
8. **Ans (b) Ondansetron** (Ref: KDT 7th/175)
9. **Ans (c) PGF₂ alpha** (Ref: KDT 7th/190)
10. **Ans. (c) Decrease gastric acid secretion** (Ref: KDT 6/e p160)
11. **Ans. (d) Patent ductus arteriosus** (Ref: KDT 6/e p181-182)
In PDA, drugs decreasing PGs are used.
12. **Ans. (b) Diclofenac sodium** (Ref: KDT 6/e p193)

13. Ans. (a) **Naproxen** (Ref: KDT 7/e p215, 217)
 - NSAIDs like naproxen have no role in chronic gout
 - Uricosuric drugs like probenecid and sulfinpyrazone are ineffective in the presence of renal insufficiency
 - Allopurinol is drug of choice for most cases of chronic gout.
14. Ans. (c) **Patent ductus arteriosus** (Ref: Goodman Gilman 12/e p952, CMDT 2014 p1184)
 - Alprostadil is used to keep the ductus open and not for already patent ductus arteriosus.
15. Ans. (b) **Fetal hypoxia** (Ref: Goodman Gilman 12/e p349)
16. Ans. (c) **Piroxicam** (Ref: KDT 7/e p201)
17. Ans. (b) **Propranolol** (Ref: KDT 7/e p179)
18. Ans. (c) **Aspirin** (Ref: KDT 7/e p193)
19. Ans. (b) **Aspirin** (Ref: KDT 7/e p193)
20. Ans. (d) **Glaucoma** (Ref: KDT 7/e p190)
21. Ans. (a) **PGE₁** (Ref: KDT 7/e p190)
22. Ans. (a) **Propranolol** (Ref: KDT 7/e p179)
23. Ans. (a) **Adrenaline** (Ref: KDT 7/e p138)
24. Ans. (c) **Sumatriptan** (Ref: KDT 7/e p178)
25. Ans. (c) **Maintenance of a wakeful state** (Ref: KDT 7/e p162)
26. Ans. (b) **Acetaminophen** (Ref: KDT 7/e p207)
27. Ans. (b) **Chlorpheniramine** (Ref: KDT 7/e p164)
28. Ans. (b) **N-acetyl cysteine** (Ref: KDT 7/e p207)
29. Ans. (b) **Xanthine oxidase** (Ref: KDT 7/e p216)
30. Ans. (b) **SC Adrenaline** (Ref: KDT 7/e p138)
31. Ans. (b) **Acetaminophen** (Ref: KDT 7/e p206)
32. Ans. (c) **Obstructive vascular disease** (Ref: KDT 7/e p176)
33. Ans. (a) **5HT_{ID/IB}** (Ref: KDT 7/e p178)
34. Ans. (b) **Increase in uric acid** (Ref: KDT 7/e p213)
35. Ans. (c) **Chlorpromazine-Promethazine** (Ref: KDT 7/e p166)
36. Ans. (b) **Cyproheptadine** (Ref: KDT 7/e p174)
37. Ans. (c) **Arachidonic acid** (Ref: KDT 7/e p181)
38. Ans. (b) **Vasodilation and inhibition of platelet aggregation** (Ref: KDT 7/e p183-184)
39. Ans. (c) **It stimulates gastric acid secretion** (Ref: KDT 7/e p186)
40. Ans. (a) **Tryptophan** (Ref: KDT 7/e p170)
41. Ans. (a) **Probenecid** (Ref: KDT 7/e p215)
42. Ans. (d) **Decreased synthesis of uric acid** (Ref: KDT 7/e p216)
43. Ans. (c) **Glaucoma** (Ref: KDT 7/e p187)

NOTES

[illegible]

CONGESTIVE HEART FAILURE

Fundamental problem in heart failure is inability of the heart to meet the metabolic demands of the body. Heart failure may be **low output failure** in which there is decreased contractility of heart leading to decreased cardiac output or it may be **high output failure** (demands of body are high, which are not met even with increased cardiac output like in cases of **severe anemia, thyrotoxicosis** and **thiamine deficiency**). Heart failure may also be divided into systolic and diastolic failure depending on whether there is abnormality in the cardiac contractility (**systolic failure**; as seen in ischemic heart disease and dilated cardiomyopathy etc.) or in the ventricular relaxation (**diastolic failure**; as seen in hypertension and hypertrophic cardiomyopathy etc.). Inotropic drugs may be used to treat systolic failure, whereas these have no role in diastolic failure or in case of high output heart failure.

Acute or decompensated heart failure is the condition in which heart is not able to pump the blood effectively; therefore it is *amenable to treatment with positive inotropic drugs*. Human body also has compensatory mechanisms to maintain the homeostasis. Thus, it leads to increased sympathetic activity that causes increased cardiac output by stimulation of β_1 adrenergic receptors in the heart. This maintains the cardiac output in short run which leads to compensation of heart failure. But, increased sympathetic activity also results in two other effects i.e. vasoconstriction due to α receptor stimulation and increased renin release from the kidney due to β_1 stimulation. Elevated renin stimulates renin angiotensin aldosterone system, thus increasing angiotensin II (causes vasoconstriction) and aldosterone (retains salt and water and is responsible for cardiac remodeling or left ventricular hypertrophy). Vasoconstriction of arterioles increases the after load and that of venules increases the preload, thus leading to increased workload on the heart. Cardiac remodeling is responsible for the increased mortality in CHF.

Treatment of Acute Heart Failure

It is aimed at *decreasing the congestive symptoms* with diuretics and *increasing the contractility* with positive inotropic agents.

DIURETICS

In heart failure, there is accumulation of fluid in the lungs and peripheral organs leading to congestive symptoms. Diuretics help in decreasing these symptoms by mobilizing the edema fluid. **Diuretics of choice are loop diuretics** like furosemide and bumetanide which possess high ceiling diuretic effect. These will decrease the preload and reduce the symptoms. Loop diuretics produce venodilation prior to diuresis and result in immediate relief from dyspnea in pulmonary edema. Same function is achieved by morphine also. Chronic use of these diuretics may lead to development of tolerance that can be overcome by combination with other diuretics like thiazides or spironolactone. Diuretics do not alter the basic pathology; therefore have no effect on mortality except *spironolactone*, which decreases *mortality*.



Spironolactone is the only diuretic which decreases mortality in patients with CHF.

INOTROPIC DRUGS

Major inotropic drugs used in CHF are dobutamine, dopamine, inodilators and cardiac glycosides. These drugs are used for **short term management of acute CHF** (*except digoxin that can be used orally for maintenance also*).

Digoxin and digitoxin are the only inotropic drugs available that can be given orally.

Raised extracellular K^+ decreases the binding of cardiac glycosides to Na^+-K^+ -ATPase that explains the increased risk of toxicity of these drugs in presence of hypokalemia.

Mechanism of action of digitalis in CHF is inhibition of Na^+-K^+ -ATPase whereas its vagonmimetic action is used for treatment of atrial fibrillation

A. Dobutamine

It is a selective β_1 agonist and has no effect on dopamine receptors. By acting on β_1 receptors, it increases cAMP in the heart that is responsible for increased cardiac contractility and thus increased output. This drug is given by i.v. infusion.

B. Dopamine

It acts on dopamine, β and α receptors depending on the concentration. At a dose of $1-2\mu\text{g/kg/min.}$, it stimulates only dopamine receptors leading to renal vasodilation. Intravenous infusion at the rate of $2-10\mu\text{g/kg/min.}$ stimulates heart by the agonistic action at β_1 receptors. At still higher dose ($>10\mu\text{g/kg/min.}$) there is intense vasoconstriction via stimulation of α receptors.

C. Cardiac Glycosides

These consist of a sugar (glycone) and a non-sugar moiety (aglycone). These drugs are collectively known as digitalis. Compounds in this group include digoxin, digitoxin, strophanthin and ouabain etc. Cardiac glycosides are positive inotropic drugs but unlike other inotropes, these do not increase heart rate or oxygen consumption (rather heart rate and oxygen consumption are decreased by digitalis). These drugs can be used as acute treatment of CHF as well as for maintenance (digoxin) but these do not alter the basic pathology and thus are unable to decrease the mortality. Cardiac glycosides are also used for treatment of atrial fibrillation, atrial flutter and paroxysmal supraventricular tachycardia (DOC is adenosine). **Digitalis** is the only inotropic drug available that can be **given orally**.

Mechanism of Action

In CHF, these drugs act by inhibiting $Na^+K^+ATPase$ of myocardial fibres by binding to its extracellular face. This results in the accumulation of sodium in the cardiac cell, which in turn results in increased intracellular calcium. Normally Na^+ comes inside the cell in exchange with Ca^{2+} by $Na^+ - Ca^{2+}$ exchanger. When intracellular Na^+ is high, more sodium is not required in the cell, so Ca^{2+} is not extruded resulting in raised Ca^{2+} in the cell. This Ca^{2+} is shifted to sarcoplasmic reticulum with the help of SERCA (sarcoplasmic endoplasmic reticulum calcium ATPase) for storage. Thus, during systole, entry of calcium from membrane Ca^{2+} channels triggers release of high amount of Ca^{2+} from the sarcoplasmic reticulum and results in increased contractility. Binding of cardiac glycosides to $Na^+K^+ATPase$ is slow and also after binding, intracellular Ca^{2+} increases gradually. These factors are responsible for the delayed action of digitalis (even on i.v. injection). Raised extracellular K^+ decreases the binding of cardiac glycosides to this enzyme that explains the increased risk of toxicity of these drugs in presence of hypokalemia.

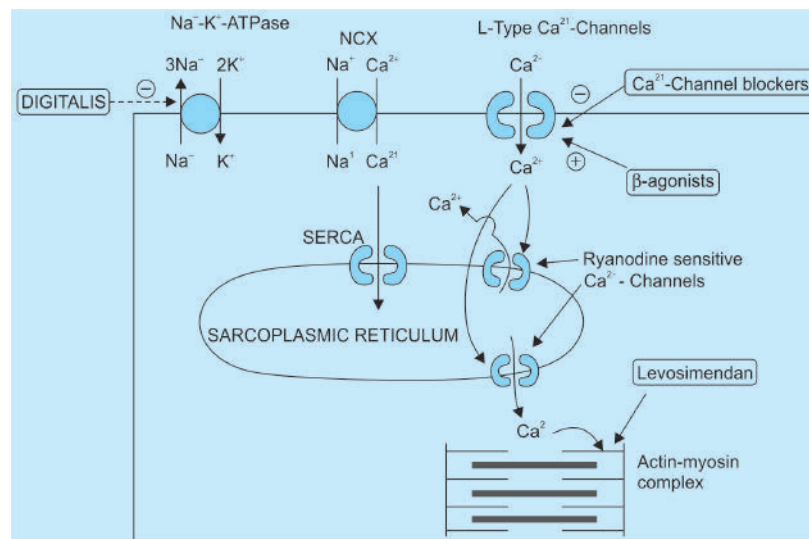


Fig. 5.1: Mechanism of action of digitalis in CHF

In atrial fibrillation (AF), the mechanism of action of digitalis is to cause *increased refractoriness of AV nodal pathway* (due to vagomimetic action). In AF, atrium beats at very high rate (500 beats/minute), and at such high rates the contractions become ineffective. This is not of very much disadvantage in case of atrium, because it has to give blood only to the ventricles. But if all the contractions are passed to ventricles, cardiac output will decrease, because ventricular contractions will also become ineffective due to this high rate. Thus, *aim of treatment in atrial fibrillation is to maintain ventricular rate at low levels*. Digitalis does so by its vagomimetic effect that decreases AV conduction. *Vagomimetic effect is also responsible for bradycardia due to digitalis therapy*. In atrial flutter, it is difficult to control the ventricular rate. **Digitalis converts atrial flutter to AF, in which ventricular rate can be controlled easily.**

Effects

Digitalis **increases the force of contraction and decreases the heart rate**. It also *decreases the AV conduction*. The changes in ECG include *inversion of T wave, increased PR interval, shortening of QT interval (duration of systole is shortened) and depression of ST segment*. It is **contra-indicated in Wolff-Parkinson-White (WPW) syndrome** because it decreases the conduction through the AV node but not through the aberrant pathway (manifested as widened QRS complex). In CHF, circulation is improved due to increased cardiac output that results in better renal perfusion and diuresis (not seen in normal individuals).

Pharmacokinetics

Two major compounds digoxin and digitoxin have important differences in the pharmacokinetic properties. These are given in the table below.

	DIGITOXIN	DIGOXIN
1. Source	Digitoxin purpurea and D. lanata	Digitalis lanata
2. Oral absorption	Very good (90 – 100%)	Good (60 – 80%), I/V also
3. Plasma protein binding	95%	25%
4. Vd	38 L/70 kg	500 L/70 kg
5. Plasma t _{1/2}	5 – 7 days	40 hrs
6. Elimination	Hepatic metabolism	Renal excretion (by glomerular filtration)
7. Dose adjustment in	Liver failure	Kidney failure
8. Uszes	Maintenance	Routine treatment and emergency
9. Target concentration	10 ng/mL	1ng/mL
10. Toxic concentration	> 35 ng/mL	> 2 ng/mL

Adverse effects and toxicity

Evaluation of adequate response to digitalis therapy is primarily done by monitoring clinical symptoms. ECG is usually not valuable unless arrhythmias occur. **Earliest appearing adverse effect** is related to GIT, including *nausea, vomiting* (both due to gastric irritation as well as CTZ stimulation) and *abdominal pain*. It can also lead to *visual disturbances (yellow vision) and gynaecomastia*. It can cause almost any cardiac arrhythmia except *Mobitz type II heart block and Atrial flutter*. **Most common** are *ventricular premature beats and bigeminy*. **Most characteristic arrhythmia** due to digitalis toxicity is *non-paroxysmal supra-ventricular tachycardia with variable atrio-ventricular block*. Mild digitalis toxicity can be decreased with potassium (It decreases binding of the drug to Na⁺K⁺ATPase) but in *severe digitalis toxicity*, K⁺ is rather *contra-indicated* because already there is excess of K⁺ in the extracellular fluid. For *ventricular arrhythmias*, lignocaine is the drug of choice (phenytoin is an alternative). For *atrial tachyarrhythmia*, beta blockers like propranolol may be administered and for *bradyarrhythmias and AV block*, atropine is the agent of choice. **For very severe toxicity**, digoxin antibody (**digibind**) is preferred.

Digitalis is **contra-indicated in Wolff-Parkinson-White (WPW) syndrome** because it decreases the conduction through the AV node but not through the aberrant pathway.

Evaluation of adequate response to digitalis therapy is primarily done by monitoring clinical symptoms.

Earliest appearing adverse effect of digitalis is *nausea and vomiting*

Digitalis can cause almost any cardiac arrhythmia except *Mobitz type II heart block and Atrial flutter*.

Most characteristic arrhythmia due to digitalis toxicity is *non-paroxysmal supra-ventricular tachycardia with variable atrio-ventricular block* whereas most common is ventricular bigeminy.

For digitalis-induced ventricular arrhythmias, lignocaine is the drug of choice

M

Istaroxime is an investigational steroid (in Phase II trials) that acts by inhibiting $\text{Na}^+ - \text{K}^+ - \text{ATPase}$. But in addition, it also increases the entry of Ca^{2+} in sarcoplasmic reticulum. This action may render the drug less arrhythmogenic than digoxin.

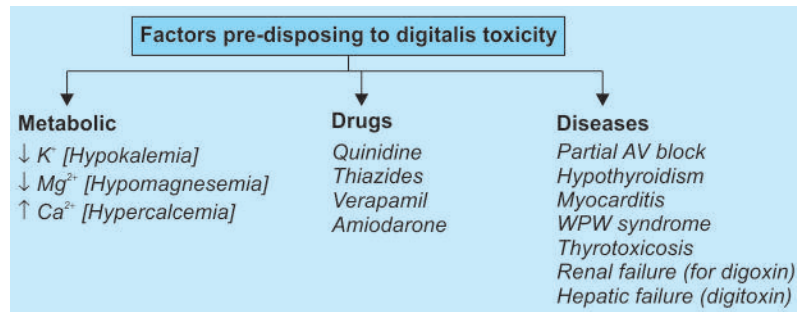
Contra-indications and interactions

- **Hypokalemia, hypomagnesemia and hypercalcemia increases the risk of digitalis toxicity.**
- *Diuretics* like thiazides and furosemide (cause hypokalemia and hypomagnesemia) should be *used cautiously*.
- **Quinidine and calcium channel blockers** (verapamil, diltiazem) decreases the renal clearance and thus *increases the toxicity by pharmacokinetic mechanisms*.
- Antacids, metoclopramide and sulfasalazine decrease the absorption of digitalis from GIT.
- *Digitalis can convert partial AV block to complete block, so should not be used in such patients.*
- Elderly, hypothyroid and patients with renal or hepatic disease are pre-disposed to digitalis toxicity.
- In thyrotoxicosis and acute myocarditis, the chances of developing digitalis induced arrhythmias are high.
- It should be used in MI only when it is accompanied by heart failure and atrial fibrillation.
- Reason for contra-indication in WPW syndrome has been discussed above.
- Digitalis is of *no value* in patients with HF, sinus rhythm and the following co-existing conditions; HOCM, myocarditis, mitral stenosis and chronic constrictive pericarditis.

M

Contraindications of digitalis

Contra-indicated	- Carditis (Myocarditis)
In	- Increased Ca^{2+} (Hypercalcemia)
Weak	- WPW Syndrome
H	- Hypokalemia and Hypomagnesemia
E	- Elderly
A	- AV Block (Partial)
R	- Renal failure (Digoxin)
T	- Thyroid (hyper or hypothyroidism)



D. Inodilators

Drugs in this group include inamrinone (previously known as amrinone), milrinone and vesnarinone. The name inodilators is obtained from their action as inotropic agents as well as their vasodilatory actions. These drugs inhibit the enzyme phosphodiesterase III and thus increase cAMP in heart and blood vessels. cAMP increases transmembrane influx of Ca^{++} in myocardial cells and thus increases contractility whereas it results in the relaxation of vascular smooth muscle (vasodilation). These drugs are indicated for short term i.v. use in severe and refractory CHF. Thrombocytopenia is the major adverse effect of inamrinone and is rare with milrinone (so, latter is preferred). Both of these drugs can result in arrhythmias. **Levosimendan** is another agent that sensitizes the myocardium to Ca^{++} apart from inhibiting phosphodiesterase.

NESIRITIDE

BNP is particularly valuable in differentiating cardiac from pulmonary causes of dyspnoea. Nesiritide is a **recombinant BNP** (brain derived natriuretic peptide, normally secreted by ventricles). Like ANP, it also **increases cGMP** and thus **causes vasodilation**. As the name suggests, it *increases the excretion of sodium through the kidney*. It has a *short half life* and has been used i.v. for acute CHF associated with dyspnoea at rest. The limiting factor is its breakdown by the enzyme, *neutral endopeptidase (NEP)* in the body. Inhibitors of this enzyme (*ecadotril*) are being tested for use in CHF.



Nesiritide is a **recombinant BNP**

Treatment of Compensated/Chronic CHF

Main aim is to decrease the work of heart by decreasing the preload and afterload and to decrease the mortality by reversing cardiac remodeling. Major drugs used for chronic CHF are vasodilators, ACE inhibitors, ARBs, beta blockers and aldosterone antagonists.

VASODILATORS

These drugs may act by reducing preload (*venodilators*), afterload (*arteriolar dilators*) or both (*combined arteriolar and venodilators*). **Nitrates preferentially dilate veins** therefore benefit in CHF is due to preload reduction. **Hydralazine, minoxidil and calcium channel blockers** like nifedipine are **primarily arteriolar dilators** and cause afterload reduction. *These drugs are preferred in forward failure with low cardiac index ($<2.5 \text{ L/min/m}^2$) and without markedly increased central venous pressure ($<18 \text{ mm Hg}$).* Calcium channel blockers should not be used in CHF because these drugs may increase the mortality in CHF patients (due to reflex sympathetic activation in case of nifedipine and direct cardiodepressant action in case of verapamil and diltiazem). Agents reducing both preload and afterload include ACE inhibitors, angiotensin receptor blockers (ARBs), nitroprusside and alpha blockers. *ACE inhibitors and ARBs are indicated for all grades of CHF unless these are contraindicated.* These will decrease the mortality via prevention and reversal of cardiac remodeling due to decreased activation of aldosterone (final mediator of remodeling). Combination of hydralazine and isosorbide dinitrate has also been shown to decrease the mortality. Other vasodilators do not prolong the survival in CHF.

Inotropic drugs are not used for treatment of right sided heart failure where the major treatment is diuretics and vasodilators. Phosphodiesterase inhibitors like inamrinone, milrinone etc. are inodilators. Thus, these can be used in right sided failure due to their ability to produce vasodilation.

ACE inhibitors and ARBs are indicated for all grades of CHF unless these are contraindicated.

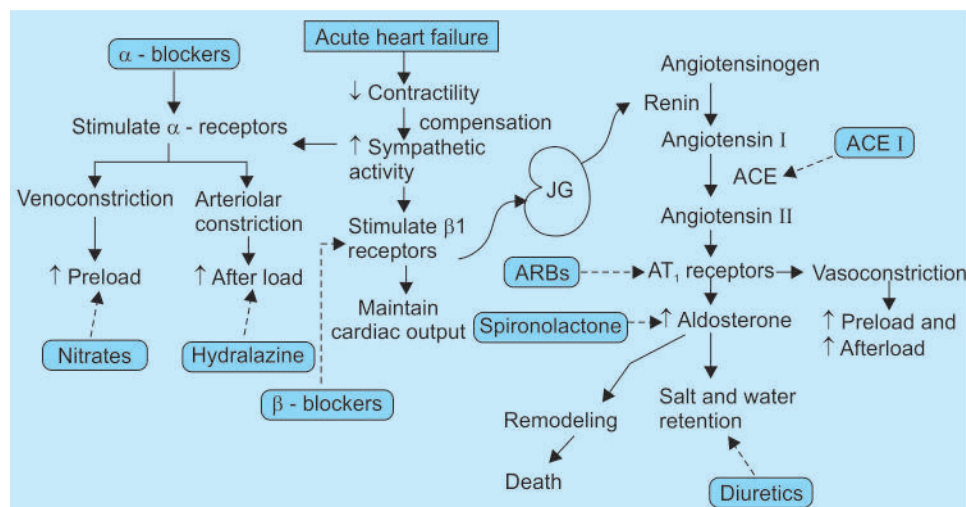


Fig. 5.2: Pathogenesis and drug therapy of chronic CHF

ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS

These drugs are indicated in all grade of CHF unless contra-indicated. These can decrease mortality in CHF.

ALDOSTERONE ANTAGONISTS

Spironolactone and epleronone are the aldosterone antagonists. These are being used as potassium sparing diuretics. Their diuretic effect is quite feeble, but in CHF these drugs **reduce the mortality** (at doses lower than diuretic doses) by antagonizing the effect of aldosterone (**reversal of remodeling**). These can also be added to thiazides if tolerance develops.

BETA BLOCKERS

Previously beta blockers were considered to be contra-indicated in CHF due to their negative inotropic action but now it has been found that if used carefully, these drugs **can increase the longevity** of CHF patients. Beta-1 causes release of renin which stimulate RAAS and finally increase in aldosterone results. Beta blockers antagonize this pathway resulting in

Combination of hydralazine and isosorbide dinitrate has also been shown to decrease the mortality in patients with CHF.

Most widely used beta blocker for CHF is carvedilol followed by metoprolol and bisoprolol.

Beta blockers are absolutely contra- indicated in decompensated heart failure

reversal of remodeling. **Most widely used beta blocker is carvedilol** followed by metoprolol and bisoprolol. These are best indicated in mild to moderate heart failure (NYHA class II and III) with dilated cardiomyopathy and are **absolutely contra-indicated in decompensated heart failure** (because beta blockers decrease cardiac contractility). These should be *started at very low doses and the dose should be gradually increased* to get the maximum benefit.

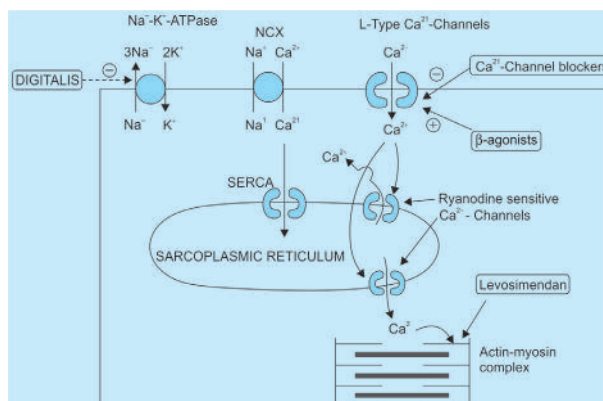
IVABRADINE

It is a **funny current blocker** used in angina pectoris. It decreases myocardial oxygen demand by causing bradycardia. European guidelines recommend it for CHF in patients with heart rate >70 bpm with ejection fraction $\leq 35\%$ and symptomatic despite treatment with beta blockers, ACE inhibitors and aldosterone antagonists. It is **not FDA-approved** for this indication.

VASOPEPTIDASE INHIBITORS

These are the drugs inhibiting two enzymes, ACE and NEP. Omapatrilat and sampatrilat are the drugs that can be used orally for the treatment of chronic CHF. These drugs possess all the actions of ACE inhibitors and also result in natriuresis due to increased BNP (decreased metabolism due to inhibition of NEP). Major limiting factor of these drugs is angioedema.

In CHF, Beta blockers should be started at very low doses and the dose should be gradually increased



HYPERTENSION

Blood pressure is the product of cardiac output and total peripheral resistance (TPR). Cardiac output is dependent on total blood volume, heart rate and the pumping action of the heart whereas peripheral resistance is determined by the diameter of arterioles (vasoconstriction leads to increase in TPR). Sympathetic system stimulates the heart directly (β_1), causes vasoconstriction (α) and also stimulates the renin-angiotensin aldosterone system (β_1 stimulates renin release). All these factors result in increased blood pressure. Four main group of drugs used for controlling hypertension are, diuretics (decrease blood volume and sodium retention), sympathoplegics, vasodilators and the agents decreasing the activity of renin-angiotensin aldosterone system (RAAS).

1. Diuretics

Sodium ions contribute to hypertension by increasing the stiffness of blood vessels and thus TPR. Salt restriction and diuretics reverse these effects of sodium. Initially, diuretics cause sodium and water loss that leads to decrease in cardiac output but later on, cardiac output returns to normal while there is net sodium deficit that results in the decrease in TPR. **Thiazides are the first line drugs in hypertension.** This group of drugs includes hydrochlorthiazide, chlorthalidone, bendroflumethiazide and indapamide etc. Thiazides

should be used at low doses only because by increasing the dose, antihypertensive effect does not increase but adverse effects tend to increase.

Indapamide is longer acting and more potent than hydrochlorothiazide. It is effective as an antihypertensive at lower doses than those required for the diuretic effect (due to its direct vasodilatory action). It also produces less metabolic adverse effects (hypokalemia, hyperglycemia, hyperuricemia etc.) and can be used as an antihypertensive in diabetic patients (whereas other thiazides are contra-indicated).

Loop diuretics (furosemide, torsemide, bumetanide, indacrinone etc.) are not indicated for mild to moderate hypertension because of the brisk diuresis leading to severe reduction in blood volume and electrolyte imbalance. However, these drugs are indicated in severe hypertension with CHF and renal dysfunction. **Indacrinone** can be used in patients of gout because it **inhibits reabsorption of uric acid in the nephron** (other loop diuretics and thiazides cause hyperuricemia).

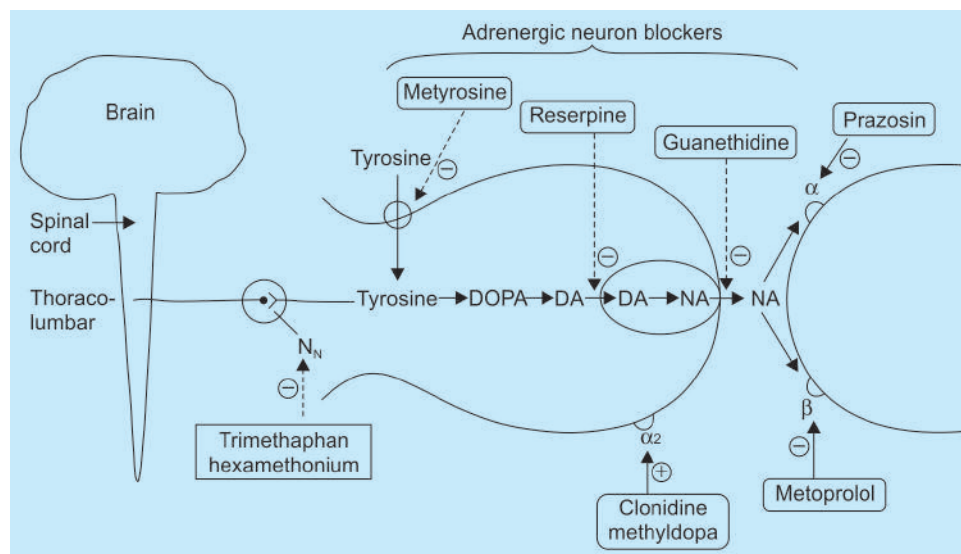
Potassium sparing diuretics (amiloride, triamterene, spironolactone and eplerenone) are used only in combination with thiazides or loop diuretics to decrease the risk of hypokalemia.

Agents Decreasing Mortality in CHF

- ACE inhibitors
- Angiotensin receptor antagonists
- Beta blockers
- Aldosterone antagonists
- Isosorbide dinitrate plus hydralazine combination

2. Sympathoplegics

This group of drugs is aimed at decreasing the activity of sympathetic system. This task may be accomplished with the use of drugs that decrease central sympathetic outflow, block the autonomic ganglia, deplete the neurotransmitter store or block the adrenergic receptors.



Thiazides, ACE inhibitors, ARBs and CCBs are the first choice drugs in hypertension unless contra-indicated (according to JNC-VIII guidelines).

Indacrinone can be used in patients of gout because it inhibits reabsorption of uric acid in the nephron (other loop diuretics and thiazides cause hyperuricemia).

Fig. 5.3: Antihypertensive drugs targeting sympathetic system

A. DRUGS INHIBITING CENTRAL SYMPATHETIC OUTFLOW

Stimulation of α_2 receptors in CNS leads to decrease in sympathetic outflow whereas stimulation of β receptors in the brain has opposite effects. Therefore, α_2 agonists and β_1 antagonists can decrease the sympathetic activity and are useful for the treatment of hypertension.

Clonidine and *α -methyl dopa* act as α_2 agonists in the brain. Clonidine acts directly whereas the effect of α -methyl dopa is due to its conversion to α -methyl norepinephrine (**α -methyl dopa is a prodrug and converted to its active metabolite in the brain**). Both of these drugs can cause sedation. Abrupt discontinuation of clonidine therapy can lead to rebound hypertension

(treated by phentolamine); therefore this drug is not suitable for people having travelling job like business executives who are likely to miss the doses. *Methyl dopa* can cause hemolytic anemia as an adverse effect. Both of these drugs are safe in pregnancy (α methyl dopa is preferred). Clonidine, if administered by i.v. route initially leads to rapid rise in blood pressure followed by prolonged fall. The initial rise is due to the activation of vascular post-synaptic α_2 receptors by high concentration of clonidine. Oral dose is slowly absorbed and such high concentrations are not attained, so orally it results only in antihypertensive effects.

New drugs like **moxonidine** and **rilmenidine** are congeners of clonidine with longer half lives. These drugs are **selective for imidazoline receptors** that modulate the central α_2 receptor activity.

β_1 receptor antagonists like *atenolol*, *metoprolol* and *propranolol* etc. can also produce reduction in the central sympathetic outflow by inhibiting the β_1 receptors, which increase the central sympathetic outflow. These drugs also act by several other mechanisms (discussed later in the chapter).

All of these drugs can result in sodium and water retention on prolonged use. Diuretics can be added to these agents to restore the sensitivity.

B. GANGLION BLOCKERS

These drugs inhibit the N_N type of nicotinic receptors that are present on the autonomic ganglia (both sympathetic and parasympathetic). The therapeutic effect (decrease in blood pressure) is due to the decrease in neurotransmission through sympathetic ganglia whereas decreased transmission through parasympathetic ganglia is responsible for the adverse effects like urinary retention and dry mouth. *Hexamethonium* and *trimethaphan* are the drugs in this group and are used rarely because of availability of drugs with lesser adverse effects. *Trimethaphan*, however is used along with *nitroprusside* as a slow i.v. infusion for hypertensive emergencies in aortic dissection. **Mecamylamine** is a ganglion blocker used for smoking cessation.

C. ADRENERGIC NEURON BLOCKERS

Drugs of this group deplete the sympathetic neurotransmitter and thus decrease the sympathetic system activity. **Reserpine**, **bretylum** and **guanethidine** are the drugs in this group and are rarely used now. **Reserpine** inhibits the vesicular uptake of neurotransmitters causing depletion of adrenaline, dopamine and serotonin in the synaptic vesicles. Due to deficiency of serotonin in the brain, **severe depression** can result with use of reserpine sometimes **leading to suicidal tendencies**. Guanethidine and bretylum is taken up inside the synaptic vesicles and displaces the stored noradrenaline (which is metabolized), resulting in the decreased neurotransmission. Both of these drugs can be given orally. These drugs can cause *postural hypotension even if used for prolonged periods* (unlike α blockers this is not first dose phenomenon).

D. ADRENERGIC RECEPTOR ANTAGONISTS

Two main types of adrenergic receptors are α and β receptors. Alpha 1 is present on the smooth muscles of blood vessels (cause vasoconstriction) whereas β_1 is present mainly in the myocardium (causing increased heart rate and cardiac output) and juxtaglomerular (JG) cells of the kidney (stimulate renin release).

- (i) **Alpha blockers:** Phenoxybenzamine, phentolamine and tolazoline are non-selective alpha blockers (at both α_1 and α_2 receptors). **Phenoxybenzamine** is used for hypertensive crisis in **pheochromocytoma** whereas **phentolamine** and **tolazoline** are **drugs of choice for hypertensive emergencies in clonidine withdrawal and cheese reaction**. These drugs cause much *greater tachycardia* than selective α_1 blockers like prazosin due to the inhibition of presynaptic α_2 receptors (α_2 decreases sympathetic outflow) in addition to reflex tachycardia due to vasodilation (caused by both non-selective as well as selective α_1 blockers). *Prazosin*, *terazosin*, and *doxazosin* are selec-



Moxonidine and rilmenidine are congeners of clonidine with longer half lives. These drugs are **selective for imidazoline receptors**.



Mecamylamine is a ganglion blocker used for smoking cessation.



Due to deficiency of serotonin in the brain, **severe depression** can result with use of reserpine sometimes **leading to suicidal tendencies**.



Phentolamine and tolazoline are drugs of choice for hypertensive emergencies in clonidine withdrawal and cheese reaction.



Diuretics has maximum risk of causing erectile dysfunction whereas ACE inhibitors decrease the risk of erectile dysfunction.

tive α_1 blockers and cause less tachycardia. These drugs are the **treatment of choice for patient with hypertension and benign hyperplasia of prostate (BHP)**. Major adverse effect of alpha blockers is **first dose hypotension** (postural hypotension occurring at the start of treatment or on dose escalation). These drugs do not impair the metabolism, thus *can be safely used in patients with diabetes* (no change in blood glucose), *coronary artery disease* (improves lipid levels) and *gout* (do not affect uric acid).

(ii) **Beta blockers:** Mechanism of action of beta blockers as antihypertensive drugs include

- Inhibition of cardiac β_1 receptors leading to decreased cardiac output.
- Decrease in renin due to inhibition of β_1 receptors in JG cells of the kidney.
- Inhibition of central and peripheral sympathetic outflow due to the inhibition of presynaptic stimulatory β_1 receptors on adrenergic neurons.
- Increased vasodilatory prostacyclin synthesis in the vascular beds.

Cardioselective beta (β_1) blockers can be used in conditions like diabetes mellitus, variant angina, bronchial asthma, Raynaud's disease and in patients having hyperlipidemia. This is because β_2 blockers lead to *hyperglycemia* (so contra-indicated in DM) and *hyperlipidemia, reverse bronchodilation* due to β_2 receptors (not used in asthma) and *can cause vasoconstriction* due to blockade of vasodilatory action of β_2 receptors (avoided in peripheral vascular disease and variant angina). *Selective β_1 blockers include nebivolol, metoprolol, esmolol, atenolol, acebutolol, betaxolol, bisoprolol and celiprolol*. Beta blockers can lead to severe bradycardia in some patients, and in such cases drugs possessing partial agonistic activity (ISA) at β_1 receptors are preferred. Celiprolol, oxprenolol, pindolol, alprenolol and acebutolol are the beta blockers with intrinsic sympathomimetic activity. *All beta blockers can lead to rebound hypertension on sudden withdrawal after prolonged use.*

(iii) **Combined α and β blockers:** Labetalol and carvedilol are the drugs having antagonistic activity at both α and β adrenergic receptors. These are used mainly for controlling hypertension in pheochromocytoma. *Carvedilol, due to its antioxidant and anti-mitogenic property is also useful in CHF.*

Major adverse effect of alpha blockers is **first dose hypotension**

Alpha blockers can be safely used in patients with diabetes coronary artery disease and gout

3. Vasodilators

Drugs may cause vasodilation by opening potassium channels, by releasing nitric oxide, by blocking calcium channels or by acting as agonists of dopamine receptors. These drugs may be mainly **arteriolar dilators** (*hydralazine, minoxidil, calcium channel blockers, diazoxide, fenoldopam*), **mainly venodilators** (*nitrates*) or may dilate **both arterioles and venules** (*sodium nitroprusside, ACE inhibitors, ARBs, α -blockers*). **All vasodilators can lead to reflex tachycardia due to vasodilation and sodium and fluid retention due to compensatory mechanisms;** therefore these are *best utilized in combination with diuretics and beta blockers*. Major adverse effect of vasodilators is *tachycardia and headache* (due to dilation of cerebral blood vessels).

Hydralazine is metabolized by acetylation and thus its effect is genetically determined due to the presence of slow and fast acetylators.

A. POTASSIUM CHANNEL OPENERS

Drugs in this group include *hydralazine, minoxidil and diazoxide*. By opening potassium channels, these drugs cause dilatation of mainly arterioles. These have negligible effect on venules. **Hydralazine in addition acts by releasing nitric oxide (NO) from the endothelium.** Latter action requires the presence of intact endothelium. Minoxidil and hydralazine can be given orally for the treatment of severe hypertension whereas diazoxide is administered in hypertensive emergencies as rapid i.v. injection. **Hydralazine is metabolized by acetylation** and thus its effect is genetically determined due to the presence of slow and fast acetylators. On prolonged administration it can lead to drug

Minoxidil can cause abnormal hair growth in females (hirsutism) and this adverse effect has been utilized as a *treatment of alopecia in males*.

contd...

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induced lupus erythematosus. **Minoxidil** is a **prodrug** and is **activated** in liver to produce minoxidil sulphate (by phase II reaction), which opens potassium channels. Its levels are not changed in renal disease, so it is particularly *useful in patients with chronic renal failure*. Minoxidil can cause abnormal hair growth in females (hirsutism) and this adverse effect has been utilized as a *treatment of alopecia in males*. **Diazoxide** is a thiazide derivative and can cause hyperuricemia and hyperglycemia (by inhibiting insulin release from beta cells of pancreas). The latter effect has lead to its *use in insulinoma*.

N

Riociguat is a stimulator of soluble guanylate cyclase indicated for **Chronic thromboembolic pulmonary hypertension**.

B. NO RELEASERS

Sodium nitroprusside and **hydralazine** act by releasing nitric oxide from the endothelium, which in turn increases intracellular cGMP by stimulation of guanylyl cyclase leading to vasodilation. **Nitroprusside**, in addition can **directly stimulate guanylyl cyclase** to cause increase in cGMP. Nitroprusside is a **very short acting drug**; therefore has to be administered by *constant i.v. infusion* for the treatment of **hypertensive emergencies**. Its solution should be freshly prepared because it is unstable and *sensitive to light*. Prolonged administration of this drug can result in accumulation of **cyanide** leading to **toxicity** particularly in patients with renal disease. It can also result in **hypothyroidism** due to the accumulation of thiocyanate (antithyroid compound). It is *contra-indicated in pregnancy*.

C. DOPAMINE AGONIST

Fenoldopam is dopamine D₁ receptor agonist that causes dilation of peripheral arteries and natriuresis. It can be used i.v. for short term control of blood pressure in *hypertensive emergencies* particularly in patients with renal dysfunction (because of improved renal perfusion). It can increase intraocular pressure and hypokalemia has also been reported with the use of this drug.

D. CALCIUM CHANNEL BLOCKERS (CCBs)

These are the drugs that **block L-type of voltage gated calcium channels** present in blood vessels and heart. Three groups of CCBs include **phenylalkylamines** (*verapamil, nor-verapamil*), **benzothiazepines** (*diltiazem*) and **dihydropyridines** (*nifedipine, nicardipine, nimodipine, nisoldipine, nitrendipine, isradipine, lacidipine, felodipine and amlodipine*). By inhibiting the calcium channels, these agents decrease the frequency of opening of calcium channels leading to relaxation of smooth muscles in blood vessels (vasodilation) and also decreased activity of the heart (decrease heart rate, AV conduction and contractility). **Dihydropyridine** (DHP) group has little direct cardiac activity and acts mainly on blood vessels, therefore are also called **peripherally acting CCBs**. Verapamil and diltiazem have strong direct cardiodepressant (verapamil > diltiazem) activity. CCBs tend to cause reflex tachycardia (because of their vasodilatory action), which is nullified by the direct depressant action on the heart (except DHPs). **Nicardipine** is **longest** acting parenteral calcium channel blocker and is **drug of choice for hypertensive emergencies** (CMDT 2014/446). It is combined with beta blockers to avoid tachycardia.

Effect of different CCBs on the heart rate and blood pressure

	Blood vessel	BP	Heart rate		
			Direct effect	Reflex action	Net effect
Verapamil	vasodilation	↓	↓↓↓	↑	↓↓
Diltiazem	vasodilation	↓	↓↓	↑	↓
DHP	vasodilation	↓	No effect	↑	↑

Reflex tachycardia is more marked in case of drugs with short half lives (nifedipine) whereas in long acting drugs like **amlodipine** (**maximum half life**), effects of reflex activity are hardly discernible. Due to the above reason, *promptly acting nifedipine can increase the risk of angina* (increases cardiac work due to increase in heart rate) whereas sustained release preparation of



DOC for hypertensive emergencies is calcium channel blockers (nicardipine or clevidipine). Nitroprusside is no longer preferred now. (Ref. CMDT 2015 Pg 460)



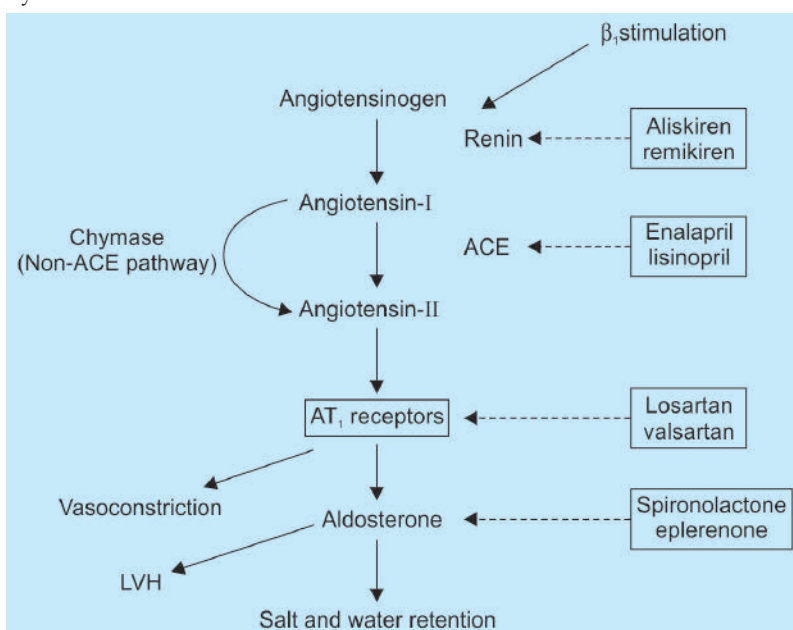
Prolonged administration of sodium nitroprusside can result in accumulation of **cyanide** leading to **toxicity** particularly in patients with renal disease.

nifedipine and amlodipine are safer in this regard. Earlier *nifedipine* was used sublingually for hypertensive emergencies but now this practice has been banned due to *increased risk of MI and mortality*. *Nifedipine*, in addition also possesses *natriuretic* property. **Nimodipine** is a relatively cerebro-selective vasodilator, thus used to reverse the compensatory vasoconstriction after **sub-arachnoid hemorrhage**. **Verapamil** has maximum depressant action on the heart and it causes vasodilation by causing blockade of calcium channel. It is indicated for the treatment of *angina, PSVT, hypertension and hypertrophic obstructive cardiomyopathy (HOCM)*. Diltiazem has lesser effect on the heart than verapamil and is also indicated for these conditions.

These drugs are especially suitable for *elderly patients, patients with low renin hypertension, patients with diseases like asthma, migraine or peripheral vascular disease* and in cases of *isolated systolic hypertension*. DHPs are *safe in pregnancy*. **CCBs (verapamil and diltiazem) should be avoided in conditions involving decreased conductivity of the heart like sick sinus syndrome, CHF and along with beta blockers** (both cause myocardial depression). **Clevidipine** is an ultrashort acting DHP, recently approved for hypertensive emergencies.

4. Drugs Decreasing the Action of RAAS

Angiotensinogen secreted from the liver is converted to angiotensin I with the help of renin (secreted by JG cells of the kidney). JG cells are stimulated either due to less fluid delivery to the macula densa or by β_1 receptors. Angiotensin I is converted to angiotensin II mainly by angiotensin converting enzyme (also known as kininase II). An insignificant amount of angiotensin II is also produced by chymase enzymes (*non-ACE pathway*). This latter pathway assumes importance when ACE is inhibited by the drugs like enalapril, and can result in the decreased effect of these drugs. ACE is also involved in the breakdown of bradykinin, which is a potent vasodilator. **Bradykinin is involved in the causation of dry cough and angioedema**. Angiotensin II acts on AT_1 (main action) and AT_2 (less important) receptors. AT_1 stimulation causes vasoconstriction (by direct action, by release of adrenaline from adrenal medulla and by increasing central sympathetic outflow) and stimulation of aldosterone release. Aldosterone is involved in salt and water retention as well as in the causation of cardiac remodeling. Thus **RAAS results in vasoconstriction as well as salt and water retention leading to increase in blood pressure**. Therefore, drugs that antagonize the action of RAAS can be used for decreasing the blood pressure. This group of drugs is more effective in sodium depleted states (like diuretic use) because activity of RAAS is more in such cases (to compensate for salt loss). *These drugs may cause postural hypotension in diuretic treated patients*, which otherwise is a relatively rare adverse effect. Beta blockers, renin inhibitors, ACE inhibitors, AT_1 antagonists and aldosterone antagonists can act by decreasing the activity of RAAS.



Nimodipine is a cerebro-selective CCB, used to reverse the compensatory vasoconstriction after sub-arachnoid hemorrhage.

Clevidipine is an ultrashort acting DHP, recently approved for hypertensive emergencies.

Bradykinin is involved in the causation of dry cough and angioedema due to ACE inhibitors.

ACE inhibitors and ARBs may cause postural hypotension in sodium depleted conditions as in diuretic treated patients.

Fig. 5.4: Renin angiotensin aldosterone system and target of drugs

RENIN INHIBITORS

Aliskiren, remikiren and enalkiren are the drugs that inhibit the enzyme renin. So these drugs will decrease the activity of RAAS causing fall in blood pressure. These drugs **can be used orally** for the treatment of chronic hypertension.

M

Aliskiren, remikiren and enalkiren are oral renin inhibitors

ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI)

This group of drugs inhibits the enzyme kininase II or ACE. So, these drugs decrease the activity of RAAS and also potentiate the vasodilatory action of bradykinin. *Because these are preventing the conversion of angiotensin I to angiotensin II, so these can decrease the action of the former but not the latter.*

- *Captopril, enalapril, lisinopril, ramipril, perindopril, trandolapril, fosinopril and moexipril* etc are the compounds in this group.
- Important differences between captopril and other ACEIs is that *captopril is less potent, has fast onset and short duration of action and less absorption in presence of food in GIT*. Because of short and fast action, it can cause *postural hypotension* which is not seen with other ACEI.
- **All ACEI are prodrugs except captopril and lisinopril.** Other drugs like enalapril are converted to its active metabolite (enalaprilat) and thus are slow acting.
- **Enalaprilat** is available as a separate drug meant for use in hypertensive emergencies by i.v. route.
- ACEI are used for the treatment of *hypertension, CHF, evolving MI, diabetic nephropathy, diabetic retinopathy, non-diabetic renal disease* and also in *scleroderma crisis*. These drugs reduce proteinuria in diabetic as well as non-diabetic renal disease and also prevent the manifestations of scleroderma crisis which are mediated by angiotensin II.
- **Most frequent adverse effect associated with these agents is dry cough.** It can be reduced by iron supplements and aspirin. ACEI can also cause **angioedema**. Both cough and angioedema is *due to elevated levels of bradykinin*.
- These can cause hyperkalemia if used along with other agents causing elevation of serum potassium (like potassium sparing diuretics).
- Other adverse effects include *rashes, dysgeusia* (altered taste sensation), and *acute renal failure* (if used in bilateral renal artery stenosis). It is important to distinguish between acute renal failure and a normal predictable rise in serum creatinine secondary to ACE inhibitor therapy. An increase in serum creatinine upto 30% within 2-5 days can be expected in most patients started on ACE inhibitors. It stabilizes in 2-3 weeks and is reversible on stopping drug therapy. These drugs are *contra-indicated in pregnancy* (teratogenic in second half of pregnancy) and *when serum creatinine is more than 3.5 mg/dl*.



All ACEI are prodrugs except captopril and lisinopril.

M

- C** - Cough
- A** - Angioedema
- P** - Prodrugs (except captopril and Lisinopril)
- T** - Taste disturbances
- O** - Orthostatic hypotension (when combined with diuretics)
- P** - Pregnancy (contra-indicated)
- R** - bilateral Renal artery stenosis (contra-indicated)
- I** - Increased K⁺ (contra-indicated)
- L** - Lower the formation of Ang II (Mechanism)



ARBs do not increase bradykinin and thus have **less** chances of causing **cough and angioedema as compared to ACE inhibitors**.

ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)

Losartan, valsartan, irbesartan, candesartan, telmisartan and eprosartan act by antagonizing the action of angiotensin II at AT₁ receptors. These drugs do not increase bradykinin and thus have **less** chances of causing **cough and angioedema**. ARB act at a distal site, so these will inhibit the activity of RAAS even when angiotensin II is generated by non-ACE pathway. Due to this reason, ARB can be combined with ACEI for various indications. Losartan results in the production of active metabolites in the liver. Losartan is also a competitive antagonist of TXA₂ and attenuates platelet aggregation. All indications, adverse effects and contra-indications of ACEI also apply to ARB except that incidence of cough and angioedema is less with ARB.

Treatment of Hypertension with Co-existing Conditions

Concomitant condition	Drugs preferred	Drugs to be avoided
Angina	β blocker, CCB	Vasodilators
BHP	α blocker	
Diabetes and Hyperlipidemia	ACEI, ARB, CCB, α blocker	β blocker, diuretics
Elderly and Isolated systolic hypertension	Diuretics, CCB	
Low renin hypertension	Diuretics, CCB	
High renin hypertension	ACEI, ARB, β blocker	
Asthma	CCB, diuretics, ACEI, ARB	β blocker
CHF	ACEI, diuretics	CCB
Post MI	β blocker, ACEI	
PVD	CCB, α blocker	β blocker
Thyrotoxicosis	β blocker	Vasodilators

- According to JNC-VII guidelines, DOC for:
 - Hypertension in pregnancy is methyldopa
 - Hypertensive emergency in pregnancy is hydralazine
- However, **Harrison**, CMDT and Obs-Gynae books recommend **labetalol** as DOC for hypertension in pregnancy as well as hypertensive emergencies in pregnancy.

Drugs Safe for the Treatment of Hypertension in Pregnancy

Better	Beta blockers (Cardioselective and Labetalol)
Mother	Methyl dopa (Preferred drug)
Care	Clonidine
During	Dihydropyridine CCB (sustained release nifedipine, amlodipine)
Hypertensive	Hydralazine (DOC for hypertensive emergencies in pregnancy, according to JNC-VII)
Pregnancy	Prazosin (and other alpha blockers)

Anti-Hypertensives and Plasma Renin Activity

Renin is secreted from JG cells, either due to stimulation by β_1 receptor activation or due to decreased fluid delivery to macula densa. Therefore, the drugs that inhibit activation of β_1 receptors (directly by β -blockers and indirectly by sympathologic drugs) will result in decrease in plasma renin activity whereas other antihypertensive drugs will increase plasma renin activity due to compensatory mechanisms (diuretics, ACEI and ARBs decrease the fluid volume resulting in reduction of fluid delivery to macula densa and vasodilators increase sympathetic activity and therefore result in activation of β_1 receptors).

The drugs that inhibit activation of β_1 receptors (directly by β -blockers and indirectly by sympathologic drugs) will result in decrease in plasma renin activity

Joint National Committee Guidelines for Hypertension

Earlier hypertension was classified into borderline, stage 1, 2 and 3 according to JNC VI report. This classification has been changed to include prehypertension and stage 1 and 2 (as given in table). **Target blood pressure goal according to JNC VII is 140/90 mm Hg for all persons except patients with diabetes and chronic renal disease, where the goal is to keep the blood pressure below 130/80 mm Hg.** All patients should be advised life style modification (physical exercise, weight reduction, salt restriction etc.) and the patients, who are not controlled with this, should be prescribed thiazides diuretics, if not contra-indicated. Combination of drugs should be considered for the patients not responding to above medication.

Beta blockers are not considered first line antihypertensives by JNC-VIII guidelines.

Classification of blood pressure according to JNC VII

Blood pressure Classification	SBP (mm Hg)	DBP (mm Hg)
Normal	< 120	and < 80
Prehypertension	120-139	Or 80-89
Stage I Hypertension	140-159	Or 90-99
Stage II Hypertension	≥ 160	Or ≥ 100

Goal BP for patients > 60 yrs without CKD or DM is < 150/90 mmHg according to JNC-VIII

SALIENT FEATURES OF JNC-8 GUIDELINES

- Goal BP should be < 140/90 mmHg in all patients < 60 years irrespective of presence or absence of diabetes (DM) or chronic kidney disease (CKD).
- **Goal BP for elderly** (> 60 years) without CKD and DM is relaxed to < 150/90 mmHg
- Goal BP for elderly (> 60 years) with CKD or DM or both is < 140/90 mmHg.
- **Beta blockers are no longer considered as first-line drugs** due to increased mortality.
- First line drugs include thiazides, ACE inhibitors, ARBs and calcium channel blockers (CCBs).
- Rest of the drugs are considered later-line drugs as blood pressure should be controlled by first line drugs alone or in combination.
- ACE inhibitors and ARBs should not be given simultaneously to a person.
- ACE inhibitors or ARBs are first choice drugs in patients with CKD irrespective of ethnic backgrounds.
- For patients with African descent without CKD, CCBs or thiazides should be preferred.

COMPARISON OF JNC-VII AND JNC-VIII GUIDELINES

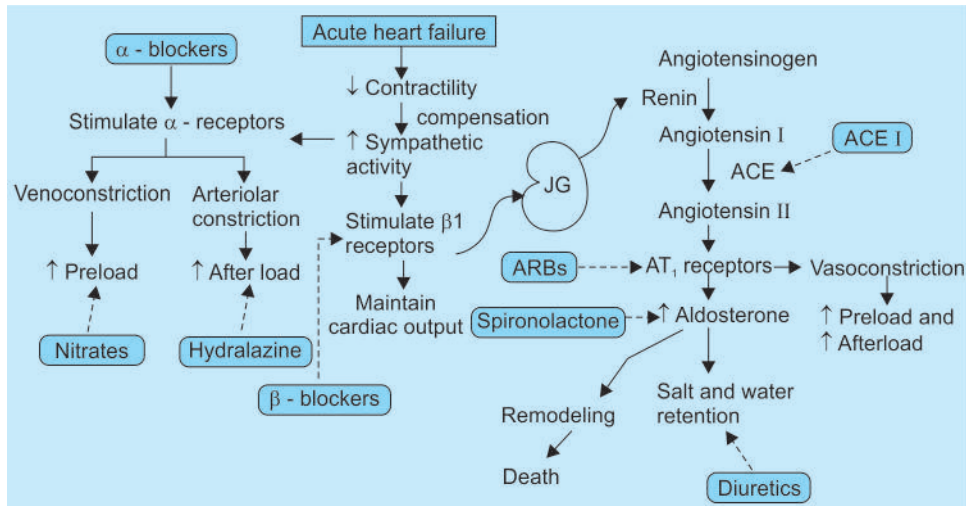
	JNC-VII	JNC-VIII
1. Goal BP		
– < 60 years without CKD or DM	< 140/90	< 140/90
– > 60 years without CKD or DM	< 140/90	< 150/90
– Any age with CKD or DM or both	< 130/80	< 140/90
2. First choice drug without compelling indications	Thiazides	Thiazides, ACE inhibitors, ARBs, CCBs
3. First-line drugs	Thiazides, beta-blockers, ACEI, ARB, CCB	Thiazide, ACEI, ARB, CCB

TREATMENT OF IDIOPATHIC PULMONARY HYPERTENSION

- If the patient responds to intravenous vasodilators, then oral calcium channel blockers (including amlodipine, diltiazem, and nifedipine) are the first-line therapy.
- If these are ineffective or the patient does not respond to vasodilators, then therapy depends on function.
 - If the patient has WHO Class 2 symptoms, then either phosphodiesterase inhibitors (sildenafil or tadalafil) or endothelin receptor blockers (bosentan or ambrisentan) are recommended.
 - If the patient has WHO Class 3 symptoms, then prostacyclin analogs (epoprostenol intravenously, iloprost by inhalation, or beraprost or treprostinil subcutaneously) should be added to the regimen.
 - For patients with WHO Class 4 symptoms, either epoprostenol or iloprost should be used as the sole agent, though some experts still advocate combination therapies.
- Most authorities advocate long-term oral anticoagulation.
- Supplemental oxygen, particularly at night, appears to improve symptoms and helps reduce pulmonary pressures.
- Diuretics help with right heart edema.
- Pulmonary transplantation is a viable option in selected centers, though the operative mortality is high (around 20–25%).
- Women with significant pulmonary hypertension should not get pregnant, and permanent birth control measures should be considered.
- Future advances in therapy include the possible use of angiogenesis inhibitors, growth factor inhibitors, and endothelial stem cells or progenitor cells.



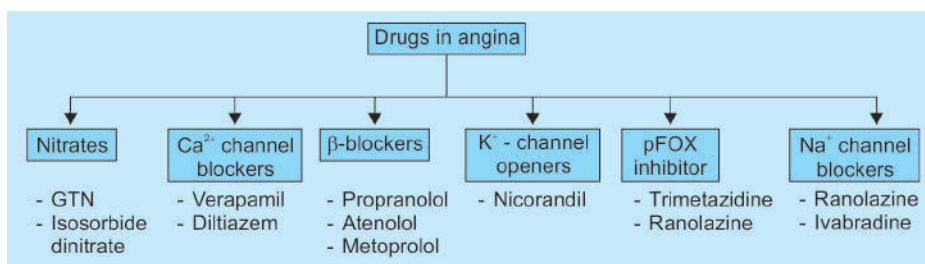
Calcium channel blockers (including amlodipine, diltiazem, and nifedipine) are the first-line therapy for idiopathic pulmonary hypertension.



ANGINA PECTORIS

Major symptom of angina is the chest pain that occurs due to imbalance between oxygen supply and demand. Coronary arteries are the large conducting arteries that run epicardially and gives collateral vessels to endocardial region. Blood flow to endocardium occurs mainly during diastole. In angina, there is a fixed atherosclerotic narrowing of the coronary arteries. At rest, the patient does not develop pain because demand is also less which can be met even with reduced flow. However, during exercise or emotional stimuli, myocardial oxygen requirement increases that result in anginal pain (because blood supply is fixed and cannot be increased). Two major strategies for the treatment and prevention of angina are to decrease the oxygen requirement or to increase the blood supply to the ischemic region.

Oxygen demand of the heart is increased by increase in heart rate, contractility and heart size. Increase in myocardial fibre tension and ventricular pressure also increases oxygen requirement. Increase in end diastolic pressure (more blood in left ventricle at the end of diastole) increases the duration of systole and heart spends less time in the diastole. This may further increase the chances of anginal attacks because coronary flow occurs mainly during diastole. *Beneficial effect of nitrates in classical angina is through the reduction of preload that leads to less end diastolic pressure. Beta blockers and calcium channel blockers act by decreasing the heart rate and contractility. Recently a new strategy developed for use in angina is to make efficient utilization of substrates by the heart.*





Tolerance can develop to nitrates on chronic use (not seen with sublingual use). Thus, for clinical use, at least 8 hours of drug free period per day is required.



Phosphodiesterase inhibitors like sildenafil should never be prescribed with nitrates due to risk of profound hypotension

NITRATES

Glyceryl trinitrate (*nitroglycerine*), **isosorbide dinitrate** (IDN), **isosorbide mononitrate** (IMN), **erythryl trinitrate**, **pentaerythritol tetranitrate** and **amyl nitrite** are important compounds in this category. These drugs *act by releasing NO*, which increase cGMP and results in *venodilation*. At high doses arteriolar dilation can also occur. *The enzyme responsible for releasing NO from the nitrates is present mainly in the veins* (therefore selective venodilator action). Venodilation results in peripheral pooling of the blood and consequently decrease in preload and end diastolic pressure. This is the main action of nitrates responsible for relief in classical angina.

Nitrates *also cause favourable redistribution of blood flow to the ischemic area* (**total coronary flow is not increased**) by dilation of large epicardial coronary arteries. Because small vessels in the ischemic area are already maximal dilated (ischemia is a powerful vasodilator), blood flow to this area is selectively increased on dilation of large vessels and collaterals. *Coronary vasodilatory action is mainly responsible for the therapeutic benefit of nitrates in variant/prinzmetal angina* (vasospasm is the main factor) On the other hand, *dipyridamole* dilates small autoregulatory vessels. Because vessels in the ischemic area cannot be dilated further, blood is diverted away from this area to non-ischemic region (dilation of blood vessels occurs in this area). This phenomenon is known as *coronary steal phenomenon* and is responsible for the therapeutic failure of this drug.

- **Nitroglycerine and isosorbide dinitrate sublingually can be used for aborting the acute attack of angina.**
- Nitroglycerine (by oral or transdermal route) and other nitrates by oral routes are used for *prophylaxis* of anginal attacks.
- *Pentaerythritol tetranitrate is the longest acting and amyl nitrite (by inhalation) is the shortest acting drug in this group.*
- All nitrates undergo very high first pass metabolism except IMN (100% bioavailability).
- Nitroglycerine can also be used for treatment of *acute LVF* by slow intravenous infusion.
- These drugs relax other smooth muscles also, therefore are useful in *biliary colic and oesophageal spasm*.
- Amyl nitrite and sodium nitrite can be used for the treatment of cyanide toxicity. Toxic effects of cyanides are present due to chelation of iron in cytochrome oxidase by this compound. *Nitrites convert hemoglobin to methemoglobin* (which possesses very high affinity for cyanide ions) and forms cyanomethemoglobin. Cytochrome oxidase is freed in this process and the toxicity is abated. Excess cyanomethemoglobin is removed from the body by administration of sodium thiosulphate (forms sodium thiocyanate that can be easily excreted).

As with all vasodilators; *tachycardia, flushing and headache* are the major adverse effects of nitrates. Another problem with nitrate use is the development of **tolerance** on chronic use (not seen with sublingual use) requiring at least 8 hours of drug free period per day. **Molsidomine** is an emerging agent in this category to which *tolerance does not develop*. Phosphodiesterase inhibitors like *sildenafil* should never be prescribed with nitrates. Cyclic GMP is increased by nitrates and its breakdown is prevented by the inhibition of phosphodiesterase, resulting in profound hypotension (due to excess cGMP) and the risk of death.

CALCIUM CHANNEL BLOCKERS

Verapamil, diltiazem and long acting DHPs can be used in angina. *Short acting DHPs like nifedipine should be avoided* because these can accentuate the symptoms of angina by causing tachycardia. CCBs are effective for the treatment of *both classical as well as variant angina*. *Nifedipine* can cause *hyperglycemia* (by decreasing insulin release) and *voiding difficulty* in elderly (by causing relaxation of urinary bladder). CCBs particularly *verapamil* can also cause *constipation and ankle edema*. These drugs should be avoided in *sick sinus syndrome* and *along with beta blockers*. These drugs also *increase plasma digoxin* concentration by decreasing its excretion.



Verapamil can cause constipation and ankle edema.

BETA BLOCKERS

Major *beneficial effect* of beta blockers in angina pectoris is by *reducing cardiac work*. These drugs do not dilate coronary vessels; rather vasoconstriction may occur (unopposed α mediated vasoconstriction due to blockade of β_2 mediated vasodilation). These drugs are therefore, **contra-indicated in variant angina**. Abrupt withdrawal may precipitate acute angina and MI (dose *should be gradually tapered*). Beta blockers can be combined with nitrates and DHPs to counteract tachycardia. **Beta blockers are the only anti-anginal drugs that decrease mortality in patients with CAD (Post-MI)**

Beta blockers are contra-indicated in variant angina.

POTASSIUM CHANNEL OPENERS

Nicorandil is the agent that causes coronary dilation by activating myocardial ATP sensitive K^+ channels. *In addition it possesses NO releasing property*; to which tolerance does not develop.

Ranolazine has no effect on heart rate and blood pressure

PARTIAL FATTY ACID OXIDATION INHIBITORS

Trimetazidine is a drug which act in angina by this new strategy. Heart normally utilizes fatty acids as fuel (not very efficient fuel). Heart starts utilizing glucose (very efficient fuel) as a fuel, if oxidation of fatty acids is inhibited by these drugs. Further by inhibiting the lipid peroxidation, these drugs *reduce the generation of free radicals* and protect the myocardium from harmful effects of ischemia. Thus, it can provide beneficial effects in angina via *non-hemodynamic mechanisms*.

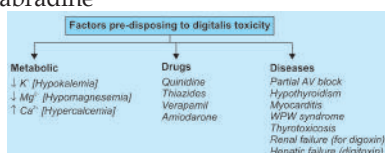
Ivabradine is a relatively selective I_f sodium channel blocker (I_f : funny current) that reduce cardiac rate by inhibiting the hyperpolarization-activated sodium channel in SA node.

- Ranolazine** was initially assigned to this group. However, now it is believed that it acts by blocking a late sodium current that facilitates calcium entry via NCX. Ranolazine is the first new antianginal drug to be approved by the FDA in many years, and it is **approved as first-line agent for chronic angina**. It has **no effect on heart rate and blood pressure**, and it has been shown in clinical trials to prolong exercise duration and time to angina, both as monotherapy and when administered with conventional antianginal therapy. It is **safe to use with erectile dysfunction drugs like sildenafil** (as compared to nitrates which can result in severe hypotension when used along with phosphodiesterase inhibitors). Because, Ranolazine **can cause QT prolongation**, it is contraindicated in patients with existing QT prolongation; in patients taking QT prolonging drugs, such as class I or III antiarrhythmics (eg, quinidine, dofetilide, sotalol); and in those taking potent and moderate CYP450 3A inhibitors. It also decreases occurrence of atrial fibrillation and results in a **small decrease in HbA1C**. It is **contraindicated in patients with significant liver and kidney disease**. **Ranolazine is not to be used for treatment of acute anginal episodes.**

Thrombolytic drugs should be administered within 12 hours for STEMI and within 3 hours of ischemic stroke

NEW DRUGS

- Ivabradine** is a new drug for angina. It is known as **bradycardiac agent** (as it decreases heart rate without affecting the conduction or contractility). It acts by blocking a hyperpolarization activated sodium channel (known to carry **funny current; I_f**). Apart from bradycardia, **visual disturbances** is the most important adverse effect of ivabradine



- Fasudil** is a selective Rho A/**Rho kinase (ROCK) inhibitor**. ROCK is an enzyme that plays important role in vasoconstriction and cardiac remodeling. By inhibiting this

enzyme, fasudil acts as a vasodilator and thus can be used in **angina** and **cerebral vasospasm**.

MYOCARDIAL INFARCTION

For the treatment of acute ST elevation MI, thrombolytic therapy (*streptokinase, urokinase, anistreplase, alteplase, reteplase, tenecteplase etc.*) should be instituted as early as possible, preferably *within first 3 hours*. Ten percent reduction in mortality can still be attained even if these are administered after 12 hours. **Morphine** like opioid is administered i.v. **to decrease pain and increased sympathetic activity** (pain in MI results in the increased sympathetic outflow). *Pentazocine and pethidine should not be used* for this indication since these agents cause tachycardia and can worsen the symptoms. *Aspirin* should be started at low doses (40-325 mg) for its antiplatelet action. If aspirin is contra-indicated *clopidogrel* can be used. **Beta blockers** like metoprolol *reduce infarct size, prevents reinfarction and decrease the incidence of arrhythmias*. Oral anticoagulants can be administered to prevent thrombus extension and embolism. Statins can be added to reduce associated dyslipidemia.

Pentazocine and pethidine should not be used for myocardial infarction since these agents cause tachycardia and can worsen the symptoms.

CARDIAC ARRHYTHMIA

Deviation from the normal pattern of cardiac rhythm is known as arrhythmia. Knowledge of the action potential of heart muscle is necessary for understanding the basic pharmacology of anti-arrhythmic drugs.

Cardiac action potential

The cardiac action potential differs significantly in different portions of the heart. At rest, myocardial cell has a negative membrane potential. Stimulation above a threshold value induces the opening of voltage-gated ion channels. Entry of cations (positively charged ions) inside the cell, results in depolarization. There are important physiological differences between nodal cells and ventricular cells that give rise to unique properties to SA node (most importantly, automaticity necessary for pacemaker activity).

Resting membrane potential (RMP)

The resting membrane potential is caused by the difference in the ionic concentration and conductance across the membrane of the cell during phase 4 of the action potential. The normal RMP of ventricles is about -85 to -95 mV. This potential is determined by the selective permeability of the cell membrane to various ions. The membrane is most permeable to K^+ and is relatively impermeable to other ions. Therefore, **K^+ is the main cation that determines the RMP of cardiac cells**. K^+ is the principal cation and phosphate and the conjugate bases of organic acids are the dominant anions within the cells whereas Na^+ and Cl^- predominate extracellularly.

Phases of the cardiac action potential

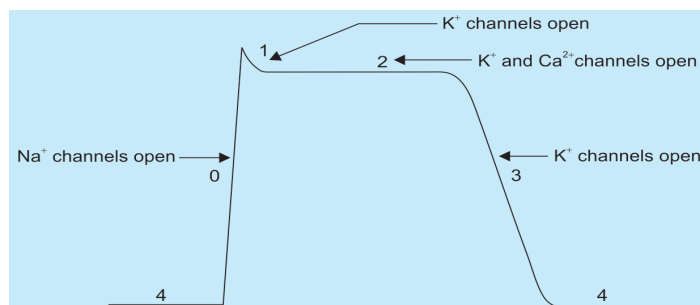


Fig. 5.5: Phases of cardiac action potential

The action potential of a ventricular cell has 5 phases (numbered 0-4).

Phase 4: Phase 4 is the resting membrane potential (when the cell is not being stimulated). This phase is associated with diastole. Certain cells of the heart have the ability to undergo spontaneous depolarization, in which an action potential is generated without any stimulation (automaticity). Spontaneous depolarization is fastest in the SA node of the heart, therefore it is the pacemaker. Electrical activity that originates from the SA node is propagated to the rest of the heart.

Phase 0: Phase 0 is the rapid depolarization phase. The slope of phase 0 represents the maximum rate of depolarization of the cell and is known as $V_{\max}$. This phase is due to the opening of the fast Na^+ channels causing a rapid influx of Na^+ ions into the cell. **Na^+ channels exist in three forms; open, inactivated and closed.** When cell is stimulated, Na^+ channels open and result in inward movement of Na^+ for a brief period. These channels then enter in an inactivated state from which these cannot be stimulated. Slowly Na^+ channels recover from this inactivated state and enter the closed state (in this stage channels can open on the arrival of a sufficiently strong stimulus). The ability of the cell to open the fast Na^+ channels during phase 0 is related to the membrane potential at the moment of excitation. If the membrane potential is at its baseline (about -85 mV), all the fast Na^+ channels are closed, and excitation will open them all, causing a large influx of Na^+ ions. If, however, the membrane potential is less negative, some of the fast Na^+ channels will be in the inactivated state (resistant to opening), thus causing a lesser response to excitation of the cell membrane and a lower $V_{\max}$. For this reason, if the resting membrane potential becomes too positive, the cell may not be excitable and conduction through the heart may be delayed. This increases the risk of arrhythmias.

Phase 1: Phase 1 of the action potential occurs with the inactivation of the fast Na^+ channels. The downward deflection of the action potential is due to the movement of K^+ and Cl^- .

Phase 2: This “plateau” phase of the cardiac action potential is sustained by a balance between the inward movement of Ca^{2+} through L-type calcium channels and outward movement of K^+ through the slow delayed rectifier potassium channels.

Phase 3: During phase 3 of the action potential, Ca^{2+} channels close, while the K^+ channels are still open. This ensures a net outward current responsible for repolarization. The delayed rectifier K^+ channels close when the membrane potential is restored to about -80 to -85 mV.



K^+ is the main cation that determines the RMP of cardiac cells.

Relation of Various Phases of Cardiac Action Potential with ECG

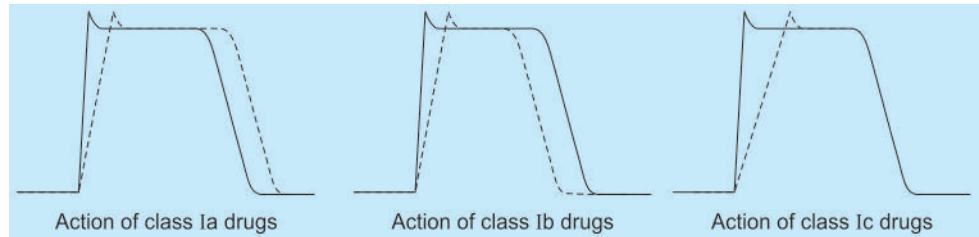
Phase 0 and 1	QRS complex (depolarization)
Phase 2	ST segment (plateau phase)
Phase 3	T wave (repolarization)

SINGH AND VAUGHAN WILLIAM'S CLASSIFICATION OF ANTIARRHYTHMIC DRUGS

This scheme classifies a drug based on its primary mechanism of action. There are five main classes of antiarrhythmic agents

Class I	Na^+ channel blockers
Class II	Beta blockers
Class III	K^+ channel blockers
Class IV	Ca^{2+} channel blockers
Class V	Miscellaneous drugs

Fig. 5.6: Effect of Class I antiarrhythmic drugs on cardiac action potential. (Bold lines indicate normal action potential and dotted lines indicate the effects of the drug)



CLASS IA AGENTS

Apart from its action on sodium channels (block Na^+ channel in open state), these drugs also block cardiac K^+ channels (thus delaying repolarization resulting in prolonged action potential duration). Due to prolongation of APD, these drugs can precipitate *torsades de pointes* (prolonged QT interval). Agents in this class also cause decreased conductivity and increased refractoriness. These drugs dissociate from the sodium channels with intermediate kinetics. Time of recovery of sodium channels (τ) is 1-10 ms. Quinidine, procainamide, and disopyramide are the important members of Class Ia.

- **Quinidine** is a derivative of cinchona plant but its antimalarial action is poorer than quinine. Nausea, vomiting and diarrhea are the most common side effects of this drug. It can cause profound *hypotension and hypoglycemia*. Due to its myocardial depressant action, it can precipitate heart failure in patients with low cardiac reserve. In overdose, it can result in **cinchonism** which manifests as *tinnitus, vertigo, deafness, headache, visual disturbances and mental changes*. It decreases renal (digoxin) and biliary (digitoxin) clearance of cardiac glycosides, thus may precipitate *digitalis toxicity*.
- **Procainamide** is an orally active derivative of a local anaesthetic, procaine. It is metabolized in liver by **acetylation** to produce N-acetyl-procainamide that retains the K^+ channel blocking activity. There are fast and slow acetylators of procainamide similar to isoniazid. Long term therapy with high dose of this drug can result in *drug induced lupus erythematosus* (DLE) particularly in slow acetylators.
- Indications for Class Ia agents are supraventricular tachycardia, ventricular tachycardia, symptomatic ventricular premature beats, and prevention of ventricular fibrillation. While procainamide and quinidine may be used for conversion of atrial fibrillation to normal sinus rhythm, they should only be used in conjunction with an AV node blocking agent (like digoxin, verapamil, or a beta blocker), because these drugs can increase AV nodal conductivity resulting in paradoxical tachycardia.

CLASS IB AGENTS

Class Ib antiarrhythmic agents (*lignocaine, mexiletine, tocainide and phenytoin*) are sodium channel blockers that possess K^+ channel opening property. Class Ib agents have fast onset and offset kinetics ($\tau < 1\text{s}$), meaning that they have little or no effect at slower heart rates, and more effects at faster heart rates. These agents shorten the APD and reduce refractoriness (because of the opening of K^+ channels). These agents will decrease V_{max} in partially

The class I antiarrhythmic agents interfere with the activity of Na^+ channels. Thus, all of these drugs can decrease the slope of phase 0 (V_{max}).

In overdose, quinidine can result in **cinchonism** which manifests as *tinnitus, vertigo, deafness, headache, visual disturbances and mental changes*.

Class Ib agents are used only for ventricular arrhythmias.

depolarized cells with fast response action potential. They either do not change or decrease the APD in non-depolarized tissues. These drugs are **used only for ventricular arrhythmia**.

- Lignocaine is the most commonly used local anaesthetic agent. It has very high first pass metabolism, therefore administered only by i.v. route. Excessive dose can lead to neurological toxicity (drowsiness, paraesthesia, convulsions and coma) and myocardial depression. It is the drug of choice for the treatment of ventricular arrhythmias due to digitalis toxicity. (ineffective in atrial arrhythmias).
- Mexiletine is an orally active lignocaine derivative with all the properties of lignocaine.
- Phenytoin is a popular antiepileptic drug. It can be used as an alternative to lignocaine for digitalis induced ventricular arrhythmias.
- Tocainide (group Ib drug having similar name as group Ic drugs like encainide and flecainide) can be given orally but not used widely because of risk of agranulocytosis.

Lignocaine is drug of choice for digitalis-induced ventricular arrhythmias

Procainamide is metabolized in liver by acetylation

Treatment of choice for WPW syndrome is radiofrequency ablation of the aberrant pathway

CLASS IC AGENTS

These agents have the most potent sodium channel blocking effects with *negligible effect on K^+ channels* (therefore no effect on APD). These have slow kinetics ($\tau > 10s$). Drugs in this group include *encainide, moricizine, flecainide and propafenone*. These drugs have *maximum pro-arrhythmic property*, therefore indicated only for the resistant and life-threatening ventricular tachycardia or ventricular fibrillation and for the treatment of refractory supraventricular tachycardia. **Flecainide can be used for acute treatment of Wolff Parkinson White (WPW) syndrome.** [Treatment of choice for WPW syndrome is radiofrequency ablation of the aberrant pathway].

Class II Agents

Class II agents are conventional *beta blockers*. They act by blocking the effects of adrenaline and nor-adrenaline at the β_1 receptors, thereby decreasing the sympathetic activity on the heart. These agents are particularly useful in the treatment of *supraventricular tachycardia*. These drugs *decrease the slope of phase 4* (responsible for automaticity) *and conduction* through the AV node. Important β blockers used as antiarrhythmic agents are *esmolol, propranolol, and metoprolol*. Esmolol is the shortest acting beta blocker. It can be used i.v. for the emergency control of ventricular rate in atrial fibrillation or flutter.

Class III Agents

Class III agents predominantly *block the potassium channels*, thereby prolonging repolarization (prolongation of APD). These drugs *may precipitate torsades de pointes* due to prolongation of QT interval.

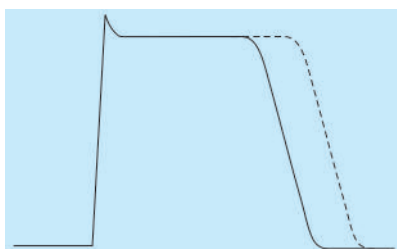


Fig. 5.7: Action of class III anti-arrhythmic agents (shown by dotted line)

These drugs exhibit *reverse use dependent prolongation of the action potential duration* (Reverse use-dependence). This means that the refractoriness increases at lower heart rates, therefore



Class III Anti-arrhythmic drugs

B	–	Bretylium
I	–	Ibutilide
n		
D	–	Dofetilide
A	–	Amiodarone
S	–	Sotalol



Amiodarone is **longest acting** whereas adenosine is **shortest acting** anti-arrhythmic drug.

these are *more efficacious at preventing a tachyarrhythmia than treating it*. Because of this property class III antiarrhythmic agents may paradoxically be more arrhythmogenic at low heart rates. Drugs in this group are *amiodarone, bretylium, sotalol, ibutilide and dofetilide*.

- **Amiodarone** is **longest acting** ($t_{1/2}$ = 3-8 weeks) anti-arrhythmic drug. It possesses **action of all classes** of antiarrhythmic drugs (Na^+ channel blockade, β blockade, K^+ channel blockade and Ca^{2+} channel blockade). Due to this property, it has the **widest anti-arrhythmic spectrum**. It carries less chances of causing torsades despite prolongation of QT interval. It **contains iodine** (approx. 37.5%) and can result in **hyperthyroidism** (similar drug dronedarone do not contain iodine). It can also cause **hypothyroidism** by inhibiting peripheral conversion of T_4 to T_3 . Other adverse effects include **peripheral neuropathy, myocardial depression, pulmonary fibrosis, hepatotoxicity, corneal microdeposits** and **photosensitivity**. **Dronedarone** is a similar drug but lacks iodine and thus adverse effects on thyroid are not seen. Amiodarone is indicated for the treatment of refractory VT or VF, particularly in the setting of acute ischemia. Amiodarone is also safe to use in individuals with cardiomyopathy and atrial fibrillation, to maintain normal sinus rhythm. It can be used for the prophylaxis of almost all arrhythmias except torsades de pointes.
- **Bretylium** is an adrenergic neuron blocking drug used only parenterally for arrhythmias. Its major adverse effect is postural hypotension.
- **Sotalol** is a non-selective lipid insoluble beta blocker. It has actions of both class II as well as class III antiarrhythmic agents. It is indicated for the treatment of atrial or ventricular tachyarrhythmias, and AV re-entrant arrhythmias.
- **Ibutilide** is a structural analog of sotalol (but no beta blocking property) used for the treatment of atrial fibrillation or atrial flutter by i.v. route only. **Ibutilide is the only antiarrhythmic agent currently approved by FDA for acute conversion of atrial fibrillation to sinus rhythm** (other drugs used in atrial fibrillation are for controlling ventricular rate).
- **Dronedarone** is non-iodinated compound which has fewer adverse effects but also less efficacy than amiodarone. It is indicated for atrial fibrillation and atrial flutter. It has lesser incidence of pulmonary fibrosis, peripheral neuropathy and hypothyroidism than amiodarone.
- **Vernakalant** is a multi-ion channel blocker that selectively prolongs atrial refractory period without affecting ventricles. It is indicated for converting atrial fibrillation of short duration (< 7 days) to sinus rhythm. It has little or no pro-arrhythmic action.

Class IV Agents

Class IV agents are the *blockers of L-type voltage gated calcium channels*. They decrease the rate of phase 4 depolarization in SA and AV nodes. This results in decreased automaticity of SA node and decreased conduction through the AV node. *Verapamil and diltiazem are mainly indicated for PSVT and for control of ventricular rate in atrial fibrillation and flutter*. **Verapamil is drug of choice for the treatment of supraventricular tachycardia (SVT) and for the prophylaxis of PSVT.**

Class V Agents

Class V agents include *digoxin, adenosine, magnesium, atropine and potassium*.

- **Digoxin** increases vagal activity and is used for controlling ventricular rate in atrial fibrillation and flutter.
- **Adenosine** opens the potassium channels and lead to hyperpolarization of AV node. It is the drug of choice for treatment of PSVT. It is very short acting ($t_{1/2}$ = 10 seconds) drug, therefore adverse effects like flushing of face and bronchospasm are also short lived. Theophylline being adenosine receptor antagonist inhibits its action whereas dipyridamole potentiates its action by inhibiting the reuptake of adenosine.
- **Magnesium** is used for treatment of both congenital and acquired long QT syndrome.

Drug Treatment of Arrhythmias

Type of arrhythmia	Drugs for acute therapy	Drugs for chronic therapy	Remarks
AF/AFL	Propanolol Esmolol	Ibutilide Digoxin Amiodarone Verapamil	Only ibutilide is indicated for conversion to sinus rhythm, other drugs control ventricular rate only
PSVT	Adenosine	Verapamil Sotalol Propanolol Amiodarone	
Ventricular tachycardia	Lignocaine Magnesium	Sotalol Amiodarone Quinidine	
Ventricular fibrillation	Lignocaine Bretylium	Amiodarone	Cardioversion is the treatment of choice
WPW syndrome	Flecainide	Propanolol Amiodarone	Laser ablation of aberrant pathway is definitive treatment
Torsades de' pointes	Magnesium (for both congenital and acquired)	Propanolol (only congenital)	Amiodarone should not be used
Digitalis induced ventricular arrhythmia	Lignocaine Phenytoin	Propanolol	For bradyarrhythmias atropine can be used.

Note: Amiodarone can be used for chronic treatment of all arrhythmias except torsades de pointes and digitalis induced arrhythmias.

DYSLIPIDEMIA

Dietary triglycerides (TGs) and cholesterol are transported by chylomicrons whereas VLDL carries endogenous TGs from the liver to blood. TG content of chylomicrons is more than the cholesterol content. In the wall of blood vessels, TGs contained in the chylomicrons are metabolized by lipoprotein lipase (LPL) and the free fatty acids so formed are utilized by various tissues like fat and muscle. Hepatic lipase (HL) present on the surface of liver metabolizes remaining TGs and the chylomicron remnants (with only cholesterol) are taken up by the liver. Net result of this process is transport of dietary cholesterol to the liver and free fatty acids to fat and muscle.

When TG production in the liver increases, VLDL is formed and is released in the circulation. It contains more TG than cholesterol ester (CE). TGs are metabolized by LPL and VLDL is converted to IDL (TG = CE). IDL has two fates; either it is converted to LDL by the metabolism of remaining TGs by HL (LDL contains only CE) or it is taken up in the liver through LDL receptors (LDLR). LDL transports its CE either to various tissues or is taken up in the liver by LDLR.

HDL is formed by taking cholesterol from tissues and helps in the transport of this cholesterol to the liver (reverse cholesterol transport). Thus HDL is a good cholesterol and

M

Adverse effects of amiodarone

The	Thyroid (both hypo and hyperthyroidism)
Periphery of My	Peripheral neuropathy Myocardial depression
Lung	Lung fibrosis
Liver and	Liver Toxicity [including cirrhosis]
Cornea is	Corneal microdeposits
Photosensitive	Photosensitivity

N

Vernakalant is a multi-ion channel blocker recommended for converting recent onset atrial fibrillation to normal sinus rhythm.

I

Adenosine is the drug of choice for treatment of PSVT.

LDL, IDL and VLDL are bad cholesterol. Altered level of these lipoproteins may be secondary to some diseases like diabetes and nephrotic syndrome. Primary hyperlipoproteinemia is familial or genetic in origin. Various types of primary hyperlipoproteinemia are given in the table and important points to remember are:

- TG is elevated in all except type IIa
- Cholesterol is elevated only in type II (IIa, IIb) and type III
- Type II is treated with statins and III and IV with fibrates
- Type I and V do not increase the risk of atherosclerosis and require no treatment.

Type of disorder	LP increased	Lipids elevated		Risk of atherosclerosis	Treatment
		TG	CH		
I	CM	+++	N	No	None
IIa	LDL	N	++	+++	Statins
IIb	VLDL and LDL	++	++	+++	Statins, fibrates, nicotinic acid
III	IDL and CMR	++	++	++	Fibrates
IV	VLDL	++	N	++	Fibrates, nicotinic acid
V	VLDL and CM	++	N	No	None

Anti-Dyslipidemic Drugs

First line drugs include *statins, bile acid binding resins and intestinal cholesterol absorption inhibitors* whereas **second line** drugs include *fibrates and niacin*.

STATINS

HMG CoA reductase catalyses the rate limiting step in cholesterol biosynthesis (conversion of HMG CoA to mevalonate). Statins act by inhibiting this enzyme competitively and result in decreased cholesterol synthesis in the liver. As liver requires cholesterol for synthesis of bile acids and steroid hormones, it responds by increasing the uptake of LDL from the plasma. This is done by *increasing LDL receptors on its surface*. **Statins are most powerful LDL lowering agents**. These drugs also lower TG, IDL and VLDL and increases HDL slightly. However, these drugs have **no effect on lipoprotein (a)**. *Most potent statin is pitavastatin followed by rosuvastatin* whereas fluvastatin and lovastatin are least potent compounds in this group. Activity of HMG CoA reductase is maximum at night, so these drugs are administered at night. *Rosuvastatin ($t_{1/2}$ = 19 hours) and atorvastatin ($t_{1/2}$ = 14 hours) are long acting drugs*, therefore can be administered at any time of the day. In addition to lipid lowering effects, statins also possess **additional antioxidant, anti-inflammatory and anti-proliferative properties**. These are **known as pleiotropic effects** of statins and are responsible, in part for lowering the risk of stroke and MI. *Pravastatin also causes decrease in plasma fibrinogen levels*.



PRAVASTATIN

- **Minimum** drug interactions [metabolized by non-microsomal enzymes]
- **Minimum** Food interactions [Food increase absorption of all statins except pravastatin]
- **Minimum** risk of myopathy
- **Minimum** CNS penetration
- **Minimize** (Decrease) Fibrinogen Level



Statins are most powerful LDL lowering agents.

- Structurally lovastatin and simvastatin are inactive lactone prodrugs, pravastatin has active lactone ring whereas atorvastatin, fluvastatin and rosuvastatin are fluorine-containing congeners.
- All statins can be **absorbed** orally (*maximum fluvastatin*). **Food increases absorption of all drugs except pravastatin**. **Lovastatin and simvastatin** undergo extensive first pass metabolism and are administered as **prodrugs**.
- Pravastatin, fluvastatin, atorvastatin and rosuvastatin are administered as active drugs. *All drugs except pravastatin are metabolized extensively by hepatic microsomal enzymes*. Pravastatin is metabolized by sulfation (non-microsomal) and thus has least chances of drug interactions.
- **Rosuvastatin** is *longest acting* whereas **pitavastatin** is *most potent* statin.

Contd...

Contd...

- Major adverse effect of these drugs is **myopathy and hepatotoxicity**. Chances of myopathy increases if these are co-administered with fibrates (maximum with gemfibrozil) or niacin. Myopathy can proceed to rhabdomyolysis with resultant renal shutdown. *Pravastatin* remains confined to the liver and is *safer in this regard*. These agents should be *avoided in pregnancy and lactation*.
- Statins are the **first line drugs for type IIa, type IIb and secondary hyperlipoproteinemia** (in these conditions, cholesterol level is raised more than TG).
- In children with heterozygous familial hypercholesterolemia, pravastatin is approved for children ≥ 8 years whereas other statins are approved for children ≥ 10 years. Pitavastatin has not been studied for this indication.

INTESTINAL CHOLESTEROL ABSORPTION INHIBITOR

Ezetimibe inhibits a transporter involved in intestinal absorption of cholesterol called NPC1L1. Due to decreased absorption, cholesterol content of the liver decreases and it responds by increasing LDL receptor synthesis. It can be used alone or combined with statins for type IIa and IIb hyperlipoproteinemia.

BILE ACID BINDING RESINS

These drugs *bind to bile acids in the intestinal lumen and decrease its reabsorption* (resulting in more excretion through faeces). Cholesterol pool of liver is depleted because it is utilized for the formation of bile acids. Liver acquires cholesterol from the plasma by increasing LDL receptors. *Bile acids inhibit TG production in the liver* and their deficiency results in **elevation of TGs**. **Bile acid binding resins are used only for type IIa disorder (TGs are normal in this condition)**. Drugs in this group include *cholestyramine, colestipol and colesevelam*.

Cholestyramine and colestipol are available as sachets. These are mixed with water, kept for some time (to increase the palatability) and then taken with meals. *Colesevelam is available as a tablet and has better patient compliance*. Major adverse effect of these drugs is constipation.

FIBRIC ACID DERIVATIVES

This group of drugs *acts by activating LPL* by activating a nuclear receptor, **PPAR α** (peroxisome proliferator activated receptor alpha). Major effect of the fibrates is to *reduce TG* (contained in VLDL) and to increase HDL. Clofibrate is not used now because it resulted in increased mortality (due to malignancies and post cholecystectomy complications) and did not prevent fatal MI. *Gemfibrozil, fenofibrate and bezafibrate are currently available*. **Fenofibrate is a prodrug with longest half life. It has maximum LDL cholesterol lowering action**. *Fibrates also reduce plasma fibrinogen level*. Fibrates are the **drugs of choice in hypertriglyceridemia (type III and IV)** and can be used with other drugs in type IIb (fenofibrate, as it has maximum LDL reducing action). **Fenofibrate is uricosuric and can be used in the setting of hyperuricemia**. GI distress and elevation of aminotransferases are important adverse effects of fibric acid derivatives. *Risk of myopathy is increased if these are used with statins except bezafibrate*.

NICOTINIC ACID

Niacin (not nicotinamide) is an inexpensive drug (vitamin B₃) that produces decrease in LDL cholesterol and VLDL triglycerides along with increase in HDL cholesterol. It **acts by inhibiting lipolysis in the adipose tissue**. Among all hypolipidemic drugs, niacin has **maximum HDL increasing property**; therefore it is useful in patients having increased risk of CAD. Further, *it can also decrease lipoprotein (a) and fibrinogen*. It is *useful for type IIb, III and IV disorders*. Main **compliance limiting feature is cutaneous flushing and pruritis**. These symptoms are due to vasodilatory action of niacin through release of PGs and can be **prevented by pretreatment with aspirin**. To minimize the side effects, niacin should be started at low doses. Other important adverse effects are **GI toxicity and hyperuricemia**. Niacin can also lead to **hepatotoxicity** which is *manifested by fall in both LDL as well HDL cholesterol*.

Pleiotropic Effects of Statins

- Antioxidant
- Anti-inflammatory
- Anti-proliferative

All statins can be absorbed orally (*maximum fluvastatin*).

Bile acids inhibit TG production in the liver and their deficiency results in elevation of TGs.

N

Mipomersen is an antisense oligonucleotide inhibitor of **mRNA of apo B-100 synthesis**. It is indicated as **once weekly injection** for treatment of **homozygous familial hypercholesterolemia**

Fibrates are drugs of choice in hypertriglyceridemia (type III and IV)



Lomitapide acts by inhibiting microsomal triglyceride transfer protein (MTP). This protein is necessary for VLDL assembly and secretion in liver.



Risk of myopathy is increased if fibrates are used with statins except bezafibrate.



Niacin has maximum HDL increasing property



Niacin can cause hepatotoxicity and hyperuricemia.

MISCELLANEOUS DRUGS

Probucol is useful because of its *antioxidant* action. It inhibits oxidation of LDL and causes reduction in levels of both HDL and LDL cholesterol. **Gugulipid** is the drug developed by Central Drug Research Institute, Lucknow. It causes modest decrease in LDL and slight increase in HDL cholesterol. Diarrhea is the only adverse effect of this drug.

NEW DRUGS

- **Avasimibe** is an *inhibitor of enzyme ACAT-1* (acyl coenzyme A: cholesterol acyl transferase-1) which forms cholesterol ester from cholesterol.
- **Torcetrapib and anacetrapib** increase HDL cholesterol by inhibiting the enzyme CETP (cholesterol ester triglyceride transport protein).
- **Lomitapide** acts by inhibiting microsomal triglyceride transfer protein (MTP). This protein is necessary for VLDL assembly and secretion in liver.

Optimal Plasma Levels of Lipids (National Cholesterol Education Program 2001)

Plasma Lipids	Desirable Plasma Concentration (mg/dl)
Total Cholesterol	< 200
LDL-C	< 100
HDL-C	> 40 (for males) > 50 (for females)
TG	< 150

LDL-C goals and cut points (in mg/dl)

Risk Category	LDL Goal	LDL level to start lifestyle changes	LDL level to start drugs
CHD or equivalent (10 year risk > 20%)	< 100	≥ 100	≥ 130
2+ Risk factors (10 year risk 10–20%)	< 130	≥ 130	≥ 130
2+ Risk factor (10 year risk < 10%)	< 130	≥ 130	≥ 160
0-1 Risk factor	< 160	≥ 160	≥ 190

DRUG OF CHOICE	
Condition	Drug of choice
• Diabetic nephropathy	ACE inhibitors or ARBs
• Scleroderma hypertensive crisis	Captopril
• Congestive heart failure	
– Decompensated	Dobutamine
– Compensated	ACEI/ARB
• Hypertrophic obstructive cardiomyopathy	Propanolol
• Angina pectoris	
– Acute attack	Sublingual nitroglycerine
– Prophylaxis	Oral/transdermal nitrates
• Esophageal spasm	Nitroglycerine
• Cyanide poisoning	Hydroxocobalamin/amyl nitrite
• Raynaud's phenomenon	Nifedipine ER or amlodipine
• Myocardial infarction	
– Pain relief	Sublingual nitroglycerine ↓ Morphine
– Prophylaxis	Aspirin
– Thrombolytic for STEMI	Reteplase or alteplase
• Hypertension	Thiazides
– With BHP	Prazosin
– With diabetes mellitus	ACE inhibitors
– With ischemic heart disease (angina)	Beta blockers
– With chronic kidney disease	ACE inhibitors
– In pregnancy	Labetalol
• Acute severe digitalis toxicity	Digibind
• Hypertensive emergencies	Nicardipine + Esmolol
– In cheese reaction	Phentolamine
– in clonidine withdrawal	Phentolamine
– In aortic dissection	Nitroprusside + esmolol
– In Pregnancy	Labetalol
• Hyperlipidemia	
– Type IIa and IIb	Statins
– Type III (hypertriglyceridemia)	Fibrates
– Type IV	Statins
– Secondary to diabetes or nephrotic syndrome	Statins
• Supraventricular tachycardia	
– Narrow QRS complex	Verapamil or beta blockers
– Wide complex	Flecainide
– WPW syndrome	Flecainide
• Paroxysmal supraventricular tachycardia (PSVT)	
– Acute treatment	Adenosine
– Prophylaxis	Verapamil
• Ventricular tachycardia	Lignocaine
– Digitalis induced	Lignocaine
• Long QT syndrome (Torsades' de pointes)	Magnesium

MULTIPLE CHOICE QUESTIONS

CONGESTIVE HEART FAILURE

- Which among the following is the best inotrope drug for use in right heart failure? *(All India 2011)*
 - Dobutamine
 - Digoxin
 - Dopamine
 - Milrinone
- All of the following are seen in digitalis toxicity except: *(All India 2011)*
 - Ventricular bigeminy
 - Paroxysmal atrial tachycardia with fast ventricular rate
 - Regularization of atrial fibrillation
 - Bidirectional ventricular tachycardia
- All are true about starting of beta-blocker therapy in a patient with congestive heart failure except: *(AIIMS Nov 2010)*
 - They should be started with optimum doses
 - They should be gradually increased over weeks
 - Special precautions should be taken in cases of NYHA class III and IV
 - Carvedilol and metoprolol are the preferred drugs.
- The positive inotropic effect of digitalis is due to inhibition of Na^+/K^+ ATPase pump in cardiac muscle cell membrane leading to: *(DPG 2011)*
 - Decreased activity of $\text{Na}^+/\text{Ca}^{++}$ exchanger causing decreased influx of sodium and decreased efflux of Ca^{++} in the sarcolemma
 - Decreased efflux of Na^+ leading to less negative resting membrane potential and opening of voltage gated Ca^{++} channels on the T tubules
 - Increased intracellular Na^+ causing increased efflux of Na^+ and increased influx of Ca^{++} through $\text{Na}^+/\text{Ca}^{++}$ exchanger in the sarcolemma
 - Increased intracellular Na^+ decreasing the activity of Ca^{++} pump in the sarcoplasmic reticulum
- All of the following drugs are used for the treatment of congestive heart failure except: *(AIIMS Nov 2009)*
 - Nitroglycerine
 - Spironolactone
 - Nesiritide
 - Trimetazidine
- Digoxin toxicity is increased by all except: *(AIIMS May 2010, 2009) (AIIMS Nov 2008) (DNB 2008)*
 - Renal impairment
 - Hyperkalemia
 - Hypercalcemia
 - Hypomagnesemia
- Which of the following is a venodilator? *(DPG 2009)*
 - Hydralazine
 - Minoxidil
 - Nitroprusside
 - Nifedipine
- All of the following statements about nesiritide are true EXCEPT: *(AI 2007, AI 2005)*
 - It is a BNP analogue
 - It can be used in decompensated CHF
 - It can be administered orally
 - It causes loss of Na^+ in the urine
- The following drugs have significant drug interactions with digoxin except: *(AI 2005)*
 - Cholestyramine
 - Thiazide diuretics
 - Quinidine
 - Amlodipine
- Digoxin is contraindicated in: *(AI 2002)*
 - Supraventricular tachycardia
 - Atrial fibrillation
 - Congestive heart failure
 - Hypertrophic obstructive cardiomyopathy
- Digoxin is not indicated in: *(AI 2001)*
 - Atrial flutter
 - Atrial fibrillation
 - High output failure
 - PSVT
- Digoxin action is not affected in: *(AIIMS May, 2007)*
 - Hepatic disease
 - Electrolyte disturbances
 - Renal failure
 - MI
- BNP is degraded by: *(AIIMS May, 2007)*
 - Neutral endopeptidase
 - Elastase
 - Omapatrilat
 - ACE
- Drugs used in CHF are: *(PGI June, 2007)*
 - Nesiritide
 - Digoxin
 - Spironolactone
 - Losartan
 - Adrenaline

15. Digoxin toxicity is aggravated by: (PGI June, 2006)
 - (a) Hypokalemia
 - (b) Hyperkalemia
 - (c) Hypercalcemia
 - (d) Hypermagnesemia
 - (e) Hypocalcemia
16. Arteriolar dilators used in treatment of CHF include: (PGI June, 2002)
 - (a) Hydralazine
 - (b) Nifedipine
 - (c) Prazosin
 - (d) Enalapril
 - (e) Nitrates
17. Drugs that have been found to be useful in compensated heart failure include all of the following except:
 - (a) Na⁺ K⁺ ATPase inhibitors
 - (b) Alpha blockers
 - (c) Beta receptor agonists
 - (d) Beta receptor antagonists
18. Which of the following conditions increases the risk of digoxin toxicity?
 - (a) Administration of quinidine
 - (b) Hyperkalemia
 - (c) Hypermagnesemia
 - (d) Hypocalcemia
19. Drugs that reduce myocardial remodelling in CHF include all of the following except:
 - (a) Carvedilol
 - (b) Digoxin
 - (c) Enalapril
 - (d) Spironolactone
20. Drugs associated with clinically useful or physiologically important positive inotropic effects include all of the following except:
 - (a) Amrinone
 - (b) Enalapril
 - (c) Digoxin
 - (d) Dobutamine
21. Which of the following is a monovalent cation that can reverse a digitalis induced arrhythmia?
 - (a) Digibind antibodies
 - (b) Lignocaine
 - (c) Magnesium
 - (d) Potassium
22. Which of the following has been shown to prolong life in patients with chronic congestive heart failure but has a negative inotropic effect on cardiac contractility?
 - (a) Carvedilol
 - (b) Digoxin
 - (c) Enalapril
 - (d) Furosemide
23. Which of the following is the drug of choice in treating suicidal overdose of digitoxin?
 - (a) Digibind antibodies
 - (b) Lignocaine
 - (c) Magnesium
 - (d) Potassium
24. Angiotensin converting enzyme inhibitors are useful in congestive heart failure as:
 - (a) First choice drugs unless contraindicated
 - (b) An alternative to diuretics
 - (c) A substitute for digitalis
 - (d) Adjuncts only in resistant cases
25. The most important channel of elimination of digoxin is:
 - (a) Glomerular filtration
 - (b) Tubular secretion
 - (c) Hepatic metabolism
 - (d) Excretion in bile
26. Advantage of using digoxin in CHF is:
 - (a) It is used to provide relief of symptoms
 - (b) It reverses the pathological changes of CHF
 - (c) It prolongs the survival of CHF patient
 - (d) All of these
27. Digitalis is used in the treatment of acute CHF. It can also be used as a long-term maintenance therapy if CHF is associated with:
 - (a) Hypertension
 - (b) Hypertrophic obstructive cardiomyopathy
 - (c) Atrial fibrillation
 - (d) Mitral stenosis
28. Which of the following drugs can prolong survival in patients with CHF?
 - (a) Furosemide
 - (b) Inamrinone
 - (c) Losartan
 - (d) Digoxin
29. A patient of atrial fibrillation is on digoxin therapy. Which of the following responses do you expect?
 - (a) Restoration of normal sinus rhythm
 - (b) Conversion of atrial fibrillation to atrial flutter
 - (c) Increase in atrial fibrillation frequency, but decrease in ventricular rate
 - (d) Decrease in atrial fibrillation frequency but increase in ventricular rate
30. The diuretic of choice for rapid relief of congestive symptoms in a patient of CHF is:
 - (a) Hydrochlorothiazide
 - (b) Furosemide
 - (c) Metolazone
 - (d) Amiloride
31. All of the following are the actions of β -adrenoceptor blockers in CHF except:
 - (a) Decrease in mortality associated with CHF
 - (b) Antagonism of vasoconstriction due to sympathetic overactivity
 - (c) Prevention of pathological remodelling of ventricular myocardium
 - (d) Prevention of dangerous cardiac arrhythmias

32. Which of the following statements about the use of β -adrenergic blockers in CHF is true?
- They are first choice drugs for treatment of decompensated heart failure
 - They are used as alternative to conventional therapy with ACE inhibitors $\pm$ digitalis/diuretic
 - They are most useful in stable patients with mild to moderate heart failure
 - They should be used at highest possible dose
33. All of the following drugs are useful for long-term treatment of congestive heart failure except:
- Digoxin
 - Ramipril
 - Dobutamine
 - Spironolactone
34. Which of the following drugs is beneficial in a refractory congestive heart failure by increasing cardiac contractility and decreasing preload and afterload?
- Amiloride
 - Amiodarone
 - Amrinone
 - Carvedilol
35. All of the following statements about the use of spironolactone in CHF are true except:
- It should be administered in low doses to prevent hyperkalemia
 - It affords prognostic benefit in severe heart failure over and above that afforded by ACE inhibitors
 - It helps to overcome the refractoriness to thiazides
 - It affords rapid symptomatic relief in CHF patients
36. Current therapeutic status of milrinone in CHF is:
- First choice drug for a patient of mild CHF
 - As an add on drug to tide over the crisis in refractory CHF
 - Best drug for long-term maintenance therapy of CHF
 - Used only to suppress digitalis induced arrhythmias
37. Which of these drugs DO NOT decrease angiotensin II activity:
- Enalapril
 - Valsartan
 - Nesiritide
 - Omapatrilat
38. Which of the following is NOT true about the use of β blockers in CHF?
- These should be started at very low dose and slowly titrated upwards
 - Carvedilol is most widely used β blocker
 - These are drug of choice in acute decompensated heart failure
 - These can reduce mortality in CHF patients
39. Mechanism of action of digitalis in atrial fibrillation is:
- By decreasing cardiac contractility
 - $\text{Na}^+ \text{K}^+$ ATPase inhibition
 - Increase in refractoriness of AV nodal tissue
 - By causing bradycardia
40. Which of the following is not given in acute severe digitalis toxicity?
- Potassium
 - Digibind
 - Lignocaine
 - None of these
41. A patient Vipin has been taking digoxin for several years and is about to receive atropine for some other indication. A common side effect of digoxin that can be blocked by atropine is:
- Decreased appetite
 - Increased cardiac contractility
 - Increased PR interval on the ECG
 - Tachycardia
42. Digoxin is used in CHF associated with: (DPG 2010)
- HOCM (Hypertrophic obstructive cardiomyopathy)
 - High output failure
 - Atrial fibrillation with high ventricular rate
 - All of the above
43. Digoxin is contra indicated in: (RJ 2006)
- Supraventricular tachycardia
 - Atrial fibrillation
 - Congestive heart failure
 - Hypertrophic obstructive cardiomyopathy
44. Which one of the following provides hemodynamic stability and prolongs survival in congestive heart failure? (Karnataka 2009)
- Lisinopril
 - Furosemide
 - Digoxin
 - Milrinone
45. The drug that is NOT useful in congestive heart failure is: (Karnataka 2009)
- Adrenaline
 - Digoxin
 - Hydrochlorothiazide
 - Enalapril
46. Which of the following is not a contraindication for use of digitalis: (DPG 2006)
- Acute rheumatic carditis
 - Thyrotoxicosis
 - WPW syndrome
 - Hyperkalemia
47. Therapeutic plasma level of digoxin is: (DPG 2005)
- 0.1-0.3 ng/ml
 - 0.8-1.5 ng/ml
 - 1.2 to 2 ng/ml
 - More than 2.4 ng/ml
48. Digibind is used to: (DPG 2001)
- Potentiate the action of digoxin
 - Decrease the metabolism of digoxin

- (c) Treat digoxin toxicity
(d) Rapidly digitalize the patient
49. All are true about digoxin except: (DPG 2000)
(a) Causes bradycardia due to increased vagal tone
(b) Acts by inhibiting Na^+K^+ ATPase in myocardial fibres
(c) It is 95% plasma protein bound
(d) Primarily excreted unchanged by glomerular filtration
50. All of the following drugs reduce afterload, EXCEPT: (DPG 1998)
(a) Enalapril
(b) Propanolol
(c) Hydralazine
(d) Sodium nitroprusside
51. Sodium-nitroprusside acts by activation of: (MPPG 2001)
(a) Guanylate cyclase
(b) K^+ channels
(c) Ca^{++} channels
(d) Cyclic AMP
52. Ouabain acts by inhibiting: (MPPG 2001)
(a) Adenyl cyclase
(b) Ca^{++} channels
(c) H^+K^+ ATPase
(d) Na^+K^+ ATPase
53. Time taken for digitalization is: (RJ 2002)
(a) 36 hours
(b) 12 hours
(c) 5 day
(d) 10 day
54. Drug directly acting on blood vessels is: (RJ 2003)
(a) Hydralazine
(b) Verapamil
(c) Propanolol
(d) Methyldopa
55. Digitalis toxicity can cause: (RJ 2004)
(a) Hyperkalemia
(b) Nausea
(c) Arrhythmias
(d) All of the above
56. In LVE, the drug which can be administered is: (RJ 2009)
(a) Propanolol
(b) Morphine
(c) Amlodipine
(d) Epinephrine
57. Digitalis has positive inotropic effect-by the virtue of its effect on: (MH 2007)
(a) $\text{Na}^+ \text{K}^+$ ATPase pump
(b) Na Glucose channels
(c) H^+K^+ ATPase pump
(d) Calcium Pump
58. Drugs causing afterload reduction is: (Kolkata 2008)
(a) Digoxin
(b) Captopril
(c) Dobutamine
(d) Frusemide
59. The biochemical mechanism of action of digitalis is associated with: (Karnataka 2005)
(a) An increase in conduction from atrium to ventricle
(b) An increase in ATP synthesis
(c) An increase in systolic intracellular calcium levels
(d) A block of calcium channels
60. Best treatment of severe digitalis toxicity is: (Jharkhand 2004) (Karnataka 2002)
(a) Potassium supplements
(b) Diphenyl hydantoin
(c) Quinidine
(d) Fab fragments of digitalis antibodies
61. Which one of the following is the most characteristic arrhythmia with digitalis toxicity? (Karnataka 2001)
(a) Atrial fibrillation
(b) Extrasystoles
(c) NPAT with block
(d) Auricular flutter

HYPERTENSION

62. Systemic vascular resistance is twice that of normal, treatment should be: (AIIMS Nov 2013)
(a) Adrenaline
(b) Nor-adrenaline
(c) Sodium nitroprusside
(d) Isoprenaline
63. Which of the following drug reduces blood pressure primarily by directly decreasing heart rate alone: (DPG 2009)
(a) Propanolol
(b) Prazosin
(c) Alpha methyl dopa
(d) Nitroprusside sodium
64. The antihypertensive which causes decreased libido and impotence is: (DNB 2001)
(a) Atenolol
(b) Enalapril
(c) Prazosin
(d) Diltiazem
65. Which of the following statements about Diazoxide is false? (AIIMS May 2011)
(a) It acts by causing prolonged opening of ATP dependent K^+ channels in beta cells
(b) It can cause severe hypoglycemia.
(c) It can be used to treat patients with insulinoma.
(d) It is used as an antihypertensive agent.
66. Alpha methyldopa is primarily used for: (AI 2010)
(a) Pregnancy induced hypertension
(b) Renovascular hypertension
(c) First line agent in hypertension
(d) Refractory hypertension

67. Calcium channel blocking agents of use in the treatment of hypertension include: (DPG 2009)
 (a) Prazosin
 (b) Lidoflazine
 (c) Captopril
 (d) Nifedipine
68. Which of the following is NOT a frontline antihypertensive agent? (DPG 2009)
 (a) Enalapril
 (b) Hydrochlorothiazide
 (c) Amlodipine
 (d) Atenolol
69. Which of the following drugs should NOT be used in setting of severe hypertension in elderly on empirical basis? (DPG 2009)
 (a) Enalapril
 (b) Amlodipine
 (c) Chlorthiazide
 (d) Prazosin
70. All of the following statements about clonidine are true EXCEPT: (AI 2007)
 (a) It is an α -adrenergic agonist
 (b) It can cause dry mouth as an adverse effect
 (c) Prazosin completely antagonizes its action
 (d) It inhibits sympathetic outflow.
71. All of the following are useful in the intravenous therapy for hypertensive emergencies except: (AI 2003)
 (a) Fenoldopam
 (b) Urapidil
 (c) Enalaprilat
 (d) Nifedipine
72. The mechanism of action of sodium nitroprusside is: (AI 2002)
 (a) Increased cAMP
 (b) Stimulation of guanylate cyclase
 (c) Calcium channel blockage
 (d) K^+ channel opener
73. A 50 year old male presents with malignant hypertension. The drug of choice is: (AI 2000)
 (a) Sodium nitroprusside
 (b) Sublingual nifedipine
 (c) Furosemide
 (d) Enalapril
74. Maximum incidence of impotence is seen with the following anti-hypertensive agent: (AIIMS May, 2007)
 (a) CCBs
 (b) Beta blockers
 (c) ARBs
 (d) ACE inhibitors
75. Which drug should not be given in pregnancy?
 (a) Labetalol (AIIMS May, 2007)
 (b) ACE inhibitors (APPG 2007)
 (c) Hydralazine (AIIMS Nov, 2004)
 (d) Methyl dopa (DPG 2008, Bihar 2006)
76. Which of the following statements about hydralazine is not true? (AIIMS Nov, 2004)
 (a) It causes direct relaxation of the blood vessels
 (b) It causes dilatation of both arteries and veins
 (c) Postural hypotension is not a common problem
 (d) It increases plasma renin activity
77. The following statement is not true about the use of clonidine in the treatment of hypertension: (AIIMS May, 2003)
 (a) Reduction in central sympathetic outflow
 (b) Increase in LDL-cholesterol on prolonged use
 (c) Sedation and xerostomia are common side effects
 (d) It can be combined with vasodilators
78. A 60-year old hypertensive patient on angiotensin II receptor antagonist (losartan) is posed for hernia repair surgery. The antihypertensive drug should be: (AIIMS May, 2003)
 (a) Continued till the day of operation
 (b) Discontinued 24 hrs preoperatively
 (c) Discontinued one week preoperatively
 (d) Administered in an increased dosage on the day of operation
79. An elderly hypertensive has diabetes mellitus and bilateral renal artery stenosis. The best management is: (AIIMS May, 2001)
 (a) Enalapril
 (b) Verapamil
 (c) Beta blockers
 (d) Thiazides
80. Drugs that can be used for the treatment of hypertension in a diabetic patient are: (PGI Dec. 2007)
 (a) Losartan
 (b) Captopril
 (c) Amlodipine
 (d) Hydrochlorothiazide
 (e) Metoprolol
81. Antihypertensive drugs beneficial or having neutral role in lipid metabolism: (PGI Dec. 2004)
 (a) Prazosin
 (b) Propanolol
 (c) Furosemide
 (d) Losartan
 (e) Chlorthiazide
82. Combination use of beta blockers and calcium channel blockers cause: (PGI Dec. 2001)
 (a) Heart block
 (b) Hypertension
 (c) Hypotension
 (d) Bradycardia
 (e) Tachyarrhythmias
83. Which of the following is true regarding enalapril treatment in patients of essential hypertension?
 (a) Decreased angiotensin II concentration in the blood
 (b) Decreased concentration of renin in the blood

- (c) Decreases sodium and increases potassium in the urine
(d) All of the above
84. **Postural hypotension is the common side effect of which of the following?**
(a) ACE inhibitors
(b) Alpha receptor blockers
(c) Arteriolar dilators
(d) Selective β_1 blockers
85. **Mr. Rushil has severe hypertension and is to receive minoxidil. Minoxidil is a powerful arteriolar vasodilator that does not act on autonomic receptors. When used in severe hypertension, its effects would probably include:**
(a) Tachycardia and increased cardiac contractility
(b) Tachycardia and decreased cardiac output
(c) Decreased mean arterial pressure and decreased cardiac contractility
(d) Decreased mean arterial pressure and increased salt and water excretion by the kidney
86. **Clonidine is used as an antihypertensive agent but if used as a fast intravenous injection, it can increase the blood pressure due to:**
(a) Stimulation of vasomotor center
(b) Release of noradrenaline from adrenergic nerve endings
(c) Agonistic action on vascular α_2 adrenergic receptors
(d) Cardiac stimulation
87. **Both methyl dopa and clonidine are safe in pregnancy. Reason for preferring the former is that:**
(a) It is less likely to cause rebound hypertension on sudden discontinuation
(b) It does not reduce plasma renin activity
(c) It has a central as well as peripheral site of antihypertensive action
(d) It does not produce central side effects
88. **Prolonged use of hydralazine for the treatment of hypertension is likely to cause:**
(a) Gynaecomastia
(b) Thrombocytopenia
(c) Hemolytic anemia
(d) Lupus erythematosus
89. **The antihypertensive agent that should be avoided in young females and is used topically to treat alopecia is:**
(a) Hydralazine
(b) Prazosin
(c) Minoxidil
(d) Indapamide
90. **All of the following antihypertensive drugs increase plasma renin activity except:**
(a) Clonidine
(b) Hydralazine
(c) Nifedipine
(d) Captopril
91. **Which antihypertensive is a prodrug and is converted to its active form in brain?**
(a) Clonidine
(b) Methyl dopa
(c) Minoxidil
(d) Nitroprusside
92. **Which of these antihypertensives DO NOT have any central action?**
(a) Propanolol
(b) Methyl dopa
(c) Clonidine
(d) Prazosin
93. **A diabetic patient with bilateral renal artery stenosis requires a drug for the treatment of high blood pressure. Which of the following drugs will be most appropriate for this patient?**
(a) Hydrochlorothiazide
(b) Metoprolol
(c) Enalapril
(d) Amlodipine
94. **When treating hypertension chronically, orthostatic hypotension is maximum with:**
(a) Clonidine
(b) Guanethidine
(c) Prazosin
(d) Propanolol
95. **Which of the following drugs is used in severe hypertensive emergencies, is very short acting and must be given by i.v. infusion?**
(a) Diazoxide
(b) Hydralazine
(c) Labetalol
(d) Nitroprusside
96. **In which of the following patients would enalapril be the best first line agent for high blood pressure control?**
(a) A 62 year old man with renal artery stenosis
(b) A 32 year old pregnant female
(c) A 41 year old woman with hyperkalemia
(d) A 56 year old diabetic woman
97. **A patient has been prescribed a drug A by a doctor for treating his hypertension. This drug can cause tachycardia and marked fluid retention. Which of the following can be the drug A?**
(a) Captopril
(b) Guanethidine
(c) Minoxidil
(d) Metoprolol
98. **A patient, Sunder is admitted to the emergency with severe bradycardia following drug overdose. The concerned drug was being taken for hypertension. Which of the following cannot be the drug?**
(a) Clonidine
(b) Hydralazine

- (c) Propanolol
(d) Reserpine
99. A pregnant patient, Lata is admitted for the workup of hemolytic anemia. She is giving the history of taking an antihypertensive drug after beginning of her pregnancy. The most likely cause would be:
(a) Minoxidil
(b) Clonidine
(c) Methyl dopa
(d) Labetalol
100. A patient Shyam is admitted to the emergency following a drug overdosage with severe tachycardia. He had been receiving therapy for hypertension and angina. Which of the following drugs can cause tachycardia?
(a) Guanethidine
(b) Isosorbide dinitrate
(c) Propanolol
(d) Verapamil
101. Devesh is working as a CEO in a company. He has a traveling job. He is a known diabetic controlled on oral hypoglycemic drugs. On his recent visit to the doctor, his blood pressure was found to be 164/102 mm Hg. Most suitable drug for this patient should be?
(a) Propanolol
(b) Enalapril
(c) Clonidine
(d) Hydrochlorothiazide
102. A 40-year-old politician suffered from attacks of chest pain diagnosed as angina pectoris. He had a tense personality, resting heart rate was 96/min blood pressure 170/104mm Hg, but blood sugar level and lipid profile were normal. Select the most suitable antihypertensive for the initial therapy in his case:
(a) Nifedipine
(b) Hydrochlorothiazide
(c) Atenolol
(d) Methyl dopa
103. Rajat jain was presented to casualty in an unconscious state. His blood pressure was found to be 220/110 mm Hg. Most suitable drug for this patient to rapidly decrease the blood pressure is:
(a) Sublingual nifedipine
(b) Intramuscular injection of hydralazine
(c) Intravenous infusion of sodium nitroprusside
(d) Intravenous injection of clonidine
104. Which of the following antihypertensive drug does not alter serum glucose and lipid levels?
(a) Propanolol
(b) Prazosin
(c) Thiazide diuretics
(d) None of the above
105. Drug not useful in hypertensive emergency is:
(a) IV hydralazine
(b) Indapamide
(c) Sublingual nifedipine
(d) Sodium nitroprusside
106. Which of the following is not an adrenergic neuron blocking drug?
(a) Reserpine
(b) Guanethidine
(c) Bretylium
(d) Minoxidil
107. Which of the following drug has a favourable effect on lipid metabolism?
(a) Atenolol
(b) Chlorothiazide
(c) Clonidine
(d) Torsemide
108. The choice of antihypertensive medication also depends upon the co-morbid illness of the patient and all of the following recommendations have been made EXCEPT:
(a) In hypertensive patients with heart failure, ACE inhibitors may be preferred
(b) In hypertensive patients with migraine, beta blockers are an excellent choice
(c) In hypertensive patients with gout, diuretics are particularly useful
(d) In hypertensive patients with peripheral vascular disease, calcium channel blockers are recommended.
109. An anti-hypertensive drug that causes positive Coomb's test is:
(a) Methyl dopa
(b) Clonidine
(c) Hydralazine
(d) Sodium-nitroprusside
110. The drug of choice in digitalis induced ventricular arrhythmias is:
(a) I.V. Lignocaine
(b) Phenytoin
(c) Quinidine
(d) Procainamide
111. Drug of choice in pregnancy induced hypertension is
(a) Amoldipine
(b) Losartan
(c) Diuretic
(d) Methyl dopa
112. Centrally acting sympatholytic agent used as anti-hypertensive agent is:
(a) Propanolol
(b) Clonidine
(c) Prazosin
(d) Phenoxybenzamine

113. All of the following are vasodilators except: (Bihar 2006)
 (a) Methyl dopa
 (b) Nitroprusside
 (c) Hydralazine
 (d) Diazoxide
114. Treatment of choice in hypertension with diabetes mellitus is: (AP 2000)
 (a) Beta-blockers
 (b) Thiazides
 (c) ACE inhibitors
 (d) Calcium channel blockers
115. Which of the following antihypertensives causes sedation: (Kolkata 2007)
 (a) Clonidine
 (b) Hydralazine
 (c) Losartan
 (d) Amlodipine
122. The nitrate which does not undergo first pass metabolism is: (AI 2000)
 (a) Isosorbide mononitrate
 (b) Nitroglycerine
 (c) Pentaerythritol tetranitrate
 (d) Isosorbide dinitrate
123. Mechanism of action of sodium nitrite in cyanide poisoning: (PGI June, 2005)
 (a) Produces methemoglobinemia
 (b) Increased blood flow to liver
 (c) Increased blood flow to heart
 (d) Increased blood flow to kidney
124. You decide not to prescribe sildenafil in a patient because the patient told you that he is taking an antianginal drug. Which of the following can it be?
 (a) Calcium channel blockers
 (b) β adrenergic blockers
 (c) Organic nitrates
 (d) Angiotensin converting enzyme inhibitors
125. Verapamil is associated with all of the following except?
 (a) Constipation
 (b) Bradycardia
 (c) Hyperglycemia
 (d) Increased PR interval
126. The antianginal effect of propranolol may be attributed to which of the following?
 (a) Block of exercise induced tachycardia
 (b) Dilation of constricted coronary vessels
 (c) Increased cardiac force
 (d) Increased resting heart rate
127. Which of the following drugs has been used in the treatment of angina by inhalation and has a very rapid onset and brief duration of action?
 (a) Amyl nitrite
 (b) Isosorbide mononitrate
 (c) Nitroglycerine
 (d) Propranolol
128. Which of the following is an active metabolite of another drug and is available as a separate drug for the treatment of angina?
 (a) Isosorbide mononitrate
 (b) Isosorbide dinitrate
 (c) Nitroglycerine
 (d) Propranolol
129. The drug effective for treatment as well as prophylaxis of angina pectoris is:
 (a) Isosorbide dinitrate
 (b) Pentaerythritol tetranitrate
 (c) Diltiazem
 (d) Dipyridamole
116. Which of the following agent is a rho kinase inhibitor? (AIIMS Nov 2013, May 2013)
 (a) Fasudil
 (b) Ranolazine
 (c) Amiloride
 (d) Nicorandi
117. All of the following drugs can worsen angina except: (AIIMS May 2011)
 (a) Dipyridamole
 (b) Oxyphedrine
 (c) Thyroxine
 (d) Sumatriptan
118. All are true about ranolazine except? (All India 2011)
 (a) It causes hypotension
 (b) It is recommended as first line treatment for angina
 (c) It improves glycemic control
 (d) It is not indicated for acute attack of angina
119. Nitrates are used for all of the following conditions except? (AIIMS Nov 2009)
 (a) Congestive heart failure
 (b) Cyanide poisoning
 (c) Esophageal spasm
 (d) Renal colic
120. Nitroglycerine causes all except: (AI 2009)
 (a) Hypotension and bradycardia
 (b) Methemoglobinemia
 (c) Hypotension and tachycardia
 (d) Vasodilation
121. Coronary steal phenomenon is seen with: (AI 2000) (MH 2000)
 (a) Dipyridamole
 (b) Diltiazem
 (c) Propranolol
 (d) Verapamil

130. Which of the following statements best explains the action of nitroglycerine on coronary vessels:
- It mitigates angina pectoris by increasing total coronary flow
 - It preferentially dilates conducting arteries without affecting resistance arterioles
 - It preferentially dilates autoregulatory arterioles without affecting the larger arteries
 - It mainly decreases the afterload
131. Isosorbide dinitrate decreases preload more than afterload. Predominant venodilator action of nitrates is due to the reason that:
- They are selectively concentrated in veins
 - Veins express larger quantities of enzymes that generate NO from nitrates
 - Venous smooth muscle has greater capacity to relax
 - All of the above are correct
132. Nitroglycerine exerts beneficial effects in classical angina pectoris primarily by:
- Increase in total coronary blood flow
 - Redistribution of coronary blood flow
 - Reduction of cardiac preload
 - Reduction of cardiac afterload
133. Nitroglycerine exerts beneficial effects in variant angina primarily by:
- Coronary vasodilation
 - Decreased ventricular contractility
 - Reduction of cardiac preload
 - Reduction of cardiac afterload
134. Organic nitrates can lead to the development of tolerance when used chronically. Which of the following preparations is least likely to develop tolerance:
- Sustained release oral nitroglycerine
 - Sublingual nitroglycerine
 - Transdermal nitroglycerine
 - Oral pentaerythritol tetranitrate
135. Nitroglycerine can be administered by all of the following routes except:
- Oral
 - Sublingual
 - Intramuscular
 - Intravenous
136. Concomitant administration of this drug with organic nitrates is contra-indicated due to marked potentiation of vasodilatory action leading to profound hypotension. This drug is:
- Propanolol
 - Fluoxetine
 - Hydrochlorothiazide
 - Sildenafil
137. Which of the following drugs is most likely to precipitate angina?
- Amlodipine
 - Nifedipine
 - Diltiazem
 - Verapamil
138. All of the following statements about amlodipine are true except:
- It acts by conversion to an active metabolite in the liver
 - It has a very large volume of distribution
 - It undergoes very little first pass metabolism and possesses high and consistent oral bioavailability
 - It has a very long elimination half life
139. Propanolol is contra-indicated in a patient of angina pectoris who is already receiving:
- Nifedipine
 - Aspirin
 - Verapamil
 - Isosorbide mononitrate
140. True statement about trimetazidine is:
- It is a novel sodium channel blocker
 - It improves tissue perfusion by modifying rheological property of blood
 - It is an inhibitor of fatty acid oxidation
 - Both (a) and (b) are correct
141. An experimental drug is found to preferentially dilate autoregulatory coronary arterioles without affecting large conducting vessels. It is likely to:
- Evoke coronary steal phenomenon
 - Mitigate classical angina but not variant angina
 - Produce tachycardia as an adverse effect
 - Useful in CHF
142. This drug is a classical example of pharmacological success but therapeutic failure. Reason for its therapeutic failure is coronary steal phenomenon. It is:
- Glyceryl trinitrate
 - Dipyridamole
 - Propanolol
 - Diltiazem
143. Calcium channel blockers with predominant peripheral effects is:
- Verapamil
 - Diltiazem
 - Amlodipine
 - None of these
144. Longest acting nitroglycerine preparation is:
- Glyceryl trinitrate
 - Amyl nitrite
 - Penta erythritol tetranitrate
 - Isosorbide dinitrate
145. A drug lacking vasodilatory properties that is effective in angina is:
- Isosorbide dinitrate
 - Metoprolol
 - Nifedipine
 - Verapamil

146. Which of the following drugs is capable of maintaining blood levels for 24 hours after a single administration but has useful antianginal effects lasting only about 10 hours?
- Amyl nitrite
 - Isosorbide mononitrate
 - Nitroglycerine (sublingual)
 - Nitroglycerine (transdermal)
147. A patient of acute myocardial infarction being treated in intensive care unit developed left ventricular failure with raised central venous pressure. It was decided to use nitroglycerine. Which route of administration would be most suitable?
- Sublingual
 - Oral
 - Intravenous bolus injection
 - Slow intravenous infusion
148. A patient on nitroprusside therapy developed cyanide toxicity. Sodium nitrite was administered i.v. to combat this poisoning. Beneficial effect of sodium nitrite in this case is dependent on:
- Direct chelation of cyanide with sodium nitrite
 - Vasodilatation caused by sodium nitrite
 - Conversion of hemoglobin to methemoglobin by sodium nitrite
 - Facilitation of cyanocobalamin formation by sodium nitrite.
149. Glyceryl trinitrate is given by sublingual route because of: (DPG 2002, UPPG 2006)
- Short $t_{1/2}$ in plasma
 - High hepatic first pass metabolism
 - High bioavailability by oral route
 - Extensive protein binding
150. Calcium channel blockers are useful in all, EXCEPT: (DPG 2001)
- Angina
 - Supraventricular arrhythmia
 - Sick sinus syndrome
 - Hypertension
151. Which of the following statements is true about nitrates? (DPG 2000)
- Acts by raising cGMP which causes dephosphorylation of MLCK
 - Metabolized by glutathione reductase
 - Used in achalasia cardia
 - All of the above
152. Nimodipine is used in: (Karnataka 2000, DPG 1999)
- Sub-arachnoid hemorrhage
 - Intra cerebral hemorrhage
 - Extra dural hemorrhage
 - Sub-dural hemorrhage
153. Nitrates decrease myocardial oxygen consumption by all of the following mechanisms EXCEPT: (MPPG 2007)
- By increasing the left ventricular end diastolic pressure
 - By direct reduction of oxygen consumption of the myocardial cell
 - By dilation of the capacitance vessels
 - By decreasing the size of heart
154. Nitrate causes all of the following EXCEPT: (MPPG 2004)
- Decrease in heart size
 - Increase in cardiac work
 - Preload reduction
 - Dilatation of cutaneous blood vessels
155. Calcium channel blockers are used in all EXCEPT: (MPPG 2002)
- Angina
 - Arrhythmia
 - Congestive heart failure
 - Hypertension
156. Drug not to be given in ischemic heart disease is: (MPPG 2001)
- Atenolol
 - ACE inhibitor
 - Isoproterenol
 - Streptokinase
157. Potassium channel opener with anti-anginal activity is: (UP 2006)
- Nicorandil
 - Dipyridamole
 - Trimetazidine
 - Oxyphedrine
158. All of the following drugs act by blocking calcium channels except: (TN 2007)
- Dantrolene
 - Nicardipine
 - Diltiazem
 - Verapamil
159. Amyl nitrite is used by which route? (MH 2000)
- Oral
 - Inhalation
 - IV
 - IM
160. Propanolol should not be given to a patient on treatment with which of the following drug? (MH 2003)
- Nifedipine
 - Nitrates
 - ACE inhibitors
 - Verapamil
161. Verapamil is contraindicated in: (MH 2005)
- Hypertension
 - Complete heart block
 - Paroxysmal supraventricular tachycardia
 - Angina pectoris
162. Enalapril increases the levels of which of the following? (Jharkhand 2004)
- Bradykinin
 - Interferon
 - PAF
 - TNF

- 163. All are dihydropyridines except:** (Jharkhand 2006)
 (a) Nifedipine
 (b) Nimodipine
 (c) Verapamil
 (d) Felodipine
- 164. The major clinical use of nimodipine is in:** (Karnataka 2006)
 (a) Hypertension
 (b) Angina pectoris
 (c) Subarachnoid haemorrhage
 (d) Raynaud's phenomenon
- 165. When nitrates are combined with calcium channel blockers:** (Karnataka 2006)
 (a) Arterial pressure will decrease
 (b) Heart rate will increase
 (c) Ejection time will decrease
 (d) End-diastolic volume will increase
- 166. Calcium channel blocker with maximum effect on conduction in heart is:** (DPG 2007)
 (a) Phenylamine
 (b) Nifedipine
 (c) Diltiazem
 (d) Verapamil
- ARRHYTHMIA**
- 167. All are toxicities seen with amiodarone therapy except:** (AIIMS May 2009)
 (a) Pulmonary fibrosis
 (b) Corneal microdeposits
 (c) Cirrhosis of liver
 (d) Productive cough
- 168. True about quinidine is/are:** (PGI Dec. 2004)
 (a) It increases effective refractory period
 (b) Used in hypertension
 (c) Causes paradoxical tachycardia
 (d) It decreases absolute refractory period
 (e) Cinchonism is seen
- 169. Drug of choice for supraventricular tachycardia is:** (AI-2008)
 (a) Verapamil
 (b) Diltiazem
 (c) Digoxin
 (d) Phenytoin
- 170. Which of the following drugs can cause Torsades'de pointes?** (AI-2008)
 (a) Quinidine
 (b) Lignocaine
 (c) Esmolol
 (d) Flecainide
- 171. Which of the following is not an adverse effect of chronic amiodarone therapy?** (AI 2004)
 (a) Pulmonary Fibrosis (RJ 2007, 2003)
 (b) Hypothyroidism
 (c) Hyperthyroidism
 (d) Systemic lupus erythematosus
- 172. Which of the following anti-arrhythmic agents does not belong to class Ic?** (AIIMS Nov 2006)
 (a) Tocainide
 (b) Encainide
 (c) Flecainide
 (d) Propafenone
- 173. The following statement is not true about sotalol:** (AIIMS May, 2003)
 (a) It is a non-selective beta-blocker
 (b) It prolongs action potential duration throughout the heart
 (c) It is excreted through bile following hepatic metabolism
 (d) Polymorphic ventricular tachycardia is a common side-effect
- 174. In a patient of congenital prolonged QT syndrome and intermittent Torsades de pointes, which of the following should be prescribed:** (AIIMS Nov, 2001)
 (a) Magnesium sulphate
 (b) Metoprolol
 (c) Cardiac pacing
 (d) Isoprenaline
- 175. Antiarrhythmic drugs causing torsades de pointes are:** (PGI June, 2003)
 (a) Quinidine
 (b) Disopyramide
 (c) Procainamide
 (d) Lidocaine
 (e) Propanolol
- 176. Urgent treatment of procainamide toxicity is:**
 (a) Calcium chelation
 (b) KCl
 (c) Nitroprusside
 (d) Sodium lactate
- 177. All of the following drugs can be used for the chronic oral treatment of arrhythmia except:**
 (a) Amiodarone
 (b) Esmolol
 (c) Quinidine
 (d) Verapamil
- 178. The anti-arrhythmic drug of choice in most of the cases of acute paroxysmal supraventricular tachycardia is:**
 (a) Adenosine
 (b) Amiodarone
 (c) Propanolol
 (d) Quinidine
- 179. Drugs that consistently reduce the potassium repolarising current and thereby prolong the action potential duration include all of the following except:**
 (a) Amiodarone
 (b) Lignocaine
 (c) Quinidine
 (d) Sotalol

180. Characteristic adverse effect of quinidine includes:
- Lupus erythematosus
 - Cinchonism
 - Increase in digoxin clearance
 - Precipitation of hyperthyroidism
181. Which of the following has the maximum half life?
- Adenosine
 - Amiodarone
 - Esmolol
 - Lidocaine
182. Which of the following antiarrhythmic drugs can decrease the slope of Phase 0 and prolong the action potential duration?
- Lignocaine
 - Propanolol
 - Quinidine
 - Adenosine
183. All of the following statements are true about quinidine except:
- It blocks myocardial Na⁺ channels primarily in the open state
 - It has no effect on myocardial K⁺ channels
 - It produces frequency dependent blockade of myocardial Na⁺ channels
 - It delays recovery of myocardial Na⁺ channels
184. Lignocaine is useful for the treatment of:
- Atrial fibrillation
 - Paroxysmal supraventricular tachycardia
 - Digitalis induced ventricular extrasystoles
 - All of the above
185. The antiarrhythmic drug having effectiveness in a wide range of ventricular as well as supra-ventricular arrhythmias and acting mainly by prolongation of action potential is:
- Quinidine
 - Amiodarone
 - Lignocaine
 - Tocainide
186. Which of the following drugs is used for termination as well as prophylaxis of paroxysmal supraventricular tachycardia?
- Digoxin
 - Verapamil
 - Propanolol
 - Quinidine
187. Which of the following statements is WRONG about amiodarone?
- It is longest acting anti-arrhythmic drug.
 - It has positive inotropic action.
 - It contains iodine
 - It causes pulmonary fibrosis.
188. Which of the following drugs hyperpolarizes AV nodal tissue, is used in PSVT and has short lasting adverse effects?
- Verapamil
 - Digoxin
 - Adenosine
 - Propanolol
189. A drug effect that is produced by therapeutic doses of both timolol and amiodarone is blockade of:
- Cardiac Na⁺ channels
 - Cardiac K⁺ channels
 - Beta-1 adrenoceptors
 - Alpha-adrenoceptors
190. In deciding on a treatment for a 60 years old patient, Golu, who has chronic heart disease and rheumatoid arthritis, you wish to give him procainamide. He is already taking digoxin, hydrochlorthiazide and potassium supplementation. Which of the following is a relevant statement?
- A possible drug interaction with digoxin suggests that digoxin blood levels should be obtained before and after starting procainamide.
 - Hyperkalemia should be avoided to reduce the likelihood of procainamide toxicity
 - Procainamide cannot be used if the patient has asthma because it has a beta blocking effect
 - Procainamide is not active by the oral route
191. Surinder singh developed acute CHF and was put on digitalis therapy. ECG of this patient revealed the presence of ventricular extrasystoles. Which of the following drugs can be administered safely to this patient in order to counteract this arrhythmia?
- Lignocaine
 - Quinidine
 - Atropine
 - Amiodarone
192. All of the following antiarrhythmic drugs are correctly matched to the group: (DPG 2000)
- Procainamide: class I
 - Amiodarone: class III
 - Esmolol: class IV
 - Diltiazem: class IV
193. The drug of choice for rapid correction of PSVT in known asthmatic is: (MPPG 2005)
- Adenosine
 - Esmolol
 - Neostigmine
 - Verapamil
194. Which of the following is wrongly matched combination of anti-arrhythmic drugs and their class: (MPPG 2001)
- Mexiletine-IB
 - Verapamil-IV
 - Amiodarone-III
 - Lignocaine-IA
195. All of the following drugs are Class I anti-arrhythmic drugs EXCEPT: (UP 2006)
- Quinidine
 - Procainamide

- (c) Flecainide
(d) Propranolol
196. Which of the following anti-arrhythmic drug decreases the action potential duration in Purkinje fibers?
(a) Quinidine
(b) Flecainide
(c) Amiodarone
(d) Lignocaine
197. All of the following decrease AV conduction EXCEPT: (Jharkhand 2003)
(a) Esmolol
(b) Digitalis
(c) Lignocaine
(d) Verapamil
198. Class III anti arrhythmic drug is: (Jharkhand 2005)
(a) Amiodarone
(b) Phenytoin
(c) Propafenone
(d) Pindolol
199. A sixteen-year-old girl is found to have paroxysmal attacks of rapid heart rate. The antiarrhythmic of choice in most cases of acute AV nodal tachycardia is: (Karnataka 2006, Karnataka 2005)
(a) Adenosine
(b) Amiodarone
(c) Propranolol
(d) Quinidine
200. Drug of choice for paroxysmal supraventricular tachycardia (PSVT) is: (Karnataka 2005)
(a) Verapamil
(b) Digitalis
(c) Quinidine
(d) Diphenylhydantoin
201. Drug of choice for ventricular arrhythmias due to myocardial infarction (MI) is: (Karnataka 2005)
(a) Quinidine
(b) Amiodarone
(c) Xylocaine
(d) Diphenylhydantoin
202. Drug of choice for ventricular premature beats (VPC) due to digitalis toxicity is: (Karnataka 2005)
(a) Diphenylhydantoin
(b) Quinidine
(c) Amiodarone
(d) Verapamil
203. Arrhythmias refractory to the treatment of lignocaine can be treated by: (Karnataka 2002)
(a) Sotalol
(b) Diltiazem
(c) Amiodarone
(d) Quinidine
204. Quinidine exerts its action on heart by: (DPG 2008)
(a) Ca^{2+} channel blockade
(b) Na^{+} channel blockade
(c) K^{+} channel opening
(d) Cl^{-} channel opening
- DYSLIPIDEMIA**
205. Ezetimibe acts by: (DPG 2009)
(a) Enhancing excretion of bile acids
(b) Decreasing absorption of cholesterol
(c) Inhibiting HMG-CoA reductase
(d) Inhibiting intracellular lipase
206. True about fibrates is all except: (AIIMS Nov., 2007)
(a) Drug of choice for Type III hyperlipoproteinemia and severe hypertriglyceremia
(b) Activate PPAR to stimulate LPL
(c) Absorbed good on empty stomach and absorption is delayed by fatty meals
(d) Side effect are rash, urticaria, myalgia and impotence
207. All of the following are true about HMG CoA reductase inhibitors except: (AIIMS May, 2002)
(a) CNS accumulation of simvastatin and lovastatin is high and less for pravastatin and fluvastatin
(b) Simvastatin is rapidly and pravastatin is least metabolized.
(c) Bioavailability is minimally modified when pravastatin is taken with food
(d) Fibrinogen levels are increased by pravastatin
208. Mechanism of action of statins is:
(a) Inhibition of HMG-CoA synthase
(b) Stimulation of HMG-CoA reductase
(c) Indirect increase of LDL receptors synthesis
(d) Inhibition of intestinal cholesterol absorption
209. Which hypolipidemic drug can exacerbate the symptoms of gout?
(a) Ezetimibe
(b) Gemfibrozil
(c) Niacin
(d) Simvastatin
210. The rate-limiting step in cholesterol synthesis is inhibited by: (TN 2007)
(a) Probucol
(b) Cholestyramine
(c) Statins
(d) Gemfibrozil
211. Lipid lowering drug that significantly reduces lipoprotein-a [Lp (a)] levels is? (MH 2008)
(a) Fenofibrate
(b) Gemfibrosil
(c) Rosuvastatin
(d) Nicotinic acid
212. Clofibrate, a lipid lowering agent inhibits both cholesterol and triglyceride synthesis by: (DPG 2001)
(a) Inhibiting HMG CoA reductase
(b) Binding to bile acids and preventing its reabsorption
(c) Inhibiting VLDL production
(d) Activating lipoprotein lipase, resulting in VLDL degradation

213. In a patient with hypertriglyceridemia and low HDL, which of the following drug will be best without risk of myopathy as side effect? (MH PGM-CET 2007) (MH 2008) (MH 2007)
- Fibric acid derivatives
 - Nicotinic acid
 - Atrovastatin
 - Clofibrate
214. HDL is specifically increased by: (Kolkata 2007)
- Lovastatin
 - Niacin
 - Gemfibrozil
 - Probucol
215. The most potent drugs to reduce plasma cholesterol level are: (Karnataka 2000)
- Plant sterols
 - Fibrates
 - Anion exchange resins
 - Statins
- RAAS AND MISCELLANEOUS**
216. Which of the following drug is associated with highest cardiac mortality? (AI 2012)
- Rofecoxib
 - Nicorandil
 - Losartan
 - Metoprolol
217. Which of the following drug is used for reversal of cerebral vasospasm and infarct following subarachnoid hemorrhage? (AI 2012)
- Nimodipine
 - Amlodipine
 - Diltiazem
 - Verapamil
218. Ivabradine is indicated in the management of: (AI 2012)
- Congestive heart failure
 - Angina pectoris
 - Cardiomyopathy
 - Irritable bowel syndrome
219. Which of the following statements regarding ACE inhibitors is TRUE? (AIIMS May 2008, Nov 2008 May 2011)
- These inhibit the conversion of angiotensinogen to angiotensin-1
 - Omission of prior diuretic dose decreases the risk of postural hypotension
 - Lisinopril is shorter acting than enalapril
 - These are contra-indicated in diabetic patients.
220. Which of the following is not used in the treatment of pulmonary hypertension? (AIIMS May 2010)
- Calcium channel blockers
 - Alpha blockers
 - Prostacyclins
 - Endothelin receptor antagonists
221. Which of the following drugs is best for reducing proteinuria in a diabetic patient? (DPG 2011)
- Metoprolol
 - Perindopril
 - Chlorthiazide
 - Clonidine
222. Which of the following ACE inhibitor is NOT a pro-drug? (AIIMS Nov 2009)
- Fosinopril
 - Enalapril
 - Ramipril
 - Lisinopril
223. A 50 years old male with type 2 diabetes mellitus is found to have 24 hour urinary albumin of 250 mg. Which of the following drugs may be used to retard progression of renal disease? (DPG 2009)
- Hydrochlorthiazide
 - Enalapril
 - Amiloride
 - Aspirin
224. Angiotensin II causes all except: (AI 2009)
- Stimulates release of ADH
 - Increases thirst
 - Vasodilation
 - Stimulates aldosterone release
225. A man presents with chest pain. ECG shows ST segment depression in leads V1-V4. Which of the following should not be given? (AIIMS May 2008)
- Beta blocker
 - Thrombolytic
 - Morphine
 - Aspirin
226. All are used for treatment of pulmonary hypertension EXCEPT: (AIIMS May 2008)
- Endothelin receptor antagonists
 - Phosphodiesterase inhibitors
 - Calcium channel blockers
 - Beta blockers
227. Vagal stimulation of heart causes? (AIIMS Nov 2008)
- Increased heart rate
 - Increased RR interval in ECG
 - Increased cardiac output
 - Increased force of contraction
228. Angiotensin converting enzyme inhibitors when used for a long time in patients with hypertension, cause: (DPG 2009)
- Rightward shift in renal pressure-natriuresis curve
 - Reduction in filtration fraction
 - Significant increase in heart rate
 - No change in compliance of large arteries
229. Which of the following treatments is appropriate for tall peaked T waves, on ECG? (DPG 2009)
- Atropine IV
 - Nitroprusside IV

- (c) Inhaled Salbutamol
(d) Inhaled betamethasone
230. A 30-year old male presents with severe chest pain, breathlessness, hypotension and ECG shows ST elevation in V3, V4, V5 and V6 leads. He will be best treated with: (DPG 2009)
(a) Streptokinase
(b) t-PA
(c) Heparin
(d) PTCA
231. Which of the following drugs causes constipation? (AI 2006)
(a) Propranolol
(b) Verapamil
(c) Nitroglycerin
(d) Captopril
232. All the following statements are true regarding losartan except: (AI 2002)
(a) It is a competitive angiotensin receptor antagonist
(b) It has a long acting metabolite
(c) Associated with negligible cough
(d) Causes hyperuricemia
233. Enalapril is contraindicated in all of the following conditions except: (AI 2000)
(a) Diabetic nephropathy with albuminuria
(b) Single kidney
(c) Bilateral renal artery stenosis
(d) Hyperkalemia
234. Which of the following is not given alone in a patient of pheochromocytoma? (AI 2000)
(a) Atenolol
(b) Prazosin
(c) Nitroprusside
(d) Metirosine
235. Renin is secreted from: (AIIMS May, 2007)
(a) Juxtaglomerular apparatus
(b) PCT
(c) DCT
(d) Collecting ducts
236. Which of the following does not result in the release of NO? (AIIMS May, 2007)
(a) Fenoldopam
(b) Hydralazine
(c) Nitroprusside
(d) Nitroglycerine
237. The most significant adverse effect of ACE inhibition is: (AIIMS May, 2006)
(a) Hypotension
(b) Hypertension
(c) Hypocalcemia
(d) Hypercalcemia
238. All of the following are indications for the use of ACE inhibitors except: (AIIMS May, 2005)
(a) Hypertension
(b) Myocardial infarction
(c) Left ventricular dysfunction
(d) Pheochromocytoma
239. A 60 year old man with rheumatic mitral stenosis and atrial fibrillation is on therapy for a fast ventricular rate. While on treatment he develops a regular pulse of 64 beats/min. Which of the following is the probable drug that the patient is receiving? (AIIMS Nov, 2004, AI 2004)
(a) Verapamil
(b) Digoxin
(c) Carvedilol
(d) Propranolol
240. Which one of the following is not an adverse effect of ACE inhibitors? (AIIMS Nov, 2003)
(a) Cough
(b) Hypokalemia
(c) Angioneurotic edema
(d) Skin rash
241. Use of which of the following drugs is contraindicated in pregnancy? (AIIMS May, 2003)
(a) Digoxin
(b) Nifedipine
(c) Amoxicillin
(d) Enalapril
242. Racemic mixture of two enantiomers with different pharmacokinetic and pharmacodynamic properties is seen in: (AIIMS May, 2002)
(a) Dilantin
(b) Digoxin
(c) Verapamil
(d) Octreotide
243. Glucose intolerance is seen with: (PGI Dec, 2006)
(a) Thiazide diuretics
(b) β -blockers
(c) Verapamil
(d) ACE inhibitors
(e) Phenytoin
244. Actions of angiotensin II include: (PGI June, 2005)
(a) Systemic vasoconstriction
(b) Systemic vasodilation
(c) Renal vasodilatation
(d) Re-absorption of Na^+ in proximal renal tubule
(e) Retention of water
245. Hyperkalemia is associated with: (PGI Dec, 2004)
(a) ACE inhibitors
(b) Chlorthalidone
(c) Amphotericin-B
(d) Amiodarone
(e) Rifampicin
246. Glucose intolerance is caused by: (PGI June, 2002)
(a) Thiazides
(b) Enalapril
(c) Propranolol
(d) Frusemide
(e) Verapamil

247. ACE inhibitors cause: (PGI Dec. 2001)
 (a) Persistent cough
 (b) Taste changes
 (c) First dose hypotension
 (d) Ankle edema
 (e) Angioedema
248. Drugs causing constipation are: (PGI June, 2001)
 (a) Verapamil
 (b) Quinidine
 (c) MAO-Inhibitors
 (d) Tricyclic antidepressants
 (e) Ferrous sulphate
249. The only drug whose over dosage is not characterized by both hypotension and bradycardia is:
 (a) Propanolol
 (b) Verapamil
 (c) Clonidine
 (d) Theophylline
250. The progression of which of the following diseases is retarded by chronic use of enalapril?
 (a) Diabetic nephropathy
 (b) Diabetic retinopathy
 (c) Hypertensive nephropathy
 (d) All of the above
251. Losartan is similar to enalapril in all of the following features except:
 (a) Anti-hypertensive efficacy
 (b) Potential to reverse left ventricular hypertrophy
 (c) Lack of effect on carbohydrate tolerance
 (d) Potential to induce cough in susceptible individuals
252. Which of the following drugs act by inhibition of AT1 subtype of angiotensin receptors?
 (a) Ramipril
 (b) Lovastatin
 (c) Candesartan
 (d) Sumatriptan
253. Valsartan differs from ramipril in the following respect:
 (a) It does not potentiate bradykinin
 (b) It can be safely administered to a patient with bilateral renal artery stenosis
 (c) It impairs carbohydrate tolerance
 (d) It does not have fetopathic potential
254. An endogenous peptide that causes vasodilation and is inactivated by angiotensin converting enzyme is:
 (a) Angiotensinogen
 (b) Angiotensin-I
 (c) Angiotensin-II
 (d) Bradykinin
255. A 60-year-old male Suresh is hospitalized with muscle pain, fatigue and dark urine. His past medical history is significant for stable angina. The patient's medications include atenolol, atorvastatin, and aspirin. His urine dipstick test is positive for blood but urine microscopy did not reveal RBCs in the urine. Serum creatinine kinase was significantly raised in this person. The addition of which of the following medications is most likely to have precipitated this patient's condition?
 (a) Erythromycin
 (b) Rifampin
 (c) Griseofulvin
 (d) Azithromycin
256. Which among the following is an angiotensin receptor antagonist? (UP 2005, Jharkhand 2003)
 (a) Losartan
 (b) Enalapril
 (c) Ramipril
 (d) Captopril
257. Drug contra-indicated in bilateral renal artery stenosis is: (DPG-2007, RJ 2003)
 (a) Propanolol
 (b) Guanethidine
 (c) Captopril
 (d) Amlodipine
258. Which of the following drugs is deposited in the muscles? (UP 2007)
 (a) Verapamil
 (b) Digoxin
 (c) Adenosine
 (d) Phenytoin
259. ACE inhibitors are contraindicated in: (MH 2003)
 (a) Diabetes mellitus
 (b) Hypertension in old age groups
 (c) Scleroderma
 (d) Bilateral renal artery stenosis
260. Indication of ACE inhibitor in diabetes mellitus is: (Jharkhand 2003)
 (a) Diabetic nephropathy
 (b) Nephropathy unrelated to diabetes
 (c) Both
 (d) None
261. Cough and angioedema in a patient receiving ACE inhibitors is due to (Jharkhand 2003)
 (a) Bradykinin
 (b) Renin
 (c) Angiotensin-II
 (d) All
262. About quinidine, which of the following statements is correct: (Jharkhand 2005)
 (a) High doses cause increase in blood pressure
 (b) It inhibits vagus
 (c) It decreases automaticity in heart
 (d) It has antianginal property
263. Food reduces the oral bioavailability of the following angiotensin converting enzyme inhibitors Except: (MP 2008)
 (a) Enalapril
 (b) Captopril
 (c) Ramipril
 (d) Fosinopril

264. **Captopril can cause all EXCEPT:** *(Kolkata 2008)*
 (a) Decrease in K^+ concentration
 (b) Decrease in afterload
 (c) Proteinuria
 (d) Blood dyscrasia
265. **Which of the following antidotes is used for calcium channel blockers overdose?** *(Karnataka 2008)*
 (a) Atropine
 (b) Calcium gluconate
 (c) Adrenaline
 (d) Digoxin
266. **Sudden withdrawal of which of the following drugs could result in serious adverse cardiovascular changes in a patient taking the drug over long time:** *(Karnataka 2003)*
 (a) Phenelezine (MAO inhibitor)
 (b) Enalapril (ACE inhibitor)
 (c) Clonidine (α_2 agonist)
 (d) Fluoxetine (serotonin reuptake inhibitor)
267. **ACE inhibitors are contraindicated in all of the following except:** *(Karnataka 2001)*
 (a) Pregnancy
 (b) Diabetes
 (c) Bilateral renal artery stenosis
 (d) Renal failure

RECENT QUESTIONS ASKED BY NATIONAL BOARD

- Which of the following causes increased renin on prolonged use ?
 (a) Clonidine
 (b) Enalapril
 (c) Methyl dopa
 (d) Beta Blockers
- Mechanism of action of fibrates is ?
 (a) They increase lipoprotein lipase activity through PPAR alpha and cause increased lipolysis of triglycerides
 (b) Inhibit lipolysis in adipose tissue
 (c) Inhibit HMG CoA reductase
 (d) Bind bile acids and bile salts in small intestine
- Statins act on which enzyme ?
 (a) Acyl CoA synthetase
 (b) Acyl CoA reductase
 (c) HMG CoA synthetase
 (d) HMG CoA reductase
- Which of the following drug has maximum oral bio-availability?
 (a) Fluvastatin
 (b) Atorvastatin
 (c) Pravastatin
 (d) Simvastatin
- Drug that prevents hypercholesterolemia by inhibiting absorption of cholesterol is:
 (a) Ezetimibe
 (b) Orlistat
 (c) Cholestyramine
 (d) Statins
- Half-life of digoxin is:
 (a) 24 hrs
 (b) 40 hrs
 (c) 48 hrs
 (d) 60 hrs
- Centrally acting antihypertensive drug is:
 (a) Phenoxybenzamine
 (b) Methyl dopa
 (c) Propanolol
 (d) Prazosin
- Mechanism of action of digitalis is:
 (a) Inhibits Na^+K^+ ATPase pump
 (b) Inhibits Na^+H^+ ATPase pump
 (c) Active metabolites are produced in the liver
 (d) Inhibits calcium concentration in blood
- All are true about guanethidine except:
 (a) It prevents exocytosis of norepinephrine
 (b) Used for treatment of erectile dysfunction
 (c) Side effects include diarrhea
 (d) No CNS related side effects seen with its use
- Which of the following potassium sparing diuretic reduces cardiac mortality ?
 (a) Spironolactone
 (b) Amiloride
 (c) Triamterene
 (d) All of these
- Anti-androgen used in heart failure is :
 (a) Carvedilol
 (b) Sildenafil
 (c) Spironolactone
 (d) Abiraterone
- Mechanism of action of lovastatin is?
 (a) HMG CoA reductase inhibitor
 (b) Decarboxylase inhibitor
 (c) Activate lipoprotein lipase
 (d) Inhibits lipolysis
- Most potent statin is:
 (a) Simvastatin
 (b) Pitavastatin
 (c) Atorvastatin
 (d) Rosuvastatin
- Mechanism of action of NO is:
 (a) $\uparrow$ cAMP
 (b) $\uparrow$ cGMP
 (c) $\uparrow$ PGE_2
 (d) $\uparrow$ PGD_4
- Iodine content in amiodarone is:
 (a) 10-20%
 (b) 20-40%
 (c) 40-60%
 (d) 60-80%

16. Dialysis is not indicated in toxicity of:
 - (a) Lithium
 - (b) Methanol
 - (c) Salicylates
 - (d) Digitalis
17. Antihypertensive which can be used in patients with gout and diabetes mellitus is:
 - (a) Thiazide
 - (b) Enalapril
 - (c) Propanolol
 - (d) Diazoxide
18. Beta blockers are antiarrhythmic agents of class:
 - (a) I
 - (b) II
 - (c) III
 - (d) IV
19. Treatment of choice for cyanide poisoning is:
 - (a) NaHCO_3
 - (b) KMnO_4
 - (c) NaCl
 - (d) Sodium nitrite followed by thiosulphate
20. Cough is an adverse reaction seen with intake of:
 - (a) Thiazide
 - (b) Nifedipine
 - (c) Enalapril
 - (d) Prazosin
21. Digoxin can accumulate to toxic levels in patients with?
 - (a) Renal insufficiency
 - (b) Chronic hepatitis
 - (c) Advanced cirrhosis
 - (d) Chronic pancreatitis
22. Which of the following drug has longest half life?
 - (a) Amiodarone
 - (b) Quinidine
 - (c) Diltiazem
 - (d) Procainamide
23. Dofetilide is which class of antiarrhythmic drug?
 - (a) Class I
 - (b) Class II
 - (c) Class III
 - (d) Class IV
24. Drug that decrease lipoprotein (a) is?
 - (a) Fibrates
 - (b) Niacin
 - (c) Statins
 - (d) All
25. All of the following are used in atrial arrhythmias except:
 - (a) Digoxin
 - (b) Verapamil
 - (c) Quinidine
 - (d) Lignocaine
26. Anti-hypertensive drug contraindicated in pregnancy is:
 - (a) Enalapril
 - (b) Cardio selective beta blockers
 - (c) Methyl dopa
 - (d) Hydralazine
27. Adverse effect of losartan are all except:
 - (a) Fetopathic
 - (b) Cough
 - (c) Hyperkalemia
 - (d) Headache
28. All the following statements regarding adenosine are true except:
 - (a) Dipyridamole potentiates its action
 - (b) Used to produce controlled hypotension
 - (c) Administered by slow I.V. injection
 - (d) Administered by rapid I.V. injection
29. Most effective method of treatment of digitalis toxicity is:
 - (a) Hemodialysis
 - (b) Cardioversion
 - (c) Digoxin antibody
 - (d) Atropine
30. Which of the following is not a direct acting anti-platelet agent?
 - (a) Aspirin
 - (b) Clopidogrel
 - (c) Atorvastatin
 - (d) Alteplase
31. Drug used to reverse remodeling of heart in congestive cardiac failure are all except:
 - (a) Beta blocker
 - (b) ACE inhibitor
 - (c) Digoxin
 - (d) Aldosterone antagonist
32. Which of the following drug decreases plasma renin activity?
 - (a) Enalapril
 - (b) Nifedipine
 - (c) Hydralazine
 - (d) Clonidine
33. Spironolactone should not be given with:
 - (a) Chlorothiazide
 - (b) Beta blockers
 - (c) ACE inhibitors
 - (d) Amlodipine
34. Which of the following is not a cardioselective β -blocker?
 - (a) Acebutolol
 - (b) Atenolol
 - (c) Pindolol
 - (d) Metoprolol

35. Which of the following does not contribute to digoxin toxicity?
 - (a) Hyperkalemia
 - (b) Hypercalcemia
 - (c) Renal failure
 - (d) Hypomagnesemia
36. Telmisartan lowers blood pressure by:
 - (a) Inhibiting formation of angiotensin I to angiotensin II
 - (b) Inhibiting conversion of renin to angiotensin I
 - (c) Blocking AT_1 receptors
 - (d) Interfering with degradation of bradykinin
37. Which of the following is not an inotropic drug:
 - (a) Amrinone
 - (b) Isoprenaline
 - (c) Amiodarone
 - (d) Dopamine
38. Which of the following 'statins' has the longest half life?
 - (a) Cerivastatin
 - (b) Rosuvastatin
 - (c) Atorvastatin
 - (d) Simvastatin
39. The vitamin which can be used for treatment of hypercholesterolemia is:
 - (a) Thiamine
 - (b) Niacin
 - (c) Pyridoxine
 - (d) Vitamine B_{12}
40. Antihypertensive may act by blocking all of the following except:
 - (a) Alpha-adrenoceptors
 - (b) ATP dependent K^+ channels
 - (c) Nor adrenaline release
 - (d) Beta adrenoceptors
41. Sildenafil's mechanism of action can be best described as:
 - (a) β -adrenoceptor blocking agent
 - (b) Selective inhibitor of phosphodiesterase type 5
 - (c) Inhibits reuptake of both serotonin and nor adrenaline
 - (d) Selective-serotonin reuptake inhibitor
42. The drug of choice in scleroderma induced hypertensive crisis is:
 - (a) ACE inhibitors
 - (b) Thiazides
 - (c) β -blockers
 - (d) Sodium nitroprusside
43. Which of the following is the drug of choice in pregnancy induced hypertension:
 - (a) Methyldopa
 - (b) Diltiazem
 - (c) Metoprolol
 - (d) Enalapril
44. Dobutamine is preferred over dopamine in cardiogenic shock because of its effect related to:
 - (a) Better cardiac stimulation
 - (b) Less peripheral vasoconstriction
 - (c) Lower risk of cardiac arrhythmias
 - (d) More CNS stimulation
45. The rate limiting step in the biosynthesis of cholesterol is catalyzed by:
 - (a) HMG CoA lyase
 - (b) Acetyl CoA carboxylase
 - (c) HMG CoA reductase
 - (d) HMG CoA synthase
46. All of the following drugs can cause gynaecomastia except:
 - (a) Digoxin
 - (b) Amiloride
 - (c) Cimetidine
 - (d) Spironolactone
47. Drug to be avoided in HOCM (Hypertrophic obstructive cardiomyopathy) is:
 - (a) Amiodarone
 - (b) Verapamil
 - (c) Digoxin
 - (d) Beta-blockers
48. All of the following are anti arrhythmic drugs except:
 - (a) Lidocaine
 - (b) Enalapril
 - (c) Atenolol
 - (d) Sotalol
49. Which of the following antihypertensive drugs is contraindicated in pregnancy:
 - (a) Labetalol
 - (b) Hydralazine
 - (c) Nifedipine
 - (d) ACE inhibitors
50. Which of the following calcium channel blocker would be useful in the treatment of supra-ventricular tachycardia by suppressing AV node conduction:
 - (a) Amlodipine
 - (b) Nimodipine
 - (c) Verapamil
 - (d) Nifedipine
51. HMG-CoA reductase is inhibited by:
 - (a) Cholestyramine
 - (b) Gemfibrozil
 - (c) Lovastatin
 - (d) Clofibrate
52. An increase in heart rate and renin release seen in patients of CHF can be overcome by which of the following drugs:
 - (a) Minoxidil
 - (b) Metoprolol
 - (c) Metolazone
 - (d) Milrinone

53. Which of the following drugs is a class III antiarrhythmic agent?
- Quinidine
 - Amiodarone
 - Propanolol
 - Lignocaine
54. Which of the following is a K^+ channel opener?
- Nifedipine
 - Minoxidil
 - Enalapril
 - Atenolol
55. Which of the following is not a Ca^{++} channel blocker?
- Enalapril
 - Nifedipine
 - Diltiazem
 - Verapamil
56. Digitalis acts in CHF by:
- $Na^+ K^+$ ATPase inhibition
 - $Na^+ K^+$ ATPase stimulation
 - Blockade of calcium channels
 - Increasing the refractory period of AV node
57. Treatment of choice in ventricular fibrillation is:
- Sotalol
 - Cardioversion
 - Ibutilide
 - Adenosine
58. Coronary steal phenomenon is caused by which drug?
- Disopyramide
 - Verapamil
 - Nitroglycerine
 - Dipyridamol
59. Antihypertensive of choice in a patient of diabetes mellitus with proteinuria is:
- Enalapril
 - Propanolol
 - Hydralazine
 - Minoxidil
60. Antiarrhythmic drug is:
- Phentolamine
 - Phenobarbitone
 - Procainamide
 - Pentamidine
61. Antihypertensive drug of choice in a diabetic patient is:
- Methyldopa
 - Beta blocker
 - ACE inhibitor
 - Thiazides
62. Which of the following drugs is used in MI?
- Cocaine
 - Pethidine
 - Morphine
 - Butorphanol
63. Coronary vasodilatation is caused by:
- Adenosine
 - Bradykinin
 - Histamine
 - Ergotamine
64. Side effect of corneal microdeposits is seen most commonly with which of the following drugs?
- Esmolol
 - Amiodarone
 - Adenosine
 - Bretylium
65. Treatment of digitalis toxicity includes:
- Stoppage of drug
 - Potassium supplements
 - FAB fragments of digitalis antibodies
 - All of the above
66. Which of the following is false about digoxin?
- Dosage reduction is required in hepatic disease
 - Dosage reduction is required in renal failure
 - It can cause bradycardia
 - It increases the force of contraction in CHF
67. Drug of choice for termination of paroxysmal supra-ventricular tachycardia is:
- Calcium channel blocker
 - Beta blocker
 - Digoxin
 - Adenosine

EXPLANATIONS

1. Ans. (d) Milrinone (Ref: Goodman and Gilman, 11/e p575, Harrison 17/e p1455)

Inotropic drugs are not used for treatment of right sided heart failure where the major treatment is diuretics and vasodilators. Milrinone being a phosphodiesterase inhibitor act as an inodilator. Thus, this is the only inotropic drug that should be used in right sided failure due to its ability to produce vasodilation. It is indicated in right heart failure with pulmonary hypertension.

2. Ans. (b) Paroxysmal atrial tachycardia with fast ventricular rate (Ref: Critical care toxicology 4/e p395, Blueprint medicine by Vincent B Young et al/28 (E-book available at internet))

Digitalis characteristically cause atrial tachycardia (paroxysmal or non-paroxysmal) with AV block, it does not cause atrial tachycardia with fast ventricular rate.

- Ventricular premature beats and bigeminy are the most common arrhythmias caused by digitalis.
- In a patient having atrial fibrillation (AF), P waves are completely absent when no organized atrial activity is present. Uncontrolled AF result in irregular tachycardia with ventricular rate of 80 to 140 beats per min. This is clinically demonstrated by irregularly irregular pulse seen in AF. However, regularization of atrial fibrillation means that complete heart block (block in conduction from atrium to ventricle) is present and thus no atrial impulse is conducted and ventricles start to beat according to their intrinsic rate (i.e. ventricles take over the function of pacemaker). Therefore, a regular heart rate of 40 to 60 beats per minute is seen. This regularization of atrial fibrillation is highly suggestive of digitalis toxicity.
- Bidirectional ventricular tachycardia is an unusual tachyarrhythmia that usually resolves spontaneously after a few seconds to a few minutes. It is often associated with severe structural heart disease or digoxin toxicity. It is also known as biventricular tachycardia.
- Arrhythmias characteristically pointing towards the diagnosis of digitalis toxicity are non-paroxysmal atrial tachycardia with atrio-ventricular block (Most characteristic), paroxysmal atrial tachycardia with atrioventricular block, bidirectional ventricular tachycardia and regularization of atrial fibrillation.

3. Ans. (a) They should be started with optimum doses (Ref: Goodman and Gilman, 11/e p1336)

Clinical use of β adrenergic receptor antagonists in heart failure

- These are now recommended for routine use in patients with an ejection fraction < 35% and NYHA class II or III symptoms in conjunction with ACE inhibitor or angiotensin-receptor antagonist, and diuretics.
- These should be initiated at very low doses, generally less than one tenth of the final target dose.
- NYHA Class IIIB and IV patients should be approached with a high level of caution; and in recently decompensated heart failure, beta-blockers should not be used until the patients are stabilized for several days to weeks.

4. Ans. (a) Decreased activity of $\text{Na}^+/\text{Ca}^{++}$ exchanger causing decreased influx of sodium and decreased efflux of Ca^{++} in the sarcolemma (Ref: Goodman and Gilman 12/e p802-803)

5. Ans. (d) Trimetazidine (Ref: CMDT – 2010/362-364)

Trimetazidine is a partial fatty acid oxidation inhibitor used for angina pectoris'

6. Ans. (b) Hyperkalemia (Ref: Katzung 11/e p216)

Digoxin toxicity can be exacerbated by:

↓ K^+	Quinidine	Renal Failure
↓ Mg^{2+}	Verapamil	
↑ Ca^{2+}	Thiazides	

7. Ans. (c) Nitroprusside (Ref: Katzung 10/e p173-174; KDT 6/e p540)

- Hydralazine, minoxidil and nifedipine are primarily arteriolar dilators whereas nitroprusside is a mixed arteriolar and venous dilator, therefore best answer here seems to be nitroprusside.

8. Ans. (c) It can be administered orally (Ref: CMDT 2014/396; KDT 6/e p507)

- Nesiritide is a recombinant BNP.
- It produces vasodilation and natriuresis.
- It has to be administered by i.v. route. [because being a peptide, it is metabolized by peptidases in GIT.]
- It is used for acutely decompensated heart failure.

9. **Ans. (d) Amlodipine** (Ref: KDT 6/e p499)

- Cholestyramine inhibits intestinal absorption of digoxin.
- Thiazides result in hypokalemia and thus may precipitate digitalis toxicity by pharmacodynamic interaction.
- Quinidine and verapamil reduces the excretion of digoxin and thus may precipitate toxicity (pharmacokinetic interaction).

10. **Ans. (d) Hypertrophic obstructive cardiomyopathy** (Ref: KDT 6/e p143)

Non selective β -blockers (propranolol) are the agents of choice for HOCM.

In hypertrophic obstructive cardiomyopathy (HOCM), the LV outflow tract is narrowed during systole due to hypertrophic septum. Obstruction is worsened by:

a. **Factors increasing myocardial contractility.**

- Digitalis
- Sympathetic stimulation

b. **Factors decreasing LV filling:**

- Valsalva maneuver
- Peripheral vasodilators

11. **Ans. (c) High output failure** (Ref: KDT 6/e p502)

Digitalis is an inotropic agent that is indicated when heart is not able to pump the blood adequately. High output failure is seen in conditions like anemia and thyrotoxicosis in which heart is already contracting vigorously. Cardiac glycosides, thus are not indicated in high output failure.

12. **Ans. (a) Hepatic disease** (Ref: KDT 5/e p463; KDT 6/e p497)

- Digoxin is eliminated mainly via excretion through kidney whereas digitoxin is metabolized by the liver. Dose of digoxin therefore, does not require adjustment in hepatic failure whereas it has to be reduced in renal failure.
- Arrhythmogenic dose of digitalis is reduced in MI. It should be used after MI only when CHF is accompanied with AF and rapid ventricular rate.
- Hypokalemia, hypomagnesemia and hypercalcemia predisposes to digitalis toxicity.

13. **Ans. (a) Neutral endopeptidase** (Ref: KK Sharma 2007/249; Katzung 11/e p303)

14. **Ans. (a) Nesiritide, (b) Digoxin, (c) Spironolactone, (d) Losartan** (Ref: KDT 6/e p502-507)

15. **Ans. (a) Hypokalemia; (c) Hypercalcemia** (Ref: KDT 6/e p499)

16. **Ans. (a) Hydralazine; (b) Nifedipine (c) Prazosin (d) Enalapril** (Ref: KDT 6/e p540)

Nitrates are primarily venodilators. Hydralazine and nifedipine dilate mainly arterioles whereas ACE inhibitors and α -blockers dilate both arterioles as well as veins.

17. **Ans. (c) Beta receptor agonists** (Ref: KDT 6/e p502)

These agents are indicated for the treatment of acute decompensated CHF. Digitalis ($\text{Na}^+ - \text{K}^+$ ATPase inhibitor) is indicated both for acute treatment as well as maintenance in CHF as digoxin is the only orally effective inotropic drug available.

18. **Ans. (a) Administration of quinidine** (Ref: KDT 6/e p499)

19. **Ans. (b) Digoxin** (Ref: KDT 6/e p502)

20. **Ans. (b) Enalapril** (Ref: KDT 6/e p486, 487)

21. **Ans. (d) Potassium** (Ref: KDT 6/e p498)

22. **Ans. (a) Carvedilol** (Ref: Katzung 10/e p150, 154)

23. **Ans. (a) Digibind antibodies** (Ref: KDT 6/e p499)

24. **Ans. (a) First choice drugs unless contra-indicated** (Ref: KDT 6/e p486)

25. **Ans. (a) Glomerular filtration** (Ref: KDT 6/e p497)
Digoxin is primarily eliminated unchanged by glomerular filtration whereas digitoxin is eliminated by hepatic metabolism.
26. **Ans. (a) It is used to provide relief of symptoms** (Ref: KDT 6/e p500)
Digitalis and diuretics are used as symptomatic therapy of CHF. These drugs do not retard ventricular remodelling or prolong survival in CHF patients.
27. **Ans. (c) Atrial fibrillation** (Ref: KDT 6/e p502)
Digitalis is used to maintain ventricular rate in this condition.
28. **Ans. (c) Losartan** (Ref: KDT 6/e p502)
29. **Ans. (c) Increase in atrial fibrillation frequency, but decrease in ventricular rate** (Ref: KDT 6/e p502)
Digitalis controls the ventricular rate in AF patients. Frequency of atrial fibrillation may actually increase. Ibutilide is approved for the conversion of AF to sinus rhythm.
30. **Ans. (b) Furosemide** (Ref: KDT 6/e p503)
31. **Ans. (b) Antagonism of vasoconstriction due to sympathetic overactivity** (Ref: KDT 6/e p505, 506)
Beta blockers may actually increase vasoconstriction by antagonizing the vasodilator action of β_2 receptors.
32. **Ans. (c) They are most useful in stable patients with mild to moderate heart failure** (Ref: CMDT 2014/392)
33. **Ans. (c) Dobutamine** (Ref: KDT 6/e p507)
Dobutamine is indicated only for the acute treatment of decompensated CHF. Cardiac glycosides (digoxin) can be used for acute treatment as well as maintenance therapy of CHF. ACE inhibitors and spironolactone are indicated only for chronic CHF.
34. **Ans. (c) Amrinone** (Ref: KDT 6/e p507)
It is a phosphodiesterase inhibitor and acts as an INODILATOR. It has positive inotropic effect (increase cardiac contractility) as well as vasodilator action (decrease preload and afterload).
35. **Ans. (d) It affords rapid symptomatic relief in CHF patients** (Ref: KDT 6/e p506)
Loop diuretics are used to provide rapid symptomatic relief whereas aldosterone antagonists decrease the mortality by reversing myocardial remodelling.
36. **Ans. (b) As an add on drug to tide over the crisis in refractory CHF** (Ref: KDT 6/e p507)
37. **Ans. (c) Nesiritide** (Ref: Katzung 10/e p205, 286)
- ACE inhibitors and AT_1 antagonists decrease angiotensin II activity.
 - Omapatrilat is a vasopeptidase inhibitor that acts by inhibiting two enzymes, ACE and NEP. As it inhibits ACE, it may also decrease angiotensin II activity.
 - Nesiritide is a recombinant BNP and has no effect on angiotensin II activity.
38. **Ans. (c) These are drugs of choice in acute decompensated heart failure** (Ref: KDT 6/e p544)
Beta blockers are contra-indicated in acute decompensated heart failure. *For more details, refer to text.*
39. **Ans. (c) Increase in refractoriness of AV nodal tissue** (Ref: KDT 6/e p502)
Digitalis acts in CHF by inhibiting $Na^+-K^+-ATPase$ whereas in AF, it acts by decreasing the conduction through AV node.
40. **Ans. (a) Potassium** (Ref: KDT 6/e p499)
Hypokalemia precipitates digitalis toxicity but in acute severe digitalis toxicity, there is already hyperkalemia.
41. **Ans. (c) Increased PR interval on the ECG** (Ref: KDT 6/e p494)
Digitalis possesses vagomimetic action and can cause bradycardia and decreased av conduction. This latter effect is manifested in the ECG as increased PR interval. Atropine can block this adverse effect.
42. **Ans. (c) Atrial fibrillation with high ventricular rate** (Ref: Katzung 11/e p219, CMDT-2010/363)
Digitalis should be used for patients
- Who remain symptomatic even on diuretics and ACE inhibitors.
 - With heart failure who are in atrial fibrillation and require ventricular rate control.

Note: Digitalis is contra –indicated in HOCM and high output cardiac failure.

43. Ans. (d) Hypertrophic obstructive cardiomyopathy (Ref: KDT 6/e p500-502)

44. Ans. (a) Lisinopril (Ref: KDT 6/e p486)

45. Ans. (a) Adrenaline (Ref: KDT 6/e p493,503-504)

46. Ans. (d) Hyperkalemia (Ref: KDT 6/e p499)

47. Ans. (b) 0.8-1.5 ng/ml (Ref: KDT 6/e p497)

	Digitoxin	Digoxin
– Therapeutic plasma conc.	15-30 ng/ml	0.5-1.4 ng/ml
– Toxic plasma conc.	> 35 ng/ml	> 2.5 ng/ml

48. Ans. (c) Treat digitalis toxicity (Ref: KDT 6/e p499)

49. Ans. (c) It is 95% plasma protein bound (Ref: KDT 6/e p497)

Plasma protein binding of digitoxin is high (95%) whereas it is low (70-80%) for digoxin.

50. Ans. (b) Propranolol (Ref: KDT 6/e p504)

Afterload is reduced by the drugs having arteriolar dilating property. Propranolol is a non-selective β -blocker. It can cause vasoconstriction by antagonizing β_2 mediated vasodilatation. It, therefore do not decrease afterload.

51. Ans. (a) Guanylate cyclase (Ref: KDT 6/e p548-549)

Nitroprusside generates NO that relaxes vascular smooth muscles by activating guanylate cyclase.

52. Ans. (d) Na^+K^+ ATPase (Ref: KDT 6/e p496)

53. Ans. (c) 5 day (Ref: KDT 6/e p497)

54. Ans. (a) Hydralazine (Ref: KDT 6/e p547)

55. Ans. (d) All of the above (Ref: KDT 6/e p498)

56. Ans. (b) Morphine (Ref: KDT 6/e p461)

57. Ans. (a) Na^+K^+ ATPase pump (Ref: KDT 6/e p496)

58. Ans. (b) Captopril (Ref: Katzung 11/e p219)

59. Ans. (c) An increase in systolic intracellular calcium levels (Ref: Katzung 11/e p214)

60. Ans. (d) Fab fragments of digitalis antibodies (Ref: KDT 6/e p499)

61. Ans. (c) NPAT with block (Ref: KDT 6/e p498)

62. Ans. (c) Sodium nitroprusside (Ref: KDT 7/e p567-568)

Increase in systemic vascular resistance means vasoconstriction, thus a vasodilator drug like nitroprusside should be used. Adrenaline and nor-adrenaline act as vasopressors whereas isoprenaline increases systolic blood pressure by acting on heart.

63. Ans. (a) Propranolol (Ref: Katzung 10/e p165, 169; KDT 6/e p137)

- Methyldopa is useful in the treatment of mild to moderately severe hypertension. It lowers blood pressure chiefly by reducing peripheral vascular resistance, with a variable reduction in heart rate and cardiac output.
- Prazosin and nitroprusside are vasodilators and produce reflex tachycardia instead of causing bradycardia.
- Propranolol is a non selective beta blocker and acts mainly by decreasing heart rate.

64. Ans. (a) Atenolol (Ref: KDT 6/e p139), Current hypertensive research May 2012; Antihypertensive treatment and sexual dysfunction.

- Diuretics have maximum risk of causing sexual dysfunction followed by beta blockers.
- Atenolol, metoprolol and carvedilol have high risk whereas nebivolol has minimum risk of erectile dysfunction.
- ACE inhibitors decrease the risk.

65. Ans. (b) It can cause severe hypoglycemia (Ref: Katzung 11/e p180)

Diazoxide cause hyperglycemia and not hypoglycemia

- Diazoxide is an effective and relatively long-acting parenterally administered arteriolar dilator that is occasionally used to treat hypertensive emergencies.
- It acts by opening ATP sensitive potassium channels.
- The most significant toxicity from diazoxide has been excessive hypotension.
- Diazoxide inhibits insulin release from the pancreas (probably by opening potassium channels in the cell membrane) and is used to treat hypoglycemia secondary to insulinoma.
- Occasionally, hyperglycemia complicates diazoxide use, particularly in persons with renal insufficiency.

66. Ans. (a) Pregnancy induced hypertension (Ref: *Katzung 11/e p173*)

'Methyl-dopa was widely used in past but is now used primarily for hypertension in pregnancy

67. Ans. (d) Nifedipine (Ref: *Katzung 10/e p175; KDT 6/e p543*)

Nifedipine, amlodipine like calcium channel blockers can be used for hypertension.

68. Ans. (d) Atenolol (Ref: *CMDT-2014/429*)

- Beta blockers are no longer considered to be the first line antihypertensive agents. According to JNC-8, ACE inhibitors, calcium channel blockers and diuretics are first line agents.

69. Ans. (d) Prazosin (Ref: *CMDT-2010/409*)

- Prazosin should be avoided as first choice because of risk of postural hypotension.

70. Ans. (c) Prazosin completely antagonizes its action (Ref: *KDT 6/e p546*)

- Clonidine is an α_2 agonist that acts by decreasing the central sympathetic outflow.
- Sedation, dry mouth and rebound hypertension are the principal adverse effects associated with clonidine.
- Prazosin is an α_1 selective blocker, therefore it is not able to block α_2 mediated actions.

71. Ans. (d) Nifedipine (Ref: *Katzung 10/e p145, 179; KDT 11/e p185*)

Nifedipine can be used rarely for the rapid control of blood pressure but the route of administration is sub-lingual. Fenoldopam is a D_1 agonist used i.v. for hypertensive emergencies whereas urapidil is an α blocker. Enalaprilat (not enalapril) can also be used for the same indication.

72. Ans. (b) Stimulation of guanylate cyclase (Ref: *KDT 6/e p549*)

Sodium nitroprusside acts by releasing nitric oxide (NO). This stimulates guanylate cyclase and results in the elevation of cGMP, which is a potent vasodilator.

73. Ans. (a) Sodium nitroprusside (Ref: *KDT 11/e p185*)

It is the first choice drug for hypertensive emergencies.

74. Ans. (b) Beta blockers (Ref: *KK Sharma 2007/619; KDT 6/e p139*)**75. Ans. (b) ACE-inhibitors** (Ref: *KDT 5/e p450; KDT 6/e p484*)

- ACE inhibitors and ARBs have fetopathic potential, therefore are contra-indicated in pregnancy.

76. Ans. (b) It causes dilation of both arteries and veins (Ref: *KDT 6/e p540, 547, 548*)

Hydralazine is a predominantly arteriolar dilator that relaxes blood vessels by releasing NO and opening K^+ channels. There is compensatory increase in plasma renin activity with all vasodilators. Postural hypotension is predominantly caused by dilatation of veins and is not a significant feature of hydralazine.

77. Ans. (b) Increase in LDL cholesterol on prolonged use (Ref: *KDT 6/e p546*)

Clonidine is a selective α_2 agonist that acts by decreasing central sympathetic outflow. Vasodilators can result in reflex increase in renin release. This can be prevented by combining vasodilators with clonidine or β -blockers. Sedation and dry mouth are prominent adverse effects of clonidine and α -methyldopa. These drugs decrease LDL and increase HDL-cholesterol.

78. Ans. (a) Continued till the day of operation (Ref: *CMDT 2014/47*)

Before surgery, antihypertensive drugs should be continued till the day of surgery.

79. Ans. (b) Verapamil (Ref: *KDT 6/e p484, 541, 544*)

Thiazides and beta blockers should be avoided in diabetes mellitus whereas ACE inhibitors should not be given to a patient with bilateral renal artery stenosis. Therefore, CCBs like verapamil are best agents to manage hypertension in such a patient.

80. Ans. (a) Losartan; (b) Captopril; (c) Amlodipine (Ref: *KDT 6/e p551*)

- ACE inhibitors (e.g. captopril) and AT_1 antagonists (e.g. losartan) are first choice antihypertensive drugs for diabetic patients.
- Calcium channel blockers (like amlodipine) and α -blockers (like prazosin) are also safe in diabetics.
- Thiazides and β -blockers should be avoided in diabetes mellitus.

81. Ans. (a) Prazosin; (d) Losartan (Ref: KDT 6/e p488-545)

Drugs		Lipid metabolism	
(i)	Prazosin and Clonidine	•	Favourable effect in metabolism.
		–	Lowers LDL cholesterol and triglyceride
		–	Increases HDL.
(ii)	ARB and ACE inhibitors	•	No significant effect in plasma lipid profile.
(iii)	Propanolol: (β-blockers)	•	Unfavourable effect on lipid profile raises triglyceride level and LDL/HDL ratio.
(iv)	Diuretics	–	Dyslipidemia, rise in total lipid and triglycerides with lowering of HDL. This increases the other atherogenic risk.
(v)	Calcium channel blockers	•	No effect on plasma lipid profile.

- Losartan has mild uricosuric effect also.

82. Ans. (a) Heart block; (c) Hypotension and (d) Bradycardia (Ref: KDT 6/e p533)

- When β-blockers are given with verapamil or diltiazem they produce:
 - Additive sinus depression, conduction defects or asystole resulting in marked bradycardia and A-V block.
 - Cardiac arrest may occur due to the combination.
 - Both decrease BP, so may result in hypotension.

83. Ans. (a) Decreased angiotensin II concentration in the blood (Ref: KDT 6/e p483, 484)

Enalapril inhibits ACE responsible for the conversion of angiotensin I to angiotensin II. There is a reflex increase in renin activity. Inhibition of aldosterone production decreases the reabsorption of Na⁺ and excretion of K⁺ in the urine. It can result in hyperkalemia.

84. Ans. (b) Alpha receptor blockers (Ref: KDT 6/e p545)

85. Ans. (a) Tachycardia and increased cardiac contractility (Ref: KDT 6/e p548)

Minoxidil is a powerful vasodilator and leads to reflex stimulation of sympathetic system. Thus, it causes tachycardia, increased contractility and retention of salt and water by the kidney.

86. Ans. (c) Agonistic action on vascular α₂ adrenergic receptors (Ref: KDT 6/e p546)

Alpha 2 receptors are present both presynaptically as well as postsynaptically. Clonidine acts as an α₂ agonist and decreases the central sympathetic outflow. However, it can also act on vascular postsynaptic α₂ receptors, leading to vasoconstriction and increase in blood pressure. Chances of this reaction is more when clonidine is administered by quick i.v. injection.

87. Ans. (a) It is less likely to cause rebound hypertension on sudden discontinuation (Ref: KDT 6/e p546)

88. Ans. (d) Lupus erythematosus (Ref: KDT 6/e p547, 548)

89. Ans. (c) Minoxidil (Ref: KDT 6/e p548)

90. Ans. (a) Clonidine (Ref: KDT 6/e p546)

Plasma renin activity is increased by reflex increase in sympathetic discharge. Clonidine decreases central sympathetic outflow and thus will decrease the plasma renin activity. Vasodilators and ACE inhibitors result in reflex increase in plasma renin activity.

91. Ans. (b) Methyldopa (Ref: KDT 6/e p547)

Although both methyldopa and minoxidil are prodrugs, conversion of methyldopa to α-methylnorepinephrine takes place in the brain whereas minoxidil is activated to minoxidil sulphate (by phase II reaction) in the periphery.

92. Ans. (d) Prazosin (Ref: KDT 6/e p545, 546)

Methyldopa and clonidine act via decreasing the central sympathetic outflow. Beta blockers act by several mechanisms, one of which is decrease in central sympathetic outflow. Alpha blockers like prazosin, do not act via central mechanism.

93. Ans. (d) Amlodipine (Ref: KDT 6/e p551)

94. Ans. (b) Guanethidine (Ref: KDT 6/e p549)

Postural hypotension caused by α-blockers is called first dose hypotension because tolerance occurs to this adverse effect on chronic use. On the other hand, adrenergic neuron blockers continue to produce orthostatic hypertension even on chronic use.

95. **Ans. (d) Nitroprusside** (Ref: KDT 6/e p554)
96. **Ans. (d) A 56 year old diabetic woman** (Ref: KDT 6/e p484, 486)
ACE inhibitors are contra-indicated in bilateral renal artery stenosis, pregnancy and in the setting of hyperkalemia.
97. **Ans. (c) Minoxidil** (Ref: KDT 6/e p548)
Vasodilators can lead to reflex increase in the sympathetic activity. Activation of β_1 receptors in the heart can cause tachycardia and release of renin. Latter can result in retention of salt and water.
98. **Ans. (b) Hydralazine** (Ref: KDT 6/e p547)
It is a vasodilator and can result in reflex tachycardia. All other drugs listed in the question (clonidine, propranolol, reserpine) decrease the activity of sympathetic system and can result in bradycardia.
99. **Ans. (c) Methyl dopa** (Ref: KDT 6/e p547)
100. **Ans. (b) Isosorbide dinitrate** (Ref: KDT 6/e p524, 525)
101. **Ans. (b) Enalapril** (Ref: KDT 6/e p541, 544, 546)
Thiazides and β -blockers are contra-indicated in diabetic patients. As the patient has frequent travelling job, he is likely to miss the doses. Therefore, clonidine should be avoided to prevent rebound hypertension. ACE inhibitors are safe and effective agents in diabetic patients with hypertension.
102. **Ans. (c) Atenolol** (Ref: KDT 6/e p544)
Tense personality and high resting heart rate (96/min.) makes β -blockers ideal candidate drugs to be used in this case. As blood sugar and lipid profile is normal, beta blockers can be used safely.
103. **Ans. (c) Intravenous infusion of sodium nitroprusside** (Ref: KDT 6/e p554)
104. **Ans. (b) Prazosin** (Ref: KDT 6/e p545-546)
105. **Ans. (b) Indapamide** (Ref: KDT 6/e p554)
Indapamide is a thiazide like diuretic, having mild diuretic effect, not used in emergency situations.
106. **Ans. (d) Minoxidil** (Ref: KDT 6/e p516, 549)
107. **Ans. (c) Clonidine** (Ref: KDT 6/e p545)
108. **Ans. (c) In hypertensive patient with gout, diuretics are particularly useful** (Ref: KDT 6/e p551)

Antihypertensive in special situations

- In patients with CHF or LV systolic dysfunction, ACE inhibitors are antihypertensive of choice.
- In hypertensive patients with migraine, CCBs are DOC. Beta-Blockers (e.g. propranolol) is also effective.
- In hypertensive patients with gout, PVD, DM, post MI, hyperlipidemia, ACE inhibitors are preferred.
- In hypertensive patients with Raynaud's phenomena and other peripheral vascular diseases and migraine CCBs are especially suitable.
 - Diuretics such as thiazides and frusemide are contraindicated in patients with hyperuricemia.

109. **Ans. (a) Methyldopa** (Ref: KDT 6/e p547)
110. **Ans. (a) I.V. Lignocaine** (Ref: CMDT 2010/364)
111. **Ans. (d) Methyldopa** (Ref: KDT 6/e p547)
112. **Ans. (b) Clonidine** (Ref: KDT 6/e p540)
113. **Ans. (a) Methyl dopa** (Ref: KDT 6/e p547)
114. **Ans. (c) ACE inhibitors** (Ref: KDT 6/e p551)
115. **Ans. (a). Clonidine** (Ref: KDT 6/e p546)
116. **Ans. (a) Fasudil** (Ref: Katzung 12/e p206)
- Rho kinase (ROCK) is a major downstream effector of the small GTPase RhoA. ROCK plays central roles in the organization of the actin cytoskeleton and is involved in a wide range of fundamental cellular functions such as contraction, adhesion, migration, proliferation and gene expression.
 - **Fasudil** is an experimental drug that acts by inhibiting the rho kinase and is found to be effective in animal models for treatment of

- Hypertension
- Pulmonary Hypertension
- Coronary artery disease
- Diabetic cardiomyopathy
- Vasospastic angina
- Ischemic stroke
- Heart failure
- Erectile dysfunction
- Cardiac remodeling

117. Ans. (b) Oxyphedrine (Ref: Katzung 11/e p283, 599, 674)

- Dipyridamole results in coronary steal phenomenon and thus can worsen angina.
- Thyroxine is a thyroid hormone and cause tachycardia which can precipitate angina by increasing the cardiac work.
- Sumatriptan cause coronary vasoconstriction and thus can worsen angina.
- Oxyphedrine is a selective beta 2 agonist. It is claimed to improve myocardial metabolism so that heart can sustain hypoxia better.

118. Ans. (a) It causes hypotension (Ref: CMDT 2014/347)

- Ranolazine is the first new antianginal drug to be approved by the FDA in many years, and it is **approved as first-line use for chronic angina**.
- Ranolazine has **no effect on heart rate and blood pressure**.
- It is **safe to use with erectile dysfunction drugs**.
- It also decreases occurrence of atrial fibrillation and results in a **small decrease in Hb_{A1C}**.
- Ranolazine is **not to be used for treatment of acute anginal episodes**.
- It can cause QT prolongation.

119. Ans. (d) Renal colic (Ref: KDT 6/e p527)

Nitrates are used in

- CHF
- Angina pectoris
- Myocardial infarction
- Biliary colic
- Diffuse esophageal spasm
- Cyanide poisoning (sodium nitrite)

120. Ans. (a) Hypotension and bradycardia (Ref: Katzung 11/e p265; KDT 6/e p524)

Nitrates are most commonly used antianginal drugs. These act by delivering nitric oxide in the blood vessels leading to vasodilation. Resulting hypotension lead to reflex tachycardia. It can cause methemoglobinemia as an adverse effect.

121. Ans. (a) Dipyridamole (Ref: KDT 6/e p535)

122. Ans. (a) Isosorbide mononitrate (Ref: KDT 6/e p525)

123. Ans. (a) Produces methemoglobinemia (Ref: KDT 6/e p527)

- Sodium nitroprusside contains one iron molecule coordinated to five cyanide molecules and one molecule of nitric oxide. Prolonged use of sodium nitroprusside may result in cyanide poisoning.
- Detoxification occurs when cyanide and methemoglobin combine to form cyanomethemoglobin. Amyl nitrite or sodium nitrite enhance the oxidation of hemoglobin to methemoglobin, ensuring a reliable mechanism of detoxification.

124. Ans. (c) Organic nitrates (Ref: KDT 6/e p295-296)

Nitrates act by increasing cGMP and sildenafil inhibits the breakdown of this compound (by inhibiting phosphodiesterase). Marked increase in cGMP levels may result in the profound hypotension and reflex tachycardia.

125. Ans. (c) Hyperglycemia (Ref: KDT 6/e p551, 554)

CCBs are safe in diabetic patients whereas thiazides and β -blockers should be avoided.

126. Ans. (a) Block of exercise induced tachycardia (Ref: KDT 6/e p527)

127. Ans. (a) Amyl nitrite (Ref: Katzung 10/e p186)

128. **Ans. (a) Isosorbide mononitrate** (Ref: KDT 6/e p525)
It is a metabolite of isosorbide dinitrate and is also available as a separate drug. It undergoes least first pass metabolism.
129. **Ans. (a) Isosorbide dinitrate** (Ref: KDT 6/e p525)
 - It can be administered sublingually for the treatment of acute attack of angina whereas by oral route it is used for prophylaxis.
 - Pentaerythritol tetranitrate and diltiazem are used only for prophylaxis of angina.
 - Dipyridamole actually worsens angina by causing coronary steal phenomenon.
130. **Ans. (b) It preferentially dilates conducting arteries without affecting resistance arterioles** (Ref: KDT 6/e p523)
Nitrates cause redistribution of blood flow without affecting total coronary flow. Autoregulatory small vessels remain unaffected whereas large conducting vessels are dilated. Nitrates are predominantly venodilators, therefore decrease mainly preload.
131. **Ans. (b) Veins express larger quantities of enzymes that generate NO from nitrates** (Ref: KDT 6/e p523)
132. **Ans. (c) Reduction of cardiac preload** (Ref: KDT 6/e p523)
Mechanism of action of nitrates in classical angina is reduction in preload (due to venodilation) and in variant angina is coronary vasodilation.
133. **Ans. (a) Coronary vasodilation** (Ref: KDT 6/e p526)
134. **Ans. (b) Sublingual nitroglycerine** (Ref: KDT 6/e p524, 525)
Tolerance develops to nitrates, when these are present constantly in the blood. Sublingual route leads to immediate action of nitrates and these act for a short time. Other preparations mentioned in the question are more likely to give consistent plasma levels of nitrates leading to development of tolerance.
135. **Ans. (c) Intramuscular** (Ref: KDT 6/e p525)
136. **Ans. (d) Sildenafil** (Ref: KDT 6/e p525)
Nitrates release NO, that acts by increasing cGMP. Phosphodiesterase inhibitors like sildenafil inhibits the breakdown of cGMP. Concomitant use of these two drugs may result in profound hypotension.
137. **Ans. (b) Nifedipine** (Ref: KDT 6/e p531)
Vasodilators and peripherally acting CCBs can cause tachycardia and thus may precipitate acute attack of angina. Risk of tachycardia is more with short acting drugs like nifedipine than with long acting agents like amlodipine.
138. **Ans. (a) It acts by conversion to an active metabolite in the liver** (Ref: KDT 6/e p531)
Amlodipine is the longest acting DHP. It undergoes little first pass metabolism and is distributed widely. Metabolites of amlodipine are inactive.
139. **Ans. (c) Verapamil** (Ref: KDT 6/e p530)
Both verapamil and propranolol decrease the conduction through AV node and their concomitant use can result in heart block.
140. **Ans. (c) It is an inhibitor of fatty acid oxidation** (Ref: Katzung 10/e p194; KDT 6/e p535-536)
141. **Ans. (a) Evoke coronary steal phenomenon** (Ref: KDT 6/e p535)
142. **Ans. (b) Dipyridamole** (Ref: KDT 6/e p535)
143. **Ans. (c) Amlodipine** (Ref: KDT 6/e p529)
144. **Ans. (c) Pentaerythritol tetranitrate** (Ref: KDT 6/e p526)
145. **Ans. (b) Metoprolol** (Ref: KDT 6/e p527, 528)
Beta blockers act in angina by decreasing exercise induced myocardial work. These do not cause vasodilation. Nitrates and CCBs act by causing vasodilation.
146. **Ans. (d) Nitroglycerine (transdermal)** (Ref: KDT 6/e p525)
Continuous presence of nitrates in blood will result in tolerance.
147. **Ans. (d) Slow i.v. infusion** (Ref: KDT 6/e p527)
Nitrates can be used in acute LVF by slow i.v. infusion.
148. **Ans. (c) Conversion of hemoglobin to methemoglobin by sodium nitrite** (Ref: KDT 6/e p527)

Cyanide has very high affinity for the enzymes of respiratory chain particularly cytochrome oxidase. Methemoglobin possesses even higher affinity for cyanides. It can free the enzymes due to competitive inhibition for cyanide. Nitrates act by reducing hemoglobin to methemoglobin, which removes cyanide from the enzymes.

149. **Ans. (b) High hepatic first pass metabolism** (Ref: KDT 6/e p7)
Main advantage of sublingual route of drug administration is that liver is bypassed and drugs with high first pass metabolism are absorbed directly into systemic circulation.
150. **Ans. (c) Sick sinus syndrome** (Ref: KDT 6/e p532, 533)
CCBs are contra-indicated in the sick sinus syndrome and along with β -blockers.
151. **Ans. (d) All of the above** (Ref: KDT 6/e p523, 524)
Nitrates act by releasing NO which increases cGMP that cause dephosphorylation of myosin light chain kinase. These are preferential dilator of venules because glutathione reductase (enzyme that releases NO from nitrates) is principally present at these sites. These agents are smooth muscle relaxants and can be used in colics and in achlasia cardia.
152. **Ans. (a) Sub-arachnoid hemorrhage** (Ref: KDT 6/e p532)
153. **Ans. (a) By increasing the left ventricular end diastolic pressure** (Ref: KDT 6/e p526)
Nitrates decreases end diastolic pressure by causing venodilation. For details, see text
154. **Ans. (b) Increase in cardiac work** (Ref: KDT 6/e p526)
155. **Ans. (c) Congestive heart failure** (Ref: KDT 6/e p502, 551)
156. **Ans. (c) Isoproterenol** (Ref: KDT 6/e p537-538)
Isoproterenol is a β adrenergic agonist and is C/I in IHD as it can increase myocardial oxygen demand by causing tachycardia.
157. **Ans. (a) Nicorandil** (Ref: Katzung 11/e p198)
158. **Ans. (a) Dantrolene** (Ref: KDT 6/e p529)
159. **Ans. (b) Inhalation** (Ref: Katzung 11/e p195)
160. **Ans. (d) Verapamil** (Ref: KDT 6/e p533)
161. **Ans. (b) Complete heart block** (Ref: KDT 6/e p543)
162. **Ans. (a) Bradykinin** (Ref: KDT 6/e p484)
163. **Ans. (c) Verapamil** (Ref: KDT 6/e p530-531)
164. **Ans. (c) Subarachnoid haemorrhage** (Ref: KDT 6/e p532)
165. **Ans. (a) Arterial pressure will decrease** (Ref: KK Sharma, 1/e p276)
Combined use of calcium channel blockers and nitrates enhances the therapeutic effects of each and minimizes the adverse effects.

Parameter	Nitrate	CCB	Combined efficacy
Heart rate	↑	↓	↓ or ±
Contractility	↑	↓	±
Arterial pressure	↓	↓	↓↓
Preload	↓↓	±	↓↓
Afterload	↓	↓↓	↓↓
End diastolic volume	↓	↑	↓ or ±
Ejection time	↓	↑	±
Coronary blood flow	↑	↑	↑↑
Collateral blood flow	↑	↑	↑↑
Endocardial ischemic area blood flow		↑	↑↑
Myocardial wall tension	↓	↓	↓↓
Ventricular volume	↓	±	↓
Heart size	↓	±	↓

166. Ans. (d) Verapamil (Ref: Katzung, 11/e p181)

167. Ans. (d) Productive cough (Ref: Katzung 11/e p241; Harrison 17/e p1953)

'Liver toxicity caused by amiodarone is also called 'pseudoalcoholic liver injury' and can range from fatty liver to hepatitis to cirrhosis'. It can also result in pulmonary fibrosis and corneal microdeposits.

168. Ans. (a) It increases effective refractory period; (c) Causes paradoxical tachycardia; (e) Cinchonism is seen (Ref: KDT 6/e p511-512)

Quinidine has following properties:

- Class I A and III antiarrhythmic properties
- Increases the ERP (effective refractory period).
- Antivagal action, causing tachycardia. This tachycardia is paradoxical, because quinidine is a cardiac depressant and thus not expected to increase the heart rate.
- Some α -blocking properties and its use can cause hypotension, but not used as antihypertensive agent.
- At higher doses, cinchonism occurs, characterized by ringing in ear, deafness, vertigo, headache, visual disturbances, mental changes and delirium.
- Antimalarial action is poorer than quinine.
- ECG changes: $\uparrow$ PR and QT interval and broadens QRS complex and change the shape of T wave.

169. Ans. (a) Verapamil (Ref: Katzung 11/e p243-244, KDT 6/e p517-518)

- Adenosine is DOC for PSVT termination.
- Verapamil is DOC for prophylaxis of PSVT and for management of sustained supraventricular tachycardia.

170. Ans. (a) Quinidine (Ref: Katzung 10/e p224; KDT 6/e p510)

- Torsades de pointes is a polymorphic ventricular tachycardia that is usually caused due to blockade of delayed rectifier K^+ channels in the heart.
- It manifests in the ECG as QTc prolongation.

- Drugs having cardiac K^+ channel blocking activities can cause this arrhythmia. These include:
 - Class Ia antiarrhythmics -Quinidine, Procainamide (Na^+ and K^+ channel blockers)
 - Class III antiarrhythmics -Bretylium, sotalol, dofetilide, ibutilide and amiodarone (K^+ channel blockers)
 - Other drugs like Terfenadine, Cisapride, Astemizole, Sparfloxacin, Gatifloxacin, Grepafloxacin, Mefloquine, Pentamidine, Thioridazine, Ziprasidone etc.

171. Ans. (d) Systemic lupus erythematosus (Ref: KDT 6/e p516)

172. Ans. (a) Tocainide (Ref: KK Sharma/307, G & G, 10/e p962)

- Although the name is similar to class Ic agents (like flecainide, encainide), tocainide comes under class Ib.

173. Ans. (c) It is excreted through bile following hepatic metabolism (Ref: KDT 6/e p140, 515)

Sotalol is a non-selective β -blocker having class III (K^+ channel blocking) anti-arrhythmic property. It prolongs APD by blocking cardiac K^+ channels. Therefore, it can prolong QT interval and result in torsades de pointes (polymorphic ventricular tachycardia). It is a lipid insoluble beta blocker that is excreted predominantly by kidney.

174. Ans. (a) Magnesium sulphate (Ref: Goodman & Gilman 11/e p929, 930)

- Magnesium is the agent of choice for the immediate treatment of torsades associated with both congenital and acquired long QT syndrome. Use of i.v. isoproterenol is limited only to acquired long QT syndrome. Long term treatment with oral beta blockers is required only for congenital disease.

175. Ans. (a) Quinidine; (b) Disopyramide; (c) Procainamide (Ref: KDT 6/e p510)

- Torsades de pointes is seen with K^+ channel blockers (class Ia and class III antiarrhythmic drugs), e.g. quinidine, disopyramide, procainamide, bretylium, ibutilide, etc.

176. Ans. (d) Sodium lactate (Ref: CMDT -2010/1445)

Pressor agents (to reverse hypotension) and sodium lactate (to reverse arrhythmias) are indicated for the treatment of procainamide toxicity.

177. Ans. (b) Esmolol (Ref: KDT 6/e p515)

It is a very short acting β -blocker. It has to be administered i.v. for acute therapy of arrhythmias. Amiodarone, verapamil and quinidine can be used for chronic oral treatment of arrhythmias.

178. Ans. (a) Adenosine (Ref: KDT 6/e p502)
179. Ans. (b) Lignocaine (Ref: KDT 6/e p515)
180. Ans. (b) Cinchonism (Ref: KDT 6/e p511, 512)
181. Ans. (b) Amiodarone (Ref: KDT 6/e p516)
182. Ans. (c) Quinidine (Ref: KDT 6/e p511)
Na⁺ channel blockers reduce the slope of phase 0 whereas K⁺ channel blockers prolong the APD. Both of these properties are present in class Ia antiarrhythmics like quinidine and procainamide.
183. Ans. (b) It has no effect on myocardial K⁺ channels (Ref: KDT 6/e p511, 512)
Quinidine is a class I antiarrhythmic agent. It blocks Na⁺ channels in the open state and also delays the recovery of these channels. Blockade by these antiarrhythmic agents is frequency dependent. Class Ia antiarrhythmics, in addition blocks myocardial K⁺ channels also.
184. Ans. (c) Digitalis induced ventricular extrasystole (Ref: KDT 6/e p502)
Lignocaine is used only for the treatment of ventricular arrhythmias, it has no role in atrial arrhythmia.
185. Ans. (b) Amiodarone (Ref: KDT 6/e p516)
186. Ans. (b) Verapamil (Ref: KDT 6/e p517)
It is used for the treatment as well as prophylaxis of PSVT whereas adenosine is used only for the treatment of acute attack of PSVT.
187. Ans. (b) It has positive inotropic action (Ref: KDT 6/e p516)
Amiodarone possesses myocardial depressant property; not positive inotropic action.
188. Ans. (c) Adenosine (Ref: KDT 6/e p518)
189. Ans. (c) Beta 1 adrenoceptors (Ref: KDT 6/e p511)
 - Amiodarone has wide spectrum of antiarrhythmic actions. It acts by all the four mechanisms i.e. blockade of Na⁺ channels, blockade of β receptors, blockade of K⁺ channels and blockade of Ca²⁺ channels.
 - Timolol is a β blocker. Therefore, common action of these two drugs is inhibition of β -receptors.
190. Ans. (b) Hyperkalemia should be avoided to reduce the likelihood of procainamide toxicity (Ref: KDT 6/e p512)
Hyperkalemia increases the toxicity of class Ia antiarrhythmics.
191. Ans. (a) Lignocaine (Ref: KDT 6/e p498)
Lignocaine is the drug of choice for ventricular arrhythmias due to digitalis toxicity.
192. Ans. (c) Esmolol: Class IV (Ref: KDT 6/e p511)
Beta blockers are classified as class II anti-arrhythmics.
193. Ans. (d) Verapamil (Ref: KDT 6/e p517-518; Katzung 11/e p243-244)
 - Adenosine is the DOC for acute termination of PSVT. Esmolol and verapamil are alternative 2nd choice drugs.
 - However adenosine may precipitate bronchospasm in asthmatics, so not preferred in asthmatics.
 - Beta-blockers should be avoided in asthmatics, however if absolutely necessary, cardioselective β blockers (e.g. esmolol) should be used.
 - Further in asthmatic patients, verapamil (as well as nifedipine) given by inhalation significantly inhibits the bronchoconstriction induced by variety of stimuli.
194. Ans. (d) Lignocaine IA (Ref: KDT 6/e p511)
"Lignocaine is class IB drug (not IA)"
195. Ans. (d) Propranolol (Ref: Katzung 11/e p235,237,239,240)
196. Ans. (d) Lignocaine (Ref: KDT 6/e p618)
197. Ans. (c) Lignocaine (Ref: KDT 6/e p495)

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198. Ans. (a) Amiodarone (Ref: KDT 6/e p511)
199. Ans. (a) Adenosine (Ref: KDT 6/e p519)
200. Ans. (a) Verapamil (Ref: KDT 6/e p519)
201. Ans. (c) Xylocaine (Ref: KDT 6/e p519, CMDT 2014/362)
- DOC for ventricular arrhythmias after MI is lignocaine (lidocaine; xylocaine).
 - DOC for supraventricular arrhythmias after MI is beta blockers if cardiac function is adequate.
202. Ans. (a) Diphenylhydantoin (Ref: KDT 6/e p498)
Phenytoin is an alternative to lignocaine for digitalis induced ventricular arrhythmia.
203. Ans. (c) Amiodarone (Ref: Katzung 11/e p241)
204. Ans. (b) Na⁺ channel blockade (Ref: Katzung. 11/e p237)
205. Ans. (b) Decreased absorption of cholesterol (Ref: Katzung 10/e p571; KDT 6/e p618-619)
Ezetimibe is an intestinal cholesterol absorption inhibitor and is combined with statins.
206. Ans. (c) Absorbed good on empty stomach and absorption is delayed by fatty meals (Ref: KDT 6/e p616-617; Katzung 11/e p615)
- Absorption of fibrates improve when they are taken with food.
 - Fibrates act by stimulating LPL by activating a nuclear receptor PPAR α (peroxisome proliferator-activated receptor alpha). Major effect of fibrates is to reduce TG (contained in VLDL) and to increase HDL.
 - Fibrates are the drugs of choice in hypertriglyceridemia (type III and IV) and can be used with other drugs in type IIb. Fenofibrate, as it has maximum LDL reducing action).
 - GI distress and elevation of aminotransferases are important adverse effect of fibrates. Risk of myopathy is increased if these are used with statins except bezafibrate.
207. Ans. (d) Fibrinogen levels are increased by pravastatin (Ref: Goodman & Gilman 11/e p950, 951, 952)
Pravastatin has the least chances of drug interactions because it is metabolized by non-microsomal enzymes. It also has minimum chances of myopathy among statins. Bioavailability of pravastatin is least affected with food intake. It has little CNS penetration. Most studies indicate that pravastatin decreases serum fibrinogen levels.
208. Ans. (c) Indirect increase of LDL receptor synthesis (Ref: KDT 6/e p614, 615)
For explanation, see text
209. Ans. (c) Niacin (Ref: KDT 6/e p618)
210. Ans. (c) Statins (Ref: KDT 6/e p614)
211. Ans. (d) Nicotinic acid (Ref: Katzung 11/e p613)
212. Ans. (d) Activating lipoprotein lipase, resulting in VLDL degradation (Ref: KDT 6/e p616, 617)
Fibrates activate PPAR- α that results in the increased transcription of genes for lipoprotein lipase.
213. Ans. (b) Nicotinic acid (Ref: KDT 6/e p618)
214. Ans. (b) Niacin (Ref: KDT 6/e p618)
215. Ans. (d) Statins (Ref: KDT 6/e p614, 615)
216. Ans. (a) Rofecoxib (Ref: KDT 6/e p534, 197)
- Angiotensin receptor blockers (like losartan) and beta blockers (like metoprolol) are cardioprotective in congestive heart failure. These decrease the mortality.
 - Nicorandil is a potassium channel opener used in angina. It is cardioprotective by causing ischemic preconditioning.
 - Rofecoxib is a selective COX-2 inhibitor that was withdrawn due to increased risk of myocardial infarction.

217. Ans. (a) Nimodipine (Ref: *Katzung 11/e p202*)

Nimodipine is a cerebroselective calcium channel blocker that can reduce mortality after subarachnoid hemorrhage. The term “cerebral vasospasm” is commonly used to refer to the clinical picture of delayed onset of ischemic neurological deficits associated with aneurysmal SAH. Arterial vasospasm typically appears 3 to 4 days after rupture and reaches a peak in incidence and severity at 7–10 days. Symptoms typically begins 4–5 days after the hemorrhage and is characterized by the insidious onset of confusion and a decreasing level of consciousness. The main goal of current treatment plan of cerebral vasospasm is to prevent or limit the severity of arterial and symptomatic vasospasm. Only two treatments are generally accepted to be of substantial value in reducing the ischemic complications related to vasospasm:

- Treatment with cerebroselective calcium channel blocker nimodipine.
- Hypervolemic, hypertensive therapy is used to elevate the cerebral perfusion pressure and thus provide blood to regions of the brain with marginal perfusion because of arterial spasm.

218. Ans. (b) Angina pectoris (Ref: *Katzung 11/e p203–204, KDT 7/e p554, CMDT 2014/393*)

- Ivabradine is a bradycardiac drug. It selectively blocks If sodium channel blocker and reduce heart rate by inhibiting the hyperpolarization-activated sodium channel in the SA node. No other significant hemodynamic effect has been noted. It reduces angina attacks similar to calcium channel blockers and beta blockers. Lack of effect on GI and bronchial smooth muscle is an advantage of ivabradine.
- It can also be used in CHF although not approved by US-FDA.

219. Ans. (b) Omission of prior diuretic dose decreases the risk of postural hypotension (Ref: *KDT 6/e p450*)**Angiotensin Converting Enzyme Inhibitors (ACEI)**

- This group of drugs inhibits the enzyme kininase II or ACE. So, these drugs decrease the activity of RAAS and also potentiate the vasodilatory action of bradykinin. Because these are preventing the conversion of angiotensin I to angiotensin II, so these can decrease the action of the former but not the latter.
- ACEI are used for the treatment of hypertension, CHF, evolving MI, diabetic nephropathy, diabetic retinopathy, non-diabetic renal disease and also in scleroderma crisis. These drugs reduce proteinuria in diabetic as well as non-diabetic renal disease and also prevent the manifestations of scleroderma crisis which are mediated by angiotensin II.
- This group of drugs is more effective in sodium depleted states (like diuretic use) because activity of RAAS is more in such cases (to compensate for salt loss). These drugs may cause postural hypotension in diuretic treated patients, which otherwise is a relatively rare adverse effect.
- Lisinopril is longer acting than enalapril. Former can be given once daily whereas latter is required twice a day.

220. Ans (b) Alpha blockers (Ref: *CMDT 2010/381*)**Management of Idiopathic Pulmonary Hypertension**

- If the patient responds to vasodilators, then calcium channel blockers (including amlodipine, diltiazem, and nifedipine) are the first-line therapy.

Other drugs that can be used are:

- Phosphodiesterase inhibitors (e.g. sildenafil)
- Prostacyclin analogs (e.g. epoprostenol)
- endothelin receptor blockers (e.g. bosentan)

221. Ans. (b) Perindopril (Ref: *CMDT 2010/1105*)

An ACE inhibitor in normotensive diabetics impedes progression to proteinuria and prevents the increase in albumin excretion rate.

222. Ans. (d) Lisinopril (Ref: *Katzung 11/e p182; KDT 6/e p23–24,485*)

All ACE-inhibitor are prodrugs except Captopril and Lisinopril.

223. Ans. (b) Enalapril (Ref: *Katzung 10/e p281; KDT 6/e p487*)

ACE inhibitors can retard the progression of diabetic complications like nephropathy, neuropathy and retinopathy.

224. Ans. (c) Vasodilation (Ref: *Ganong Review of Medical Physiology 22nd; KDT 6/e p480–481*)

- Angiotensin II binds to AT1 receptors and causes vasoconstriction and release of aldosterone.
- **Angiotensin II is one of the most potent vasoconstrictors in body.**
- Angiotensin II increases thirst sensation through the subfornical organ (SFO) of the brain.
- It increases secretion of ATCH in the anterior pituitary.
- It also potentiates the release of norepinephrine by direct action on postganglionic sympathetic fibers.

225. **Ans. (b) Thrombolytic** (Ref: Harrison 17/e p1537; KDT 6/e p607; Braunwald 7/e p1183, 118)

Thrombolytics are indicated only in ST elevation MI (STEMI) whereas these are contra-indicated in non-STEMI.

226. **Ans. (d) Beta blockers** (Ref: Harrison 17/e p1577, 1578; KDT 6/e p295)

For details see chapter 19

227. **Ans. (b) Increased RR Interval in ECG** (Ref: Ganong 22/e p554; KDT 6/e p495)

Vagus is a parasympathetic nerve. It depresses the heart and result in decreased heart rate which is seen as increased RR interval in ECG. It also decreases the force of contraction and cardiac output slightly.

228. **Ans. (b) Reduction in filtration fraction** (Ref: Goodman & Gilman 11/e p804)

- Angiotensin II shifts the renal pressure natriuresis curve to right and helps to adjust the sodium level of the body according to dietary intake of sodium (more excretion with more intake and less excretion with less consumption). ACE inhibitors block this action of angiotensin II and cause leftward shift of renal pressure natriuresis curve, so that if sodium intake is decreased much more natriuresis can occur.
- ACE inhibitors increase renal blood flow without increasing GFR and thus result in reduction of filtration fraction
- ACE inhibitors do not significantly increase heart rate.
- There are variable effect on various vascular beds with ACE inhibitors, these can dilate large arteries.

229. **Ans (c) Inhaled salbutamol** (Ref: Harrison, 17/e p284; KDT 6/e p124)

- The characteristic features given in the question are of hyperkalemia. It can be treated by calcium gluconate, insulin (glucose is added to prevent hypoglycemia) or sodium bicarbonate which can shift K^+ in the cells. Salbutamol by i.v. or inhalational route promote cellular uptake of K^+ and thus can be used for hyperkalemia.

230. **Ans. (d) PTCA** (Ref: Harrison 17/e p1537; KDT 6/e p538)

- It is a characteristic case of ST elevation MI (STEMI). Treatment of choice for STEMI is percutaneous coronary intervention (PCI). Thrombolytics like t PA may also be employed.

231. **Ans. (b) Verapamil** (Ref: KDT 6/e p530)

All CCBs cause smooth muscle relaxation in blood vessels and extravascular (bronchus, GIT, urinary bladder, uterus) organs.

232. **Ans. (d) Causes hyperuricemia** (Ref: KDT 6/e p488)

Losartan is a non-competitive AT1 receptor antagonist. It does not increase bradykinin levels and thus is not associated with cough and angioedema. It produces a long acting metabolite. It does not cause hyperuricemia.

233. **Ans. (a) Diabetic nephropathy with albuminuria** (Ref: KDT 6/e p484)

ACE inhibitors are first choice drugs for diabetic patients with hypertension. These are however contra-indicated in pregnancy and other conditions mentioned in the question.

234. **Ans. (a) Atenolol** (Ref: KDT 6/e p142, 143)

Beta blockers should never be given alone (or before α -blockers) in pheochromocytoma. There is excess of catecholamines in the circulation in this condition. They increase BP by acting on α -receptors. Beta blockers will result in further increase in blood pressure by antagonizing β_2 mediated vasodilatation. Thus, the patient may end in hypertensive crisis. To avoid this complication, α -blockers should be given before β -blockers or combined α and β -blockers should be given.

235. **Ans. (a) Juxtaglomerular apparatus** (Ref: KK Sharma 2007/250; KDT 6/e p482)

236. **Ans. (a) Fenoldopam** (Ref: KK Sharma 2007/176, 261, 292; Katzung 11/e p180-181)

- Nitric oxide donors include:

- Sodium nitroprusside
- Organic nitrates
- Nitrites
- Hydralazine
- Propofol
- Nebivolol

- Fenoldopam is a selective D_1 agonist useful in hypertensive emergencies.

237. **Ans. (a) Hypotension** (Ref: KDT 6/e p484)
Short acting ACE inhibitors like captopril may result in postural hypotension. ACE inhibitors do not affect serum calcium levels.
238. **Ans. (d) Pheochromocytoma** (Ref: KDT 6/e p486, 487)
ACE inhibitors are useful in hypertension, MI and left ventricular dysfunction. These should be avoided in high renin situations like pheochromocytoma due to the risk of severe postural hypotension.
239. **Ans. (b) Digoxin** (Ref: KDT 6/e p502)
Digitalis is used to control ventricular rate in atrial fibrillation. It increases the refractoriness of AV node and decreases the conduction through AV node.
240. **Ans. (b) Hypokalemia** (Ref: KDT 6/e p484)
ACE inhibitors result in hyperkalemia and not hypokalemia.
241. **Ans. (d) Enalapril** (Ref: KDT 6/e p484)
242. **Ans. (c) Verapamil** (Ref: Goodman & Gilman 11/e p836)
Verapamil is present as a racemic mixture of R and S-verapamil. S-verapamil has more stronger negative dromotropic action and higher first pass metabolism than R-verapamil.
243. **Ans. (a) Thiazide diuretics; (b) β -blockers; (e) Phenytoin** (Ref: Harrison's 17/e p2153; KDT 6/e p274)
244. **Ans. (a) Systemic vasoconstriction; (e) Retention of water** (Ref: KDT 6/e p481)
245. **Ans. (a) ACE inhibitors** (Ref: Harrison 17/e p281)
ACE inhibitors cause hyperkalemia whereas amphotericin B and thiazides (e.g. chlorthalidone) can cause hypokalemia.
246. **Ans. (a) Thiazides; (c) Propanolol; (d) Frusemide** (Ref: KDT 6/e p274; Harrison 17/e p2305)
247. **Ans. (a) Persistent cough; (b) Taste changes; (c) First dose hypotension; (e) Angioedema** (Ref: KDT 6/e p484)
For details, see text
248. **Ans. (a) Verapamil; (c) MAO-Inhibitors; (d) Tricyclic antidepressants; (e) Ferrous sulphate** (Ref: KDT 6/e p530-655)
- The drugs causing constipation are:
 - Verapamil, MAO-inhibitors
 - Tricyclic antidepressants
 - Ferrous sulphate
 - Other important drugs which cause constipation are ganglion blockers, opioids, calcium carbonate, sedatives, antihistamines and laxative abuse itself.
 - Quinidine causes diarrhoea
249. **Ans. (d) Theophylline** (Ref: KDT 6/e p219)
Propanolol, verapamil and clonidine cause hypotension as well as bradycardia. Theophylline results in reflex tachycardia due to its vasodilatory action.
250. **Ans. (d) All of the above** (Ref: KDT 6/e p486, 487)
251. **Ans. (d) Potential to induce cough in susceptible individuals** (Ref: KDT 6/e p488)
252. **Ans. (c) Candesartan** (Ref: KDT 6/e p488)
253. **Ans. (a) It does not potentiate bradykinin** (Ref: KDT 6/e p488)
254. **Ans. (d) Bradykinin** (Ref: KDT 6/e p490, 491)
255. **Ans. (a) Erythromycin** (Ref: KK Sharma 2/e p331)
The diagnosis in this condition is rhabdomyolysis suggested by myoglobinuria (red coloured urine without RBCs) and raised creatinine kinase levels. Statins can cause serious side effects like myopathy and hepatitis. Most statins are metabolized by cytochrome P-450 3A4, with the exception of pravastatin. Concomitant administration of drugs that inhibit statin metabolism (e.g. macrolides) is associated with increased incidence of statin induced myopathy and rhabdomyolysis. Acute renal failure is a possible sequela of rhabdomyolysis.
256. **Ans. (a) Losartan** (Ref: KDT 6/e p488)
257. **Ans. (c) Captopril** (Ref: KDT 6/e p484)
258. **Ans. (b) Digoxin** (Ref: KDT 6/e p497)

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259. Ans. (d) Bilateral renal artery stenosis (Ref: KDT 6/e p484)
 260. Ans. (c) Both (Ref: KDT 6/e p487)
 261. Ans. (a) Bradykinin (Ref: KDT 6/e p484)
 262. Ans. (c) It decreased automaticity in heart (Ref: KDT 6/e p511)
 263. Ans. (a) Enalapril (Ref: KDT 6/e p485)

Effect of food on bioavailability of ACE inhibitors	
Rate and Extent reduced	Captopril Benazepril Moexipril
Rate of absorption reduced	Fosinopril Quinapril Ramipril
No effect	Enalapril Lisinopril Trandolapril Perindopril

264. Ans. (a) Decrease in K^+ concentration (Ref: Katzung 11/e p183)
 265. Ans. (b) Calcium gluconate (Ref: Harrison 17/e p35)
Treatment of Calcium channel blocker poisoning
 - Calcium and glucagon for hypotension and symptomatic bradycardia.
 - Dopamine, epinephrine, norepinephrine, atropine, and isoproterenol are less often effective but can be used adjunctively.
 - Amrinone, high-dose insulin (with glucose and potassium to maintain euglycemia and normokalemia), electrical pacing, and mechanical cardiovascular support for refractory cases
 266. Ans. (c) Clonidine (α_2 agonist) (Ref: KDT 6/e p546)
 267. Ans. (b) Diabetes (Ref: KDT 6/e p484-87)

ANSWERS OF RECENT QUESTIONS ASKED BY NATIONAL BOARD

- Ans (b) Enalapril (Ref: KDT 7th/501)
- Ans (a) They increase lipoprotein lipase activity through PPAR alpha and cause increased lipolysis of triglycerides (Ref: KDT 7th/638)
- Ans (d) HMG CoA reductase (Ref: KDT 7th/636)
- Ans (a) Fluvastatin (Ref: KDT 7th/768)
- Ans (a) Ezetimibe (Ref: KDT 7th/641)
- Ans (b) 40 hrs (Ref: KDT 7th/515)
- Ans (b) Methyl dopa (Ref: KDT 7th/566)
- Ans (a) Inhibits Na^+K^+ ATPase pump (Ref: KDT 7th/270)
- Ans (b) Used for treatment of erectile dysfunction (Ref: KK Sharma 2nd/195)
Guanethidine
 - Acts by inhibiting exocytosis of NA.
 - Does not cross blood brain barrier.
 - Postural hypotension, delayed ejaculation and diarrhea are important adverse effects.
- Ans (a) Spironolactone (Ref: KDT 7th/524)
- Ans (c) Spironolactone (Ref: KDT 7th/524)
- Ans (a) HMG CoA reductase inhibitor (Ref: KDT 7th/502)

13. Ans (b) Pitavastatin (Ref: KDT 7th/637)
14. Ans (b) ↑cGMP (Ref: KDT 7th/568)
15. Ans (b) 20-40% (Ref: KDT 7th/533)
16. Ans. (d) Digitalis (Ref: KDT 6/e p499, CMDT 2014/1515)
17. Ans. (b) Enalapril (Ref: KDT 6/551)
18. Ans. (b) II (Ref: KDT 6/e p511)
19. Ans. (d) Sodium nitrite followed by thiosulphate (Ref: KDT 6/e p527)
20. Ans. (c) Enalapril (Ref: KDT 6/e p984)
21. Ans. (a) Renal insufficiency (Ref: KDT 6/e p497)
22. Ans. (a) Amiodarone (Ref: KDT 7/e p533)
23. Ans. (c) Class III (Ref: KDT 7/e p529)
24. Ans. (b) Niacin (Ref: Goodman Gilman 12/edn. p 900)
25. Ans. (d) Lignocaine (Ref: KDT 7/e p531)
26. Ans. (a) Enalapril (Ref: KDT 7/e p572)
27. Ans. (b) Cough (Ref: KDT 7/e p506)
28. Ans. (c) Administered by slow I.V. injection (Ref: KDT 7/e p576)
29. Ans. (c) Digoxin Antibody (Ref: KDT 7/e p516)
30. Ans. (c) Atorvastatin (Ref: KDT 7/e p629)
31. Ans. (c) Digoxin (Ref: KDT 7/e p520)
32. Ans. (d) Clonidine (Ref: KDT 7/e p500)
33. Ans. (c) ACE inhibitors (Ref: KDT 7/e p502)
34. Ans. (c) Pindolol (Ref: KDT 7/e p144)
35. Ans. (a) Hyperkalemia (Ref: KDT 7/e p516-517)
36. Ans. (c) Blocking AT₁ receptors (Ref: KDT 7/e p561)
37. Ans. (c) Amiodarone (Ref: KDT 7/e p519)
38. Ans. (b) Rosuvastatin (Ref: KDT 7/e p637)
39. Ans. (b) Niacin (Ref: KDT 7/e p640)
40. Ans. (b) ATP dependent K⁺ channels (Ref: KDT 7/e p558-559)
41. Ans. (b) Selective inhibitor of phosphodiesterase type 5 (Ref: KDT 7/e p303)
42. Ans. (a) ACE inhibitors (Ref: KDT 7/e p505, CMDT 2014/808)
43. Ans. (a) Methyl dopa (Ref: KDT 7/e p566)
44. Ans. (b) Less peripheral vasoconstriction (Ref: KDT 7/e p134)
45. Ans. (c) HMG CoA reductase (Ref: KDT 7/e p636)
46. Ans. (b) Amiloride (Ref: KDT 7/e p589)
47. Ans. (c) Digoxin (Ref: KDT 7/e p517)
 - Drugs increasing cardiac contractility should be avoided in HOCM.
48. Ans. (b) Enalapril (Ref: KDT 7/e p529)
49. Ans. (d) ACE inhibitors (Ref: KDT 7/e p570)
50. Ans. (c) Verapamil (Ref: KDT 7/e p535)
51. Ans. (c) Lovastatin (Ref: KDT 7/e p636)

52. Ans. (b) Metoprolol (Ref: KDT 7/e p523)
53. Ans. (b) Amiodarone (Ref: KDT 7/e p529)
54. Ans. (b) Minoxidil (Ref: KDT 7/e p567)
55. Ans. (a) Enalapril (Ref: KDT 7/e p562)
56. Ans. (a) $\text{Na}^+ \text{K}^+$ ATPase inhibition (Ref: KDT 7/e p514)
57. Ans. (b) Cardioversion (Ref: KDT 7/e p538)
58. Ans. (d) Dipyridamol (Ref: KDT 7/e p553)
59. Ans. (a) Enalapril (Ref: KDT 7/e p504)
60. Ans. (c) Procainamide (Ref: KDT 7/e p529)
61. Ans. (c) ACE inhibitor (Ref: KDT 7/e p504)
62. Ans. (c) Morphine (Ref: KDT 7/e p556)
63. Ans. (a) Adenosine (Ref: KDT 7/e p536)
64. Ans. (b) Amiodarone (Ref: KDT 7/e p534)
65. Ans. (d) All of the above (Ref: KDT 7/e p516)
66. Ans. (a) Dosage reduction is required in hepatic disease (Ref: KDT 7/e p516)
67. Ans. (d) Adenosine (Ref: KDT 7/e p536)

DIURETICS

Diuretics mainly exert their effect by the inhibition of renal tubular reabsorption of sodium and water. These may be classified according to their efficacy as high ceiling (loop and osmotic diuretics), medium ceiling (thiazides) and low ceiling (carbonic anhydrase inhibitors and potassium sparing) diuretics. In this chapter, we will classify diuretics based on their site of action.

Diuretics Acting on the Proximal Tubule (PT)

These are **non-competitive but reversible** inhibitors of carbonic anhydrase and act by inhibiting the reabsorption of sodium in the proximal tubular portion of the nephron.

CARBONIC ANHYDRASE (CA) INHIBITORS

Luminal membrane of proximal tubules contain $\text{Na}^+\text{-H}^+$ antiporter which helps in the excretion of H^+ in exchange with the reabsorption of Na^+ . The H^+ is formed inside the tubular cells due to the action of carbonic anhydrase according to the reaction:



The secreted H^+ combines with HCO_3^- in the lumen of PT with the help of carbonic anhydrase to form carbonic acid (H_2CO_3), which is converted to H_2O and CO_2 . Latter are absorbed in the tubular cell and again converted to HCO_3^- and H^+ . Thus, the *net effect of carbonic anhydrase is to cause the absorption of sodium and bicarbonate*. Inhibitors of this enzyme (acetazolamide, dichlorophenamide and methazolamide) result in the excretion of sodium and bicarbonate in the urine. Due to urinary excretion of bicarbonate, *metabolic acidosis (and urinary alkalosis) ensues that result in reduced filtration of HCO_3^- at the glomerulus*. Therefore, *action of these diuretics is self limiting*.

Acetazolamide, dorzolamide and brinzolamide are non-competitive but reversible inhibitors of carbonic anhydrase

Action of carbonic anhydrase inhibitors is self limiting.

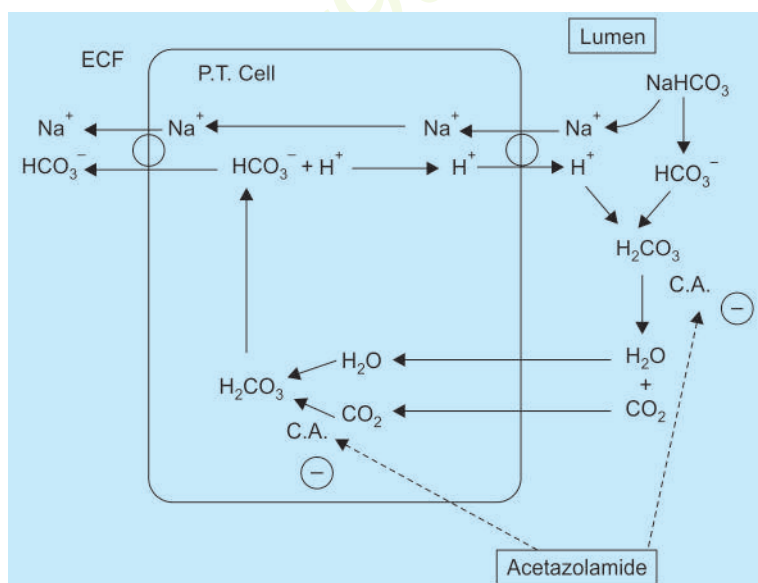


Fig 6.1: Mechanism of action of carbonic anhydrase inhibitors

At equally natriuretic doses, K^+ excretion is maximum with Carbonic Anhydrase Inhibitors

Carbonic Anhydrase Inhibitors should not be used in the presence of liver disease due to the risk of precipitation of hepatic coma.



Uses of carbonic anhydrase inhibitors

Glaucoma (Angle closure)
Alkalinization of Urine
Mountain Sickness
Epilepsy

G A M E

Loop diuretics decrease positive as well as negative free water clearance whereas thiazides decrease positive free water clearance only.

Loop diuretics are the diuretics of choice in the presence of moderate to severe renal failure.

These agents also decrease the secretion of H^+ in the distal tubules and collecting ducts. Due to less reabsorption of sodium in the PT, more is delivered to the distal tubules (DT). At this site (also known as cortical diluting segment), Na^+ is exchanged with K^+ and H^+ . Drugs that increase the delivery of Na^+ to this site (thiazides, loop diuretics, CA inhibitors), will result in greater exchange and thus can cause hypokalemia. **At equally natriuretic doses, K^+ excretion is maximum with CA inhibitors because Na^+ delivered to the distal tubules is exchanged only with K^+ (excretion of H^+ is inhibited by these drugs).**

CA inhibitors also *decrease aqueous humor formation* (therefore used in glaucoma) and *raise seizure threshold* (basis of their use in absence seizures). Acetazolamide can be *used orally for the treatment of glaucoma, epilepsy, acute mountain sickness and to alkalinize urine* (for excretion of acidic drugs). **Dorzolamide and brinzolamide** are topically acting CA inhibitors for use in glaucoma as eye drops.

Acetazolamide is a sulfonamide derivative and can result in *bone marrow suppression and hypersensitivity reactions*. Other adverse effects include *metabolic acidosis (urinary alkalosis) and hypokalemia*. These diuretics **should not be used in the presence of liver disease** due to the risk of precipitation of hepatic coma. In liver disease, NH_3 is not converted to urea and if present in excess, can cross the blood brain barrier resulting in encephalopathy. It is excreted through kidney after conversion to NH_4^+ (combines with H^+ in the nephron). CA inhibitors decrease the excretion of H^+ resulting in enhanced reabsorption of ammonia (because it is in non-ionized form in the alkaline medium) and thus more toxicity.

Diuretics Acting on the Loop of Henle

INHIBITORS OF $Na^+K^+ATPase$

These are also known as **loop diuretics** and act by causing **inhibition of $Na^+K^+2Cl^-$ symporter** present at the luminal membrane of the ascending limb of loop of Henle. **Furosemide, torsemide, bumetanide, ethacrynic acid, axosemide, piretanide, tripamide and mersalyl** are the important members of this group. These have greater maximal natriuretic effect than all other diuretics (**high ceiling diuretics**). These drugs are *faster acting with short duration of action*. Loop diuretics and thiazides gain access to the tubular lumen through secretion (by organic anion transporter) in the PT. Loop of Henle is responsible for maintaining the difference in osmotic pressure between cortex and medulla (corticomedullary osmotic gradient). This gradient results from the absorption of water from descending limb of loop of Henle (permeable to water) and reabsorption of salt in ascending limb (impermeable to water).

Loop diuretics *abolish corticomedullary osmotic gradient and decrease positive as well as negative free water clearance*. Free water clearance is the amount of water excreted in the urine in excess of that required to excrete the solutes iso-osmotically. It is positive for dilute urine, negative for concentrated urine and zero for isotonic urine.

By inhibiting $Na^+K^+2Cl^-$ symporter, absorption of Na^+ in loop of Henle decreases. This unabsorbed Na^+ reaches DT, where it is exchanged with K^+ and H^+ resulting in hypokalemia and alkalosis. At equivalent doses, loop diuretics cause less hypokalemia than thiazides. These drugs are also weak CA inhibitors (except ethacrynic acid, it does not increase bicarbonate excretion in the urine). Loop diuretics also change intrarenal hemodynamics resulting in decreased absorption of Na^+ and water in the PT. These changes are mediated by the release of PGs (NSAIDs attenuate diuretic effect). Since GFR is not altered, loop diuretics are the **diuretics of choice in presence of moderate to severe renal failure**.

- **Furosemide** possesses *vasodilatory action which is responsible for the quick relief in LVF and pulmonary edema* (used i.v.).
- **Bumetanide** is the most potent loop diuretic (Ref. Goodman & Gilman Pg. 750) and produces less adverse effects than furosemide.
- **Ethacrynic acid** is *highly ototoxic* with steep DRC.
- **Mersalyl** like organomercurials are not used now due to the risk of kidney damage.
- **Torsemide** has *longest half life* (Ref. Goodman & Gilman Pg. 750)

Uses

Main use of loop diuretics is to remove the edema fluid in renal, hepatic or cardiac diseases. These can be administered i.v. for prompt relief of acute pulmonary edema (due to vasodilatory action). These drugs cause excretion of Ca^{++} , therefore can be used for the treatment of hypercalcemia.

Adverse Effects

Hypokalemia, hypomagnesemia, hyponatremia, alkalosis, hyperglycemia (C/I in DM), hyperuricemia (C/I in gout) and dyslipidemia are seen with both thiazides as well as loop diuretics. Effect on Ca^{++} excretion is opposite to thiazides (**LOOP LOOSES CALCIUM**). Loop diuretics cause hypocalcemia by increasing the excretion of Ca^{2+} whereas thiazides cause hypercalcemia by decreasing its excretion. Ethacrynic acid can cause ototoxicity more often than other loop diuretics. Furosemide and bumetanide are sulfonamides in chemical structure (should be avoided in persons allergic to sulfonamides).

OSMOTIC DIURETICS

Mannitol, glycerol, urea and isosorbide are inert drugs that can cause osmotic diuresis. Previously it was thought that osmotic diuretics act primarily in proximal tubules but recent studies have suggested that, these drugs act both in PT as well as **loop of Henle**, but latter is the major site of action. (Ref. Goodman & Gilman Pg. 747) When administered i.v., mannitol increases the osmotic pressure in the blood vessels and the consequent removal of excess fluid from the cells (basis of its use in glaucoma and cerebral edema) results in the expansion of extracellular fluid volume. Consequently, renal blood flow and GFR increases. Further, it is filtered at the glomerulus and reaches the proximal tubule (PT) and loop of Henle. It inhibits the reabsorption in ascending limb of loop of Henle by decreasing medullary tonicity (decreased medullary tonicity prevents reabsorption of water from descending limb that results in decreased absorption of solutes from ascending limb). Along with water, excretion of all the cations and anions is increased. Properties for a substance to act as an ideal osmotic diuretic are:

- It should exert osmotic effect.
- It should be pharmacologically inert.
- It should be freely filtered at the glomerulus.
- It should not be reabsorbed.

Mannitol is a low molecular weight compound possessing all these properties. It is used i.v. for the treatment of glaucoma and cerebral edema. It can also be used to maintain GFR in the impending renal failure. It is contraindicated in acute renal failure because ECF volume increases but it cannot be filtered. It is **also contraindicated in cerebral hemorrhage (active bleeding)** because in this situation, mannitol can leak from ruptured cerebral blood vessels resulting in the increased ICT (more fluid retention due to its osmotic effect in the cells). If given orally, mannitol can result in osmotic diarrhea. Isosorbide and glycerol can be used orally for the treatment of glaucoma and cerebral edema.

Diuretics Acting on the Distal Tubules and Collecting Ducts

THIAZIDES

Drugs in this group include bendroflumethiazide, chlorthiazide, hydrochlorthiazide, methiclothiazide, polythiazide, trichlormethiazide, benzthiazide, hydroflumethiazide, chlorthalidone, metolazone, quinethazone and indapamide. Chlorthalidone, indapamide, metolazone and quinethazone are thiazide like diuretics whereas other agents in this group are thiazides. These drugs act by **inhibiting $\text{Na}^+\text{-Cl}^-$ symporter** at the luminal membrane of early DT. This part of DT is

Properties of both loop and thiazide diuretics

↓ Na^+	↑ Lipids
↓ K^+	↑ Glucose
↓ Mg^{2+}	↑ Uric Acid
↓ H^+	

Furosemide possesses vasodilatory action which is responsible for the quick relief in LVF and pulmonary edema.

Bumetanide is the most potent loop diuretic whereas Torsemide has longest half life

Ethacrynic acid is highly ototoxic diuretic.

Properties of an ideal osmotic diuretic are:

- Exerts osmotic effect.
- Is pharmacologically inert.
- Is freely filtered at the glomerulus.
- Is not reabsorbed.

Mannitol can be used to maintain GFR in the impending renal failure.

impermeable to water and absorbs only solutes. By increasing excretion of solutes, thiazides make the urine concentrated (i.e. *decrease positive free water clearance without affecting negative free water clearance*). These drugs reach the lumen of nephron by secretion through organic acid transporter system. Additional CA inhibitory action is also exhibited by thiazides. Decreased absorption of Na^+ results in its greater delivery to late DT and CD that is responsible for *hypokalemia* (more than loop diuretics). **Chlorthiazide has minimum potency and efficacy** whereas other drugs differ only in potency (efficacy is similar). *Thiazides are moderate efficacy diuretics with low ceiling effect (flat DRC, natriuretic effect does not increase appreciably with increase in dose)*. These drugs tend to reduce GFR, therefore are *not indicated in renal failure patients*.

- Polythiazide and trichloromethiazide are most potent thiazides.
- Chlorthalidone is the longest acting thiazide.
- Metolazone is useful even in severe renal failure.
- Indapamide has no CA inhibitory action. It has vasodilatory property because of which, its antihypertensive effect precedes the natriuretic effect.



Thiazides are used for the treatment of patients with recurrent Ca^{++} stones in the kidney.

Uses

Thiazides are used as first line antihypertensive drugs. These are also used to mobilize the edema fluid in mild to moderate heart failure. Paradoxically, these drugs *decrease urine output in diabetes insipidus*. Thiazides reduce the excretion of Ca^{++} in the kidney, so can be used for the treatment of patients with hypercalciurea and recurrent Ca^{++} stones in the kidney.

Adverse effects

These are similar to loop diuretics except the effect on Ca^{++} excretion. Incidence of *erectile dysfunction* is greater with thiazides than with other antihypertensive drugs (like β blockers, CCBs, ACE inhibitors and α blockers).

Interactions of thiazides and loop diuretics

- Thiazides and loop diuretics enhance digitalis toxicity by causing hypokalemia and hypomagnesemia.
- Loop diuretics can enhance nephrotoxicity and ototoxicity of aminoglycosides.
- NSAIDs attenuate the actions of loop diuretics.
- Lithium toxicity can occur if used with diuretics (due to increased absorption of lithium in the PT).
- Resistance to loop diuretics can be reversed by addition of thiazides and resistance to latter can be decreased by adding potassium sparing diuretics.

POTASSIUM SPARING DIURETICS

These diuretics act in the late DT and CD cells to preserve K^+ . Luminal membrane of these portions of renal tubule contains *epithelial Na^+ channels* responsible for reabsorption of Na^+ . Due to decreased positive charge in the lumen, a transepithelial potential difference is generated (lumen negative). Under this potential gradient, K^+ and H^+ are secreted. These actions are promoted by aldosterone. Drugs that inhibit the epithelial Na^+ channels or the actions of aldosterone can decrease the reabsorption of Na^+ (diuretic effect) and excretion of K^+ (potassium sparing effect) and H^+ .



Amiloride is drug of choice for lithium-induced diabetes insipidus.

(a) Epithelial Na^+ channel inhibitors

These drugs are basic in nature and reach the lumen of PT by **secretion through organic base secretory system**. By travelling through the lumen, these drugs reach its site of action i.e. late DT and CD. Important members of this group are **amiloride and triamterene**. *Pentamidine and high dose trimethoprim (used for pneumocystis) are also weak inhibitors of this channel*.

- Amiloride is more potent and longer acting than triamterene.
- Triamterene is less often used because of incomplete absorption, photosensitivity and impairment of glucose tolerance. It is also associated with interstitial nephritis and renal stones.
- Triamterene is a weak folic acid antagonist and can lead to megaloblastic anemia especially in cirrhotic persons.
- Amiloride decreases Mg^{++} and Ca^{++} excretion and increases urate excretion.
- Lithium is absorbed through epithelial Na^+ channels in the CD cells and at toxic doses can cause diabetes insipidus. Amiloride is the drug of choice for this condition; it acts by blocking the entry of lithium through these channels.
- Amiloride can also be used as an aerosol to decrease the secretions in cystic fibrosis.

Aldosterone antagonists act from the interstitial site of tubular cell whereas all other diuretics act from luminal side.

(b) Aldosterone antagonists

Spironolactone, canrenone, potassium canrenoate and epleronone antagonize the action of aldosterone and produce effects similar to amiloride. These drugs **act from the interstitial site** of tubular cell (*all other diuretics act from luminal side*). These agents have maximum effect when aldosterone levels are high (e.g. hepatic cirrhosis, CHF, nephrotic syndrome etc.) and are ineffective in its absence (e.g. Addison's disease). **Spironolactone increases Ca^{++} excretion whereas amiloride decreases it.** Spironolactone is converted to canrenone and other active metabolites in the liver.

Uses: These are weak diuretics and are used only in combination with thiazides or loop diuretics to counteract K^+ loss. These can be used for CHF (decrease mortality), hypertension and cirrhotic edema (diuretic of choice is spironolactone) (Ref. Goodman & Gilman Pg. 762). Spironolactone can be used for the treatment of hirsutism because of its anti-androgenic action. (Its structure is similar to testosterone and thus it acts as a competitive antagonist at testosterone receptors).

Adverse effects and interactions: Spironolactone can cause **gynaecomastia and impotence**. Hyperkalemia, abdominal pain and aggravation of peptic ulcer can also occur. ACE inhibitors and potassium supplements increase the risk of hyperkalemia, if used along with these agents. Hyperkalemia and GI disorders are the main adverse effects of epleronone. It is metabolized by microsomal enzymes; therefore, is prone to drug interactions.

ANTIDIURETICS

The drugs that decrease urine volume are called antidiuretics. Primary indication of antidiuretics is the treatment of diabetes insipidus (DI).

Anti-Diuretic Hormone (ADH)

Physiological antidiuretic is vasopressin (antidiuretic hormone or ADH) that is synthesized in the hypothalamus and secreted by the posterior pituitary. It is secreted in response to increased plasma osmolality or decreased volume of extracellular fluid (ECF). ADH acts via 3 receptors V_1 , V_2 and V_3 .

ADH increases the permeability of collecting ducts by its action on V_2 receptors.

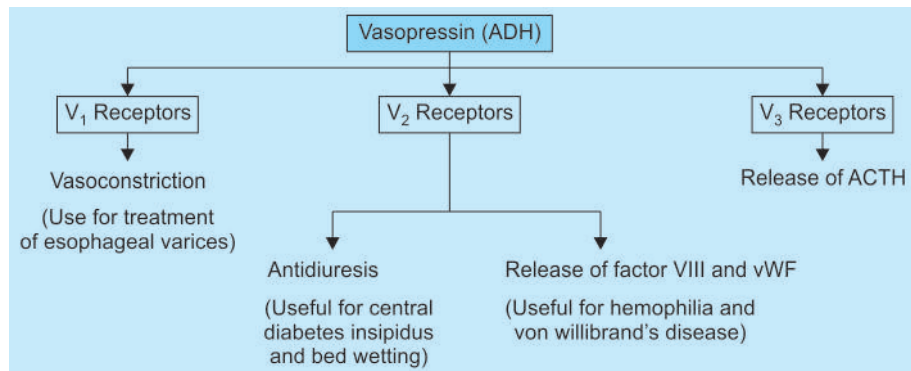
Actions of ADH

- In the absence of ADH, collecting ducts (CD) of the nephron are impermeable to water. ADH increases the permeability of CD by its action on V_2 receptors. Stimulation of these receptors elevates cAMP levels that increase aquaporins on the apical membrane of CD (by decreasing endocytosis and increasing exocytosis). V_2 receptor activation also increases permeability of CD to urea by stimulating the urea transporter.
- Vasopressin (ADH) as the name suggests is a potent pressor of blood vessels. Vasoconstrictor action is mediated by the activation of V_1 (also called V_{1a}) receptors. This action requires much higher concentration than V_2 receptor activation. V_2 receptor mediated vasodilatory action (due to the release of NO) has also been demonstrated.
- ADH is also involved in the release of vWF and factor VIII from the endothelium. This action is also mediated by V_2 receptors.
- V_3 receptors (previously known as V_{1b} receptors) are involved in the release of ACTH.

Vasoconstrictor action of ADH is mediated by the activation of V_1 (also called V_{1a}) receptors.

ADH induced release of vWF and factor VIII from the endothelium is mediated by V_2 receptors.

V_3 receptors (previously known as V_{1b} receptors) are involved in the release of ACTH.



Uses

- Major indication of ADH is central DI. DI is a condition in which there is excessive formation of urine due to decreased activity of ADH. It may be due to decreased production of ADH (central DI) or due to defective receptors in the kidney (nephrogenic DI). **ADH is effective only for central DI.** Use of ADH (arginine vasopressin) for this indication is limited due to two reasons; its short half life (require frequent daily dosing) and non-specific action on V_1 and V_2 receptors (V_1 mediated vasoconstriction can result in increased BP). Both of these shortcomings have been overcome in **desmopressin**. It is longer acting and V_2 selective analogue of vasopressin and is the drug of choice for the treatment of central DI. It can be administered orally or intranasally.
- Desmopressin (oral) is also the drug of choice for **nocturnal enuresis** and bed wetting in children. Intranasal desmopressin is not used for this indication now because of risk of dilutional hyponatremia.
- Another V_2 receptor mediated use of desmopressin is to **check bleeding in patients with hemophilia and von Willebrand's disease**. It acts by releasing factor VIII and vWF from the endothelium.
- Arginine vasopressin (AVP) has vasoconstrictor action that can be utilized to **stop bleeding in esophageal varices**. **Lypressin** has longer duration of action but is non-specific (action on both V_1 and V_2). **Terlipressin** (prodrug of vasopressin) is the preferred agent for this indication.
- Felypressin** can also be used along with local anaesthetics to prolong their duration of action (like adrenaline).

Adverse Effects and Contra-indications

Intranasal desmopressin can cause nasal irritation and rhinitis. AVP can cause hypertension and precipitation of angina, so it is contra-indicated in the patients with ischemic heart disease and hypertension.

Other Antidiuretics

Thiazides

These drugs are used as diuretics but, **exert paradoxical effect (decrease urine formation) in DI**. This paradoxical effect is believed to be due to increased formation of cAMP in the distal tubules. Another proposed mechanism is that thiazides cause dehydration that result in compensatory increase in reabsorption of Na^+ and water from the proximal portions of nephron. These are low efficacy antidiuretics but are beneficial in both central as well as nephrogenic DI.

Chlorpropamide, Clofibrate and Carbamazepine

These drugs increase the action of ADH on the kidney and are useful only in the central DI.

Desmopressin is longer acting and V_2 selective analogue of vasopressin and is the drug of choice for the treatment of central diabetes insipidus.

Vasopressin receptors

V_1 (V_{1a})

- Vascular smooth muscle – Vasoconstriction
- Platelets – Aggregation
- Hepatocytes – Glycogenolysis
- Uterus – Contraction

V_2

- Collecting tubules – Insertion of AQP2 water channels
- Endothelium – Release of vWF and factor 8
- Vascular smooth muscle – Vasodilation

V_3 (V_{1b})

- Ant pituitary – ACTH release

Amiloride

It is the agent of choice for *the treatment of Lithium induced DI*.

VASOPRESSIN RECEPTOR ANTAGONISTS

- V_1 receptor antagonists may be useful when total peripheral resistance is increased (e.g. CHF and hypertension) whereas V_2 antagonists may be useful for the treatment of SIADH.
- **Relcovaptan** is *selective V_1 antagonist* whereas **lixivaptan, mozavaptan and tolvaptan** are *V_2 selective antagonists*.
- **Conivaptan** is V_{1a}/V_2 receptor antagonist used as an aquaretic (increase water excretion without affecting electrolytes like sodium) in CHF.
- **Conivaptan** is administered by **i.v. injection** whereas **lixivaptan and tolvaptan** can be given **orally**.

SYNDROME OF INAPPROPRIATE ADH SECRETION (SIADH)

ADH is secreted in response to hypovolemia, in which case its secretion is appropriate. However, if ADH is secreted in high quantities in the presence of euolemia or hypervolemia, it is called inappropriate secretion (SIADH). The resultant water retention can result in hyponatremia. Thus, SIADH is characterized by normovolemic or hypervolemic hyponatremia.

- **Fluid restriction** is **treatment of choice** for SIADH.
- Hypertonic saline (3% NaCl) + loop diuretics (depending upon volume status) is treatment of choice for severe symptomatic hyponatremia.
- Among drugs, tolvaptan (oral), conivaptan (i.v.) are preferred for long-term use.
- Alternatives are demeclocycline and lithium (not preferred now).

DRUG OF CHOICE	
Condition	Drug of choice
• Edema	
– Due to CHF	Furosemide
– Due to renal disease or nephrotic syndrome	Furosemide
– Pulmonary edema	Furosemide
– Cerebral edema	Mannitol
– Edema due to cirrhosis	Spironolactone
• Diabetes insipidus	
– Central	Desmopressin
– Nephrogenic	Thiazides
– Lithium-induced	Amiloride
• Recurrent calcium stones in kidney due to hypercalciuria	Thiazides
• Acute congestive glaucoma	Acetazolamide
• Acute mountain sickness	Acetazolamide
• Nocturnal enuresis	Desmopressin
• SIADH	Fluid restriction + Hypertonic saline + Furosemide

MULTIPLE CHOICE QUESTIONS

DIURETICS

1. Thiazide diuretics can be used for the treatment of all of these conditions EXCEPT: (AI 2012)

- (a) Idiopathic hypercalciuria with nephrocalcinosis
- (b) Hyperlipidemia
- (c) Congestive Heart Failure
- (d) Hypertension

2. If a thiazide diuretic is administered for hypertension, the response seen within 24 hrs on excretion of different electrolytes is: (AIIMS Nov 2011)

	Sodium	Potassium	Calcium
(a)	↑	↑	↑
(b)	↑	↓	↑
(c)	↑	↑	↓
(d)	↑	↓	↑

3. Acetazolamide is: (AIIMS Nov 2011)

- (a) Competitive and reversible carbonic anhydrase inhibitor
- (b) Non-competitive and reversible carbonic anhydrase inhibitor
- (c) Competitive and irreversible carbonic anhydrase inhibitor
- (d) Non-competitive and irreversible carbonic anhydrase inhibitor

4. Thiazides can cause: (AIIMS Nov, 2009)

- (a) Hyperkalemic paralysis
- (b) Hypouricemia
- (c) Hypolipidemia
- (d) Impotence

5. Free water clearance is decreased by? (AIIMS May, 2008)

- (a) Vincristine
- (b) Vinblastine
- (c) Chlorpropamide
- (d) Furosemide

6. Which diuretic could be considered appropriate for combining with ACE inhibitors? (DPG 2009)

- (a) Spironolactone
- (b) Eplerenone
- (c) Hydrochlorothiazide
- (d) Amiloride

7. In patient of head injuries with rapidly increasing intracranial tension without haematoma, the drug of choice for initial management would be: (DPG 2009)

- (a) Furosemide
- (b) Steroids

- (c) 20% Mannitol
- (d) Glycine

8. Spironolactone is contraindicated with which of the following drugs? (DNB 2007, AI 2000)

- (a) Enalapril
- (b) Atenolol
- (c) Verapamil
- (d) Chlorthiazide

9. Thiazides diuretics causes all EXCEPT:

- (a) Hyperglycemia (AIIMS Nov, 2007)
- (b) Increased calcium excretion
- (c) Useful in congestive heart failure
- (d) Decreased uric acid excretion

10. Regarding furosemide true statement is:

- (a) Acute pulmonary edema is an indication
- (b) Acts on PCT (AIIMS Nov, 2007)
- (c) Mild diuresis
- (d) Given only by parenteral route

11. One of the following diuretics does not require its presence in the tubular lumen for its pharmacological effects: (AIIMS Nov, 2004, AIIMS May, 2003)

- (a) Thiazide diuretics
- (b) Loop diuretics
- (c) Carbonic anhydrase inhibitors
- (d) Aldosterone antagonists

12. Aldosterone antagonists are not useful in the treatment of: (AIIMS May, 2004)

- (a) Hypertension
- (b) Congestive heart failure
- (c) Gynaecomastia
- (d) Hirsutism

13. Carbonic anhydrase inhibitor should not be given in:

- (a) Sulfonamide hypersensitivity (PGI Dec. 2006)
- (b) Glaucoma
- (c) High altitude sickness
- (d) Metabolic acidosis
- (e) COPD

14. Potassium sparing diuretics include:

- (a) Spironolactone
- (b) Triamterene
- (c) Amiloride
- (d) Ethacrynic acid
- (e) Bumetanide

15. **Intravenous furosemide is used for rapid control of symptoms in acute left ventricular failure. It provides quick relief of dyspnoea by:**
- Producing bronchodilation
 - Causing rapid diuresis and reducing circulating blood volume
 - Causing venodilation
 - Stimulating left ventricular contractility
16. **Most potent loop diuretic is:**
- Furosemide
 - Bumetanide
 - Torsemide
 - Ethacrynic acid
17. **Both loop diuretics and thiazides can cause hypokalemia by:**
- Inhibiting proximal tubular K^+ reabsorption
 - Inhibiting $Na^+-K^+-2Cl^-$ cotransport in the ascending limb of loop of Henle
 - Increasing the availability of Na^+ in the distal tubular fluid to exchange with interstitial K^+
 - Potentiating the action of aldosterone
18. **Indomethacin can antagonize the diuretic action of loop diuretics by:**
- Preventing prostaglandin mediated intrarenal-hemodynamic actions
 - Blocking the action in ascending limb of loop of Henle
 - Enhancing salt and water reabsorption in distal tubules
 - Increasing aldosterone secretion
19. **Which of the following diuretics can result in metabolic acidosis?**
- Indapamide
 - Furosemide
 - Hydrochlorothiazide
 - Acetazolamide
20. **Long-term use of which diuretic agent can result in gynecomastia?**
- Amiloride
 - Spironolactone
 - Triamterene
 - Acetazolamide
21. **Amiloride can cause hyperkalemia due to its action on:**
- Electrogenic K^+ channels
 - Electrogenic Na^+ channels
 - Non electrogenic Na^+-Cl^- symporter
 - $H^+-K^+-ATPase$
22. **Amiloride differs from spironolactone in that:**
- It has greater natriuretic action
 - Its diuretic action is more in the presence of conditions with elevated aldosterone levels
 - It acts from the luminal membrane side of the distal tubular cells
 - It can cause hypokalemia on long term use
23. **All of the following statements about amiloride are true EXCEPT:**
- It antagonises the action of aldosterone
 - It is the drug of choice for the treatment of lithium induced diabetes insipidus
 - It decreases calcium loss in the urine
 - It is more potent than triamterene
24. **Which of the following is NOT associated with thiazide diuretics?**
- Hypercalciuria
 - Hyponatremia
 - Hypokalemia
 - Hyperuricemia
25. **Eplerenone is:**
- Aldosterone antagonist
 - Can cause hyperkalemia in predisposed patients
 - A diuretic
 - All of these
26. **A 50-year-old man has a history of frequent episodes of renal colic with high calcium renal stones. The most useful diuretic in the treatment of recurrent calcium stones is:**
- Furosemide
 - Spironolactone
 - Hydrochlorothiazide
 - Acetazolamide
27. **A 46-year-old male, Jorawar Singh presented to the emergency with muscle weakness and cramping. He has been taking hydrochlorothiazide for recently diagnosed hypertension. Which of the following is the most likely cause of his symptoms?**
- Hypocalcemia
 - Hyponatremia
 - Hypokalemia
 - Hypoglycemia
28. **Furosemide should not be administered with NSAIDs because latter:** (DPG 2007)
- Prevent platelet aggregation
 - Inhibit prostacyclin synthesis
 - Decrease sodium reabsorption
 - Increase the secretion of furosemide in urine
29. **All of the following diuretics inhibit $Na^+ - K^+ - 2Cl^-$ symporter, EXCEPT:** (DPG 2006)
- Furosemide
 - Thiazide
 - Ethacrynic acid
 - Mersalyl

30. Which of the following statements is not true about diuretics? (DPG 1997)
- Acetazolamide is a carbonic acid anhydrase stimulant
 - Thiazides act on cortical diluting segment of nephron
 - Furosemide is a high ceiling diuretic
 - Spironolactone is an aldosterone antagonist
31. Which of the following diuretics cause hypercalcemia and can be used in recurrent renal calcium stones? (UP 2007)
- Spironolactone
 - Furosemide
 - Chlorthiazide
 - Mannitol
32. Which one is a mineralocorticoid antagonist? (TN 2003)
- Thiazide
 - Cyproterone acetate
 - Furosemide
 - Spironolactone
33. In cirrhotic ascites, which diuretic is preferred? (RJ 2005)
- Furosemide
 - Acetazolamide
 - Spironolactone
 - Any of the above
34. Aldosterone action is on: (RJ 2006)
- Proximal tubule
 - Distal tubules
 - Loop of Henle
 - Collecting duct
35. Thiazide diuretic does not cause: (RJ 2006)
- Hyper calcaemia
 - Hypo magnesemia
 - Hyperkalemia
 - Hyperuricemia
36. Potassium sparing diuretics acts on: (RJ 2007)
- $\text{Na}^+ \text{K}^+$ pump
 - Aldosterone receptor
 - Carbonic anhydrase
 - $\text{Na}^+ \text{Cl}^-$ symporter
37. Drug causing deafness is: (MH 2000)
- Thiazide
 - Spiranolactone
 - Ethacrynic acid
 - Triamterene
38. Drug that can be used for producing alkalinization of urine is? (MH 2002) (MH 2005)
- Hydrochlorthiazide
 - Furosemide
 - Acetazolamide
 - Spironolactone
39. Which of the following is aldosterone antagonist? (MH 2007)
- Eplerenone
 - Deoxycorticosterone
 - Fenoldopam
 - Furosemide
40. In a patient on cisplatin therapy, which of the following diuretics would be preferred? (Bihar 2003)
- Mannitol
 - Acetazolamide
 - Thiazide
 - Furosemide
41. Triamterene causes: (Jharkhand 2005)
- Hypokalemia
 - Muscle cramps
 - Decrease in urea level
 - Better glucose tolerance
42. Acetazolamide side effects include all except: (AP 2002)
- Hypokalemia
 - Drowsiness
 - Diarrhea
 - Paraesthesia
43. Canrenone is a metabolite of: (AP 2004)
- Ampicillin
 - Spironolactone
 - Furosemide
 - Acetazolamide
44. Acetazolamide can be used in all except: (AP 2008)
- Epilepsy
 - Acute mountain sickness
 - Cirrhosis
 - Glaucoma
45. Furosemide causes all except: (Kolkata 2005)
- Hyperglycemia
 - Hypomagnesemia
 - Hypokalemia
 - Acidosis
46. Spironolactone is contraindicated with enalapril because it causes: (Kolkata 2007)
- Hyperkalemia
 - Hypercalcemia
 - Hypernatremia
 - Hypokalemia
47. Loop diuretics acts on: (Kolkata 2007)
- PCT
 - DCT
 - Thick ascending limb of loop of Henle
 - Collecting duct
48. Which of the following diuretics is contraindicated in the presence of cardiac failure? (Karnataka 2008)
- Mannitol
 - Spironolactone
 - Furosemide
 - Hydrochlorthiazide

49. Thiazide diuretics do not produce ONE of the adverse effects: (Karnataka 2007)

- (a) Hypoglycemia
- (b) Hyponatremia
- (c) Hypokalemia
- (d) Hyperuricemia

50. Loop diuretics such as furosemide act by: (Karnataka 2005)

- (a) Decreasing tubular reabsorption of Na^+ and increase GFR
- (b) Decreasing H^+ secretion with resultant increase in Na^+ and K^+ excretion
- (c) Inhibiting $\text{Na}^+-\text{K}^+-2\text{Cl}^-$ co transporter in the medullary thick ascending limb
- (d) Inhibiting Na^+-K^+ exchange in the collecting duct

51. Side effects of thiazides may include: (Karnataka 2002)

- (a) Hypokalemia
- (b) Hyperuricemia
- (c) Hyperglycemia
- (d) All of above

52. Furosemide is useful in: (Karnataka 2001)

- (a) Hypertension
- (b) Refractory oedema
- (c) Hypocalcemia
- (d) Hypokalemia

■ ANTIDIURETICS

53. Vasopressin antagonist acts on: (AIIMS May, 2013)

- (a) Proximal convoluted tubule
- (b) Distal convoluted tubule
- (c) Cortical collecting tubule
- (d) Medullary collecting duct

54. Drug of choice for central diabetes insipidus is: (AI 2011)

- (a) Desmopressin
- (b) Leuprolide
- (c) Thiazide diuretics
- (d) Insulin

55. Which is wrongly matched in vasopressin? (AIIMS Nov, 2010)

- (a) V_1 : Vascular Smooth Muscle
- (b) V_2 : Distal Nephron
- (c) V_3 : Anterior Pituitary
- (d) V_4 : Central Nervous System

56. Drug used in mild hemophilia is: (DPG 2002)

- (a) Corticosteroids
- (b) DDAVP
- (c) Vitamin K
- (d) Tranexamic acid

57. All of the following drugs can be used for diabetes insipidus, except: (TN 2002)

- (a) Amiloride
- (b) Furosemide

(c) Chlorpropamide

(d) Carbamazepine

58. Drug causing gynecomastia is: (AI 2000)

- (a) Spironolactone
- (b) Rifampicin
- (c) Penicillin
- (d) Bumetanide

59. Which of the following is the drug of choice for the treatment of Syndrome of Inappropriate Antidiuretic Hormone secretion? (AIIMS May, 2005)

- (a) Demeclocycline
- (b) Vasopressin
- (c) Thiazide diuretics
- (d) Chlorpropamide

60. Selective V_2 receptor agonist useful for the treatment of central diabetes insipidus is:

- (a) Arginine vasopressin
- (b) Desmopressin
- (c) Lypressin
- (d) Terlipressin

61. Vasopressin decreases the volume of urine primarily by causing:

- (a) Decrease in glomerular filtration rate
- (b) Decrease in renal blood flow
- (c) Decrease in water permeability of descending limb of loop of Henle
- (d) Increase in water permeability of collecting duct cells

62. All of the following indications of vasopressin are based on stimulation of V_2 receptors EXCEPT:

- (a) Central diabetes insipidus
- (b) Bed wetting in children
- (c) von-Willebrand's disease
- (d) Esophageal varices

63. Desmopressin can be used for all of the following conditions EXCEPT:

- (a) Neurogenic diabetes insipidus
- (b) Nephrogenic diabetes insipidus
- (c) Bed wetting in children
- (d) Bleeding due to hemophilia

64. Desmopressin is a synthetic analog of ADH. It is preferred over arginine vasopressin in the treatment of diabetes insipidus for all of the following reasons EXCEPT:

- (a) It is a more potent antidiuretic
- (b) It is a selective vasopressin V_1 receptor agonist
- (c) It has a little vasoconstrictor activity
- (d) It is longer acting

65. Which of the following agents is useful for the oral treatment of both pituitary as well as renal diabetes insipidus?

- (a) Vasopressin
- (b) Hydrochlorthiazide
- (c) Chlorpropamide
- (d) Carbamazepine

66. Advantage of desmopressin over vasopressin in the treatment of diabetes insipidus is that desmopressin:
- Causes less formation of factor VIII
 - Causes less hypernatremia
 - Is more selective for V_2 receptor subtype
 - Provides greater relief of excessive thirst the patient is experiencing
67. A 30-year-old male, Rajinder presents to OPD your office with fatigue, muscle weakness and headache. His blood pressure is 170/120 mmHg and his heart rate is 100/min. Laboratory evaluation reveals hypokalemia, metabolic alkalosis and decreased plasma renin activity. On CT scan, a mass was noted on left suprarenal gland. Patient was prescribed a drug for few weeks and the symptoms subsided. Laboratory values and blood pressure returned to normal values. The likely drug given to this patient is?
- Clonidine
 - Propanolol
 - Hydrochlorothiazide
 - Spironolactone
68. Drug not used in SIADH is:
- Demeclocycline
 - Desmopressin
 - Restriction of free water intake
 - 3% NaCl
69. Which of the following agents will not cause rise in K^+ levels in chronic renal failure? (Kolkata 2007)
- Furosemide
 - Beta blockers
 - ACE inhibitors
 - Losartan
- (b) More selective for V_1 receptor
(c) Has little vasoconstrictor activity
(d) Longer acting
5. Side effect of thiazide diuretics are all except?
- Hyponatremia
 - Hypokalemia
 - Erectile dysfunction
 - Hypocalcemia
6. Site of action of anti diuretic hormone is:
- Loop of Henle
 - Proximal tubule
 - Distal tubule
 - Cortical collecting duct
7. Drug of choice for neurogenic diabetes insipidus is?
- Vasopressin
 - Terlipressin
 - Desmopressin
 - Pralipressin
8. True regarding acetazolamide is:
- Irreversible inhibitor of carbonic anhydrase
 - Structural resemblance to sulfonamides
 - It decreases potassium excretion
 - It cause metabolic alkalosis
9. All of the following adverse effects can be caused by loop diuretics except:
- Hypercalcemia
 - Hyperglycemia
 - Hypomagnesemia
 - Hyperuricemia
10. Treatment of choice for SIADH is?
- Lithium carbonate
 - Demeclocycline
 - Vasopressin
 - Hypertonic Saline
11. Side effects of thiazides may include
- Hypokalemia
 - Hyperuricemia
 - Hyperglycemia
 - All of the above
12. All of the following diuretics cause increase in K^+ excretion except:
- Ethacrynic acid
 - Acetazolamide
 - Furosemide
 - Triamterene
13. High ceiling diuretics are useful in the treatment of all of the following conditions except:
- Generalized edema
 - Cerebral edema
 - Acute pulmonary edema
 - Pulmonary hypertension
1. True regarding conivaptan is:
- Vasopressin antagonist
 - V_2 selective action
 - Given orally
 - Used in the treatment of hypernatremia
2. In diabetes insipidus, diuretic showing paradoxical antidiuretic activity is:
- Thiazide
 - Triamterene
 - Spironolactone
 - Furosemide
3. Thiazide can cause:
- Metabolic alkalosis
 - Metabolic acidosis
 - Respiratory alkalosis
 - Respiratory acidosis
4. Desmopressin is preferred over vasopressin because desmopressin has all the properties except -
- More potent

RECENT QUESTIONS ASKED BY NATIONAL BOARD

14. Which one of the following is not a clinical use of spironolactone?
- (a) Pulmonary edema
 - (b) Hypertension
 - (c) Congestive heart failure
 - (d) To counteract hypokalemia due to thiazide diuretics
15. All of the following are potassium sparing diuretics except:
- (a) Triamterene
 - (b) Spironolactone
 - (c) Amiloride
 - (d) Indapamide
16. Site of action of ADH is:
- (a) PCT
 - (b) DCT
 - (c) Collecting tubule
 - (d) Ascending loop
17. K^+ sparing diuretic is:
- (a) Furosemide
 - (b) Spironolactone
 - (c) Thiazide
 - (d) None
18. Hypercalcemia is caused by which drug:
- (a) Bumetanide
 - (b) Spironolactone
 - (c) Thiazide
 - (d) Furosemide
19. Furosemide acts at:
- (a) PCT
 - (b) DCT
 - (c) Ascending limb of loop of Henle
 - (d) Descending limb of loop of Henle
20. Diuretics that can be used in renal failure is:
- (a) Furosemide
 - (b) Chlorthiazide
 - (c) Mannitol
 - (d) Chlorthalidone
21. Thiazides act on:
- (a) PCT
 - (b) DCT
 - (c) Glomerulus
 - (d) Ascending limb of loop of Henle

EXPLANATIONS

1. Ans. (b) Hyperlipidemia (Ref: KK Sharma 2/e p230-231)

Thiazides cause hyperlipidemia as adverse effect and thus cannot be used to treat this condition.

Indications of thiazides:

Diuretic Uses	Non-diuretic Uses
Hypertension (First line drugs)	Diabetes insipidus
Congestive heart failure	Idiopathic hypercalciurea with Nephrocalcinosis

2. Ans. $\uparrow \text{Na}^+ \uparrow \text{K}^+ \downarrow \text{Ca}^{++}$ (Ref: Goodman and Gilman 12/e p678)

The following table taken from Goodman and Gilman clearly explains the answer:

Excretory and Renal Hemodynamic Effects of Diuretics

	Na^+	K^+	H^+	Ca^{2+}	Mg^{2+}	Cl^-	HCO_3^-
Carbonic anhydrase inhibitors	$\uparrow$	$\uparrow\uparrow$	$\downarrow$	NC	V	$\uparrow$	$\uparrow\uparrow$
Osmotic diuretics	$\uparrow\uparrow$	$\uparrow$	I	$\uparrow$	$\uparrow\uparrow$	$\uparrow$	$\uparrow$
Loop Diuretics	$\uparrow\uparrow$	$\uparrow\uparrow$	$\uparrow$	$\uparrow\uparrow$	$\uparrow\uparrow$	$\uparrow\uparrow$	$\uparrow$
Thiazides	$\uparrow$	$\uparrow\uparrow$	$\uparrow$	$\downarrow$	$\uparrow$	$\uparrow$	$\uparrow$
Epithelial sodium channels blockers	$\uparrow$	$\downarrow$	$\downarrow$	$\downarrow$	$\downarrow$	$\uparrow$	$\uparrow$
Aldosterone antagonists	$\uparrow$	$\downarrow$	$\downarrow$	I	$\downarrow$	$\uparrow$	$\uparrow$

$\uparrow$: Increase, $\downarrow$: Decrease, NC: No change, V: Variable change, I: Insufficient data

Do not get confused by the term 'within 24 hours' in the question. These are the acute effects of diuretics and these may be modified later on by the compensatory responses of the body.

3. Ans. (b) Non-competitive and reversible carbonic anhydrase inhibitor (Ref: KDT 7/e p586)

Carbonic anhydrase inhibitors act by non-competitive but reversible inhibition of the enzyme. Examples include acetazolamide, dorzolamide and brinzolamide.

4. Ans. (d) Impotence (Ref: Katzung 11/e p261; KDT 6/e p566-567)

Antihypertensive agents like thiazides and β -blockers can cause impotence. It is maximum with thiazides among anti-hypertensive drugs and is thought to be due to volume depletion.

5. Ans. (d) Furosemide (Ref: KDT 6/e p562)

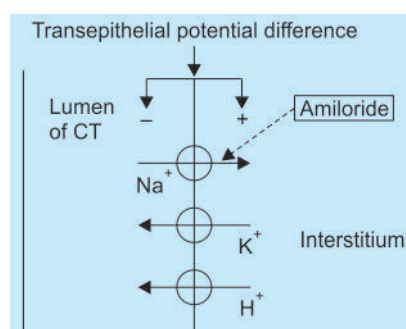
- The volume of water in urine, excreted per unit time in excess of that required to excrete the contained solutes isoosmotically with plasma is called free water clearance.
- Free water clearance is positive for dilute urine, negative when concentrated urine is passed and zero when isotonic urine is passed.
- To understand the effect of different diuretics on free water clearance one should know the following facts:
 - The nephron of the kidney is arranged in such a way that some portion of it lies in the cortex and some portion of it lies in the **medulla**.

Parts of nephron in the cortex	Parts of nephron in the medulla
Proximal convoluted tubule	Descending thin limb of Henle's loop
Distal convoluted tubule	Ascending thin limb of Henle's loop
Thick ascending limb of Henle's loop	Medullary collecting duct
Cortical collecting duct	

- The cortical portion of the nephron are responsible for diluting the urine (i.e., positive free water clearance).

- The medullary portions of the nephron are responsible for concentrating the urine (i.e., negative free water clearance).
 - Thus, the diuretics which act on both medulla and cortex can affect both the positive and negative free water clearance whereas diuretics, which act on either cortex or medulla can affect either the negative or the positive free water clearance.
 - Furosemide is a drug which act on **both cortex and medulla**. It acts on the **ascending limb of loop of Henle** which has both **cortical and medullary components**. Thus, furosemide can block positive as well as negative free water clearance.
 - *Vincristine increases the secretion of the hormone ADH and thus blocks free water clearance.*
 - *Chlorpropamide sensitizes the kidney to ADH action.* Thus it may **impair the free water clearance** and in some patients may result in hyponatremia and water intoxication.
 - Most probably the question should have been framed as
 - "All of the following blocks free water clearance, except"
 - But if you have to choose one answer, go for **Furosemide** as it will always block free water clearance whereas other drugs will cause them occasionally as it is their adverse effect.
6. **Ans (c) Hydrochlorthiazide** (Ref: *Katzung 10/e p571; KDT 6/e p484*)
- ACE inhibitors are contra-indicated in the presence of hyperkalemia. Aldosterone antagonists (like spironolactone and eplerenone) and epithelial sodium channel blockers (like amiloride and triamterene) are potassium sparing diuretics and should not be combined with ACE inhibitors. Thiazides on the other hand cause hypokalemia and can be combined with ACE inhibitors.
7. **Ans. (c) 20% mannitol** (Ref: *Katzung 10/e p248; KDT 6/e p572*)
- Mannitol is an osmotic diuretic indicated for cerebral edema and glaucoma. It is contra-indicated in active bleeding in the brain.
8. **Ans. (a) Enalapril** (Ref: *KDT 6/e p571*)
- Spironolactone is a K⁺ sparing diuretic. It should be used cautiously if the patient is receiving K⁺ salts or drugs increasing serum K⁺ levels.
 - ACE inhibitors can also cause hyperkalemia as an adverse effect. If these are combined with K⁺ sparing diuretics, cardiac arrhythmia due to high serum K⁺ levels may develop.
9. **Ans. (b) Increased calcium excretion** (Ref: *Katzung 10/e p245, 246*)
- Loop diuretics cause hypocalcemia by more excretion whereas thiazides cause hypercalcemia by decreasing its excretion.
10. **Ans. (a) Acute pulmonary edema is an indication** (Ref: *Katzung 10/e p250*)
- Furosemide possesses vasodilatory action which is responsible for quick relief in LVF and pulmonary edema (used i.v.). It can be used orally as well as parenterally.
11. **Ans. (d) Aldosterone antagonists** (Ref: *KDT 6/e p569*)
- Most of the diuretics act from the luminal side of membrane in the nephron.
 - Thiazides, loop diuretics, carbonic anhydrase inhibitors and epithelial Na⁺ channel blockers (e.g. amiloride and triamterene) are secreted in the proximal tubules through organic anion/cation transport process.
 - Osmotic diuretics reach the lumen of proximal tubules via glomerular filtration.
 - Aldosterone antagonists like spironolactone do not act through luminal side rather they act from basolateral side of the membrane. Therefore, these agents do not require access to the tubular lumen.
12. **Ans. (c) Gynaecomastia** (Ref: *KDT 6/e p570, 571*)
- Aldosterone antagonists cause gynaecomastia as an adverse effect.
13. **Ans. (a) Sulfonamide hypersensitivity; (d) Metabolic acidosis; (e) COPD** (Ref: *KDT 6/e p569, Goodman Gilman's 11/e p746*)
- Carbonic anhydrase inhibitors (CAIs) are more likely to produce acidosis in patients of COPD, CRF and DM. They are contraindicated in COPD as they may precipitate respiratory acidosis.
 - They are sulfonamides in structure, so should not be given in hypersensitive persons.
14. **Ans. (a) Spironolactone; (b) Triamterene; (c) Amiloride** (Ref: *KDT 6/e p569, 571, 572*)
15. **Ans. (c) Causing venodilation** (Ref: *KDT 6/e p563*)
- Furosemide is a high ceiling diuretic.
 - Its major mode of benefit in acute pulmonary edema is vasodilation. Due to its vasodilatory action, it shifts the fluid from pulmonary to systemic circulation. This results in the rapid relief of symptoms.
 - Diuretic action develops later.

16. **Ans. (b) Bumetanide** (Ref: KDT 6/e p563)
- Bumetanide is most potent and furosemide is longest acting loop diuretic.
17. **Ans. (c) Increasing the availability of Na^+ in the distal tubular fluid to exchange with interstitial K^+** (Ref: KDT 6/e p562, 564)
- Diuretics prevent the reabsorption of Na^+ in various parts of tubules. Due to decreased reabsorption, more amount of Na^+ reaches the distal portion of the nephron i.e. late DT and collecting ducts. Here, Na^+ is exchanged with K^+ and H^+ . Increased distal delivery of Na^+ results in more exchange and thus hypokalemia.
18. **Ans. (a) Preventing prostaglandin mediated intrarenal hemodynamic actions** (Ref: KDT 6/e p568)
19. **Ans. (d) Acetazolamide** (Ref: KDT 6/e p569)
20. **Ans. (b) Spironolactone** (Ref: KDT 6/e p571)
21. **Ans. (b) Electrogenic Na^+ channels** (Ref: KDT 6/e p571)
- Amiloride and triamterene are K^+ sparing diuretics that act by inhibiting epithelial Na^+ channels.
 - In the distal tubules and collecting ducts, three separate channels are present (one for Na^+ , K^+ and H^+ each). Aldosterone acts on DCT and CD to cause reabsorption of Na^+ . This generates a lumen negative potential difference across the membrane of this part of the nephron. To maintain the electric neutrality, K^+ and H^+ are secreted in the lumen.



- When amiloride and triamterene inhibits epithelial Na^+ channels, transepithelial potential difference is not generated and therefore K^+ and H^+ are not secreted in the lumen. Thus due to more retention of K^+ , amiloride may result in hyperkalemia.
22. **Ans. (c) It acts from luminal membrane side of the distal tubular cells** (Ref: KDT 6/e p571)
- Amiloride is a K^+ sparing diuretic and like other diuretics, act from luminal membrane side. On the other hand, spironolactone does not require access to tubular lumen for action.
 - Diuretic action of both amiloride and spironolactone is quite feeble.
 - Due to its aldosterone receptor blocking action, spironolactone is more effective in the presence of conditions with elevated levels of aldosterone (like CHF).
 - Both of these diuretics can cause hyperkalemia when used with K^+ supplements or ACE inhibitors.
23. **Ans. (a) It antagonises the action of aldosterone** (Ref: KDT 6/e p571)
- Amiloride acts by blocking epithelial Na^+ channels. It has no effect on aldosterone receptors.
 - It is more potent than triamterene.
 - It decreases Ca^{2+} loss in the urine
 - It is the drug of choice for lithium induced DI.
24. **Ans. (a) Hypercalciurea** (Ref: KDT 6/e p567)
- Thiazides cause hypercalcemia by decreasing its excretion (hypocalciurea) whereas loop diuretics cause hypocalcemia by increasing its excretion. [remember LOOP LOOSES CALCIUM].
25. **Ans. (d) All of the these** (Ref: KDT 6/e p506, 571)
- Eplerenone is an aldosterone antagonist (like spironolactone). It is used as potassium sparing diuretic and can cause hyperkalemia in susceptible individuals particularly in the patients on ACE inhibitors.
26. **Ans. (c) Hydrochlorothiazide** (Ref: KDT 6/e p566)
- Thiazides cause hypercalcemia by decreasing the renal excretion of Ca^{2+} . These are useful in a patient having hypercalciurea. In such a patient, thiazides decrease the excretion of Ca^{2+} in the kidney and thus reduces the chances of stone formation.

27. **Ans. (c) Hypokalemia** (Ref: KK Sharma 2/e p231)
A decrease in the intravascular fluid volume stimulates aldosterone secretion and leads to increased excretion of potassium and hydrogen ions in the urine. This results in hypokalemic metabolic alkalosis, which is a common side effect of most diuretics other than the potassium-sparing class. Hypokalemia manifests with muscle weakness and cramping.
28. **Ans. (b) Inhibit prostacyclin synthesis** (Ref: Goodman & Gilman 11/e p753)
29. **Ans. (b) Thiazide** (Ref: KDT 6/e p564)
 - Thiazide diuretics inhibit $\text{Na}^+\text{-Cl}^-$ symport at the luminal membrane of DCT.
 - All other options are loop diuretics.
30. **Ans. (a) Acetazolamide is a carbonic anhydrase stimulant** (Ref: KDT 6/e p568, 569)
 - Acetazolamide is an inhibitor of the enzyme carbonic anhydrase.
31. **Ans. (c) Chlorthiazide** (Ref: KDT 6/e p564)
32. **Ans. (d) Spironolactone** (Ref: KDT 6/e p569)
33. **Ans. (c) Spironolactone** (Ref: KDT 6/e p570)
34. **Ans. (d) Collecting duct** (Ref: KDT 6/e p569)
35. **Ans. (c) Hyperkalemia** (Ref: KDT 6/e p566-567)
36. **Ans. (b) Aldosterone receptor** (Ref: KDT 6/e p569)
37. **Ans. (c) Ethacrynic acid** (Ref: Katzung 11/e p259)
38. **Ans. (c) Acetazolamide** (Ref: KDT 6/e p569)
39. **Ans. (a) Eplerenone** (Ref: KDT 6/e p571)
40. **Ans. (a) Mannitol** (Ref: KDT 6/e p572)
41. **Ans. (b) Muscle cramps** (Ref: KDT 6/e p571)
42. **Ans. (c) Diarrhea** (Ref: KDT 6/e p569)
43. **Ans. (b) Spironolactone** (Ref: KDT 6/e p570)
44. **Ans. (c) Cirrhosis** (Ref: KDT 6/e p569)
45. **Ans. (d) Acidosis** (Ref: KDT 6/e p567-568)
46. **Ans. (a) Hyperkalemia** (Ref: KDT 6/e p571)
47. **Ans. (c) Thick ascending limb of loop of Henle** (Ref: KDT, 6/e p562)
48. **Ans. (a) Mannitol** (Ref: KDT 6/e p573)
49. **Ans. (a) Hypoglycemia** (Ref: KDT 6/e p566-567)
50. **Ans. (c) Inhibiting $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter in the medullary thick ascending limb** (Ref: Katzung 11/e p258)
51. **Ans. (d) All of above** (Ref: KDT 6/e p566-67)
52. **Ans. (b) Refractory oedema** (Ref: KDT 6/e p563)
53. **Ans. (d) Medullary collecting duct** (Ref: Goodman and Gilman 12/e p707)
Vasopressin receptors (V2) are present on principal cells of inner medullary collecting tubule. The antagonist like Conivaptan and Tolvaptan may be used in conditions like SIADH and CHF.
54. **Ans. (a) Desmopressin** (Ref: CMDT 2010/996)
 - **Desmopressin is treatment of choice for central diabetes insipidus.**
 - It acts selectively at V2 receptors to increase urine concentration and decrease urine flow in a dose-dependent manner.
 - It is also more resistant to degradation than AVP and has a three- to fourfold longer duration of action.
 - Desmopressin can be given by IV or SC injection, nasal inhalation, or oral tablet.

55. **Ans (d) V_4 : Central Nervous System** (Ref: Ganong, 21/e p246-47)

There are at least three kinds of vasopressin receptors: V_{1A} (also called V_1), V_{1B} (known as V_3), and V_2 .

- V_1 receptors are involved in causing vasoconstriction
- V_2 receptors are present in distal nephron and decrease the urine outflow.
- The V_{1B} receptors (also called V_3 receptors) appear to be unique to the anterior pituitary, where they mediate increased ACTH secretion from the corticotropes.

56. **Ans. (b) DDAVP** (Ref: KDT 6/e p577)

- DDAVP is an analogue of ADH. It acts on V_2 receptors to cause increased release of factor VIII and vWF from the endothelium. Due to this property, it can be used for the treatment of mild hemophilia.

57. **Ans. (b) Furosemide** (Ref: KDT 6/e p578)

58. **Ans. (a) Spironolactone** (Ref: KDT 6/e p571)

Important drugs causing gynaecomastia are:

- D - Digitalis
- I - Isoniazid
- S - Spironolactone
- C - Cimetidine (and Ketoconazole)
- O - Oestrogens (and anti-testosterones)

59. **Ans. (a) Demeclocycline** (Ref: Katzung 10/e p249)

SIADH is due to excessive secretion of anti-diuretic hormone. It is diametrically opposite disease to diabetes insipidus. Vasopressin, thiazides and chlorpropamide are used for the treatment of diabetes insipidus whereas demeclocycline is used for SIADH management. Now-a-days, vasopressin receptor antagonists like tolvaptan and conivaptan are preferred for SIADH.

60. **Ans. (b) Desmopressin** (Ref: KDT 6/e p576, 577)

61. **Ans. (d) Increase in water permeability of collecting duct cells** (Ref: KDT 6/e p575)

In the absence of ADH, collecting ducts are impermeable to water. ADH increases the exocytosis and decreases the endocytosis of water channels (aquaporins) in the collecting duct cells. This results in increase in permeability of collecting ducts to water.

62. **Ans. (d) Esophageal varices** (Ref: KDT 6/e p577)

Vasoconstriction is caused by V_1 receptors whereas anti-diuresis and release of vWF from endothelium is mediated by V_2 receptors of vasopressin.

63. **Ans. (b) Nephrogenic diabetes insipidus** (Ref: KDT 6/e p577)

- Desmopressin is the agent of choice for central diabetes insipidus. It has no role in nephrogenic DI (because ADH is already present in this condition).
- Pituitary DI and that due to head trauma are examples of central DI.
- Li induced DI is nephrogenic. Drug of choice for this condition is amiloride.

64. **Ans. (b) It is a selective V_1 receptor agonist** (Ref: KDT 6/e p576)

Vasopressin can act on V_1 and V_2 receptors whereas desmopressin is a selective V_2 receptor agonist.

65. **Ans. (b) Hydrochlorothiazide** (Ref: KDT 6/e p577, 578)

- Thiazides are useful in the treatment of central as well as nephrogenic DI.
- Vasopressin, chlorpropamide and carbamazepine are useful only in central DI.

66. **Ans. (c) Is more selective for V_2 receptor subtype** (Ref: KDT 6/e p576)

67. **Ans (d) Spironolactone** (Ref: KK Sharma 2/e p233)

Mostly likely diagnosis in this patient is aldosterone secreting tumor (adenoma) leading to primary hyperaldosteronism

(Conn's Syndrome). Aldosterone excess will cause hypertension, hypokalemia, metabolic alkalosis and depressed renin. Aldosterone antagonists such as spironolactone or eplerenone can be used as medical therapy for Conn's syndrome.

68. Ans. (b) **Desmopressin** (Ref: CMDT-2010/792)

Desmopressin is ADH and will exacerbates the symptoms of SIADH. Hypertonic saline (3%NaCl) is used for severely symptomatic patients with hyponatremia. Demeclocycline decreases the release of ADH.

69. Ans. (a) **Furosemide** (Ref: KDT, 6/e p566)

ANSWERS OF RECENT QUESTIONS ASKED BY NATIONAL BOARD

1. Ans (a) **Vasopressin antagonist** (Ref. CMDT 7th/866)
2. Ans (a) **Thiazide** (Ref. KDT 7th/598)
3. Ans (a) **Metabolic alkalosis** (Ref. KDT 7th/585)
4. Ans (b) **More selective for V_1 receptor** (Ref. KDT 7th/596)
5. Ans (d) **Hypocalcemia** (Ref. KDT 7th/585)
6. Ans. (d) **Cortical collecting duct** (Ref: KDT 7/e p594)
7. Ans. (c) **Desmopressin** (Ref: KDT 7/e p 597)
8. Ans. (b) **Structural resemblance to sulfonamides** (Ref: KDT 7/e p586-87)
 - Acetazolamide is non-competitive but reversible inhibitor of carbonic anhydrase
 - It is a sulfonamide derivative
 - It causes hypokalemia and metabolic acidosis.
9. Ans. (a) **Hypercalcemia** (Ref: KDT 7/e p584-585)
10. Ans. (d) **Hypertonic saline** (Ref: CMDT 2014/842)
11. Ans. (d) **All of the above** (Ref: KDT 7/e p584-585)
12. Ans. (d) **Triamterene** (Ref: KDT 7/e p589)
13. Ans. (d) **Pulmonary hypertension** (Ref: KDT 7/e p582)
14. Ans. (a) **Pulmonary edema** (Ref: KDT 7/e p588-589)
15. Ans. (d) **Indapamide** (Ref: KDT 7/e p579)
16. Ans. (c) **Collecting tubule** (Ref: KDT 7/e p594)
17. Ans. (b) **Spironolactone** (Ref: KDT 7/e p579)
18. Ans. (c) **Thiazide** (Ref: KDT 7/e p584)
19. Ans. (c) **Ascending limb of loop of Henle** (Ref: KDT 7/e p579)
20. Ans. (a) **Furosemide** (Ref: KDT 7/e p581)
21. Ans. (b) **DCT** (Ref: KDT 7/e p582)

Hormones are the substances which are produced by specific cells in the body and act away from their site of production. These are produced by endocrine glands.

Endocrine gland	Part	Hormones released	Controlling hormones
Pituitary	Anterior Lobe	Growth Hormone (GH) Corticotrophin (ACTH) Thyrotropin (TSH) Gonadotropin (FSH/LH) Prolactin	GHRH and Somatostatin CRH TRH GnRH (FSHRH/LHRH) PRIH (same as dopamine)
	Intermediate Lobe	Melanocyte Stimulating Hormone (MSH)	
	Posterior Lobe	Oxytocin Vasopressin (ADH)	
Thyroid	Follicular Cells Parafollicular Cells	T ₃ , T ₄ Calcitonin	
Parathyroid		Parathyroid Hormone (PTH)	
Pancreas	α Cells β Cells δ Cells	Glucagon Insulin Somatostatin	
Adrenal	Cortex	Glucocorticoids Mineralocorticoids Sex Corticoids	
	Medulla	Adrenaline (Epinephrine) Nor-adrenaline (Nor-epinephrine)	
Gonads	Testes Ovary	Androgens (Testosterone and Dihydrotestosterone) Estrogens Progestins	

MECHANISM OF ACTION OF HORMONES

NUCLEAR RECEPTORS		T ₃ , T ₄ , Estrogen, Progesterone, Testosterone
CYTOPLASMIC RECEPTORS		Glucocorticoids Mineralocorticoids
MEMBRANE RECEPTORS		
1. Tyrosine Kinase		Insulin Growth Hormone Prolactin
2. GPCRs	a) IP ₃ /DAG/Ca ²⁺	Vasopressin (V ₁ receptors) Oxytocin Gonadotropin Releasing Hormone Thyrotropin Releasing Hormone
	b) K ⁺ Channel Opening	Somatostatin
	c) Decrease cAMP	Prolactin Inhibiting Hormone (Dopamine)
	d) Increase cAMP	Rest all hormones including V ₂ receptors of vasopressin

GH controls growth of almost all organs of the body except brain and eye.

HYPOTHALAMUS AND ANTERIOR PITUITARY HORMONES

Anterior lobe of pituitary secretes several hormones; each of which is under the control of hypothalamus (increases release of all hormones except prolactin).

Growth Hormone (GH) and Growth Hormone Releasing Hormone (GHRH)

GH controls growth of almost all organs of the body except brain and eye. It acts by elaboration of somatomedins, which are also known as insulin like growth factors (IGF-1 and IGF-2). Apart from causing growth, this hormone also increases blood glucose.

- Hypothalamus secretes GHRH (increases GH release) and somatostatin (inhibits GH release).
- Dopamine increases GH release in normal subjects but decreases it in acromegalics. Best response with dopamine agonists is seen in patients secreting both GH and prolactin.
- Excess of GH causes acromegaly and its deficiency results in dwarfism.
- Recombinant growth hormones (**somatrem and somatropin**) are approved for
 - Pituitary dwarfism
 - AIDS related wasting.
 - Patients with short bowel syndrome who are dependent on total parenteral nutrition.

Fundoscopy examination of children is recommended at initiation of therapy and at periodic intervals thereafter (because, rarely GH therapy is associated with intracranial hypertension with papilledema, visual changes, headache and vomiting).

- Sermorelin and hexarelin** are recombinant GHRH analogs that are used for pituitary dwarfism.
- Mecasermin** is a complex of recombinant human IGF-1 (Insulin-like Growth Factor - 1) and IGF-binding protein-3. It is indicated for growth failure due to deficiency of IGF-1 that is not responsive to GH. It is administered subcutaneously. IGF-binding protein-3 is needed to maintain adequate half-life of IGF-1. Most important adverse effect of mecasermin is hypoglycemia
- Pegvisomant** is a **GH receptor antagonist** indicated for the treatment of acromegaly.

PEG	VI	SOM	ANT
↓	↓	↓	↓
Polyethylene glycol; Reduces the clearance	Visual field defects (Adverse effect)	Somatropin (Growth Hormone)	Antagonist

Somatostatin

It is secreted by hypothalamus, GIT as well as by δ -cells of pancreas. It inhibits the secretion of GH, TSH, prolactin, insulin, glucagon, gastrin, and HCl.

- It is indicated for the management of acromegaly, islet cell tumors, bleeding due to esophageal varices and secretory diarrhea but has the disadvantage of short duration of action.
- Octreotide** is a somatostatin analogue having high potency and long duration of action. It is preferred over somatostatin for all the indications.
- Octreotide also inhibits TSH secretion and is the *treatment of choice* for TSH-secreting adenoma in patients who are not the candidates of surgery.
- Lanreotide is another somatostatin analog that can be given i.m. in slow release formulation
- Vapreotide, pasireotide and seglitide** are other somatostatin analogs.

Mecasermin is a complex of recombinant human IGF-1 (Insulin-like Growth Factor- 1) and IGF-binding protein-3. It is indicated for growth failure due to deficiency of IGF-1 that is not responsive to GH.



Indications of Somatostatin

Secretory diarrhea
 Oesophageal varices
Malignancy [Islet cell tumors]
 Acromegaly
 TSH-Secreting adenoma
 Overdose of Sulfonylureas
SOMATOSTatin



Pasireotide is a new somatostatin analog approved for treatment of Cushing's disease.

Prolactin

It causes growth and development of breast during pregnancy and induces milk secretion after delivery. It inhibits hypothalamic pituitary-gonadal axis and its excess is responsible for amenorrhea (lactational), inhibition of ovulation and infertility. Excess of this hormone can also cause galactorrhoea in female and infertility in males. Hypothalamus secretes **prolactin release inhibitory hormone (same as dopamine)**. Thus, dopamine agonists like bromocriptine possess inhibitory actions on prolactin and D₂ blockers like antipsychotics and metoclopramide can cause hyperprolactinemia.

- **Bromocriptine** is a dopamine agonist useful in the *treatment of hyperprolactinemia* (amenorrhoea in females, impotence and sterility in males). Although less effective than octreotide, it can also be used in the treatment of *acromegaly*. Other uses of bromocriptine include *Parkinsonism* and *suppression of lactation*. Recently, it has been **approved for treatment of type 2 diabetes mellitus**.
- Nausea, vomiting and postural hypotension are marked at the initiation of therapy with bromocriptine whereas on prolonged use it can result in behavioral alterations, hallucinations and abnormal movements.
- **Cabergoline** is a **longest acting** dopamine agonist (ergot derivative) that is better tolerated than bromocriptine.
- **Quinagolide** is a non-ergot dopamine agonist having less adverse effects.



Uses of dopamine agonists e.g. bromocriptine

Diabetes mellitus type 2
(Bromocriptine)
Oversecretion of prolactin
Parkinsonism
Acromegaly
Milk secretion **INH**ibition
[suppression of lactation]
DOPAMINE

PHARMACOTHERAPY OF ACROMEGALY

Dopamine agonists e.g. cabergoline	Somatostatin analogs e.g. octreotide, lanreotide	GH-receptor antagonist e.g. pegvisomant	Tamoxifen (Ref. CMDT 2015 Pg 1090)
– Effective orally – Usually started first – More successful for tumors secreting both GH and prolactin – Safe during pregnancy	– Given by s.c. route – Injected once monthly – Safe during pregnancy – Expensive	– Given s.c. – Safe during pregnancy – Cause hepatitis, edema, flu like syndrome and hypertension – Aggravates hypoglycaemia – Extremely expensive	– Is SERM – do not decrease GH levels but reduces IGF-I levels – Used for persistent acromegaly in men and women who had breast cancer.

Gonadotropins and Gonadotropin Releasing Hormone (GnRH)

Follicle stimulating hormone (FSH) and luteinising hormone (LH) are the gonadotropins secreted by anterior lobe of pituitary gland. FSH is involved in spermatogenesis and the secretion of estrogen whereas LH stimulates progesterone and testosterone secretion. *Mid cycle LH surge is responsible for ovulation*. Secretion of these hormones is controlled by GnRH that is secreted from the hypothalamus in a pulsatile manner.

- Deficiency of gonadotropins can lead to anovulatory infertility in females and oligozoospermia and infertility in males (hypogonadotropic hypogonadism). Excessive secretion of these hormones is associated with precocious puberty, endometriosis, prostatic carcinoma, fibroids and polycystic ovarian disease (PCOD).
- Synthetic GnRH (**gonadorelin**) is used to *differentiate between pituitary and hypothalamic defect in patients with hypogonadotropic hypogonadism*. If LH levels increase (> 10 mIU/ml) after administration of GnRH, it indicates that pituitary is normal.

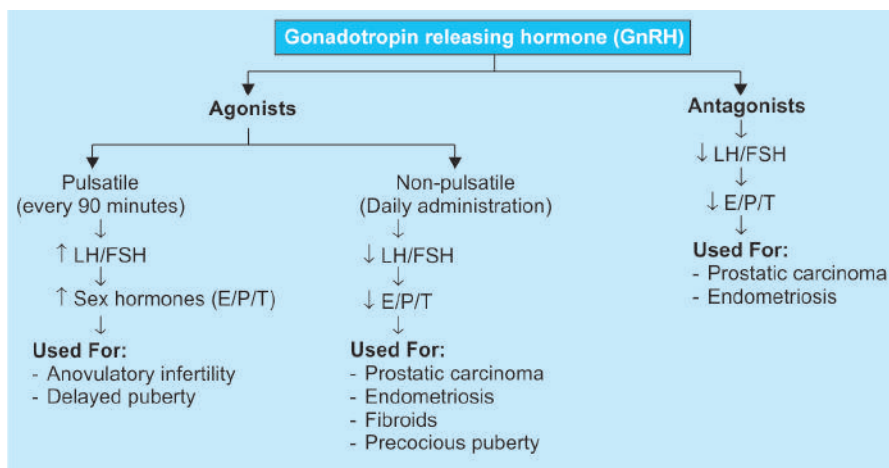


GnRH agonists stimulate gonadotropin secretion when given in a pulsatile manner whereas inhibit the release on continued administration.



Nafarelin and busurelin can be administered by *nasal* route

- **GnRH analogues** like *busurelin*, *goserelin*, *leuprolide*, *nafarelin*, *deslorelin*, *triptorelin* and *histrelin* are more potent and **longer acting** than natural GnRH. These drugs **stimulate gonadotropin secretion when given in a pulsatile manner whereas inhibit the release on continued administration**. Therefore, these agents can be used in *pulsatile manner* for the treatment of *anovulatory infertility*, *hypogonadotropic hypogonadism*, *delayed puberty* and *cryptorchidism* (these conditions require excess of gonadotropins for treatment). On the other hand, if given *continuously*, reduction in gonadotropin secretion is seen that is beneficial in the conditions like *precocious puberty*, *endometriosis*, *prostatic carcinoma*, *PCOD* and *uterine fibroids*. Most of these drugs are used by s.c. route whereas *nafarelin* and *busurelin* can be used by *nasal* route and *goserelin* can be used as *s.c. implant*. Major disadvantage of GnRH analogues is that there is stimulation of gonadotropin release initially (**flare up reaction**) that can be dangerous in conditions like *prostatic carcinoma* and *endometriosis*.
- *Cetrorelix*, *ganirelix* and *abarelix* are **GnRH antagonists**. These do not cause initial flare up reaction. These are administered subcutaneously for the treatment of uterine fibroids and endometriosis. Another use of these drugs is controlled ovarian stimulation in **in-vitro fertilization**. In this process, recombinant FSH is given to prepare the ova for ovulation induction. Constant monitoring of serum estradiol is done and when sufficient levels are reached, GnRH antagonists are given to prevent premature spontaneous ovulation.
- GnRH agonists as well as antagonists can cause *hot flushes*, *loss of libido* and *osteoporosis* as adverse effects.



LH; Leutenizing hormone, FSH; Follicle stimulating hormone, E; Estrogen, P; Progesterone, T; Testosterone

THYROID HORMONES

Thyroid gland contains follicular cells and parafollicular (C) cells. Former secretes thyroid hormones (T_3 and T_4) whereas the latter is responsible for the secretion of calcitonin. Thyroid hormones are synthesized and stored in thyroid follicles in the following manner:

- Iodine is first taken up in the follicular cell with the help of Na^+ : I^- symporter (NIS).
- After entry in the follicular cells, iodine is oxidized to form iodinium (I^+) ions. These ions combine with tyrosine residues of thyroglobulin to form mono-iodo tyrosine (MIT) and di-iodo-tyrosine (DIT). This process is known as organification of iodine.
- DIT combines with DIT to form 3, 5, 3', 5' tetra-iodo-thyronine (T_4) and with MIT to form 3, 5, 3' tri-iodo-thyronine (T_3). This process is known as coupling.
- Oxidation, organification and coupling reactions are catalyzed by thyroid peroxidase enzyme.
- After formation, T_3 and T_4 are transported to the follicles where these remain stored as colloid. On stimulation via TSH, these hormones are released in the circulation.

Oxidation, organification and coupling reactions are catalyzed by **thyroid peroxidase** enzyme.

- In the liver and kidney, T_4 is converted to T_3 (peripheral conversion) with the help of 5'-deiodinase and taken up by target tissues (*brain and pituitary take up T_4 and conversion to T_3 takes place in their own cells*). If 5-deiodinase acts in place of 5'-deiodinase, reverse T_3 (3, 3', 5'-tri-iodo-thyronine) is formed which is inactive.

Liothyronine (T_3)	L-Thyroxine (T_4)
More potent and more active thyroid hormone.	Less potent but main circulating thyroid hormone.
Short acting, therefore beneficial in emergency situations like myxedema coma.	Long acting, therefore preferred for long term use in hypothyroidism.

ACTIONS

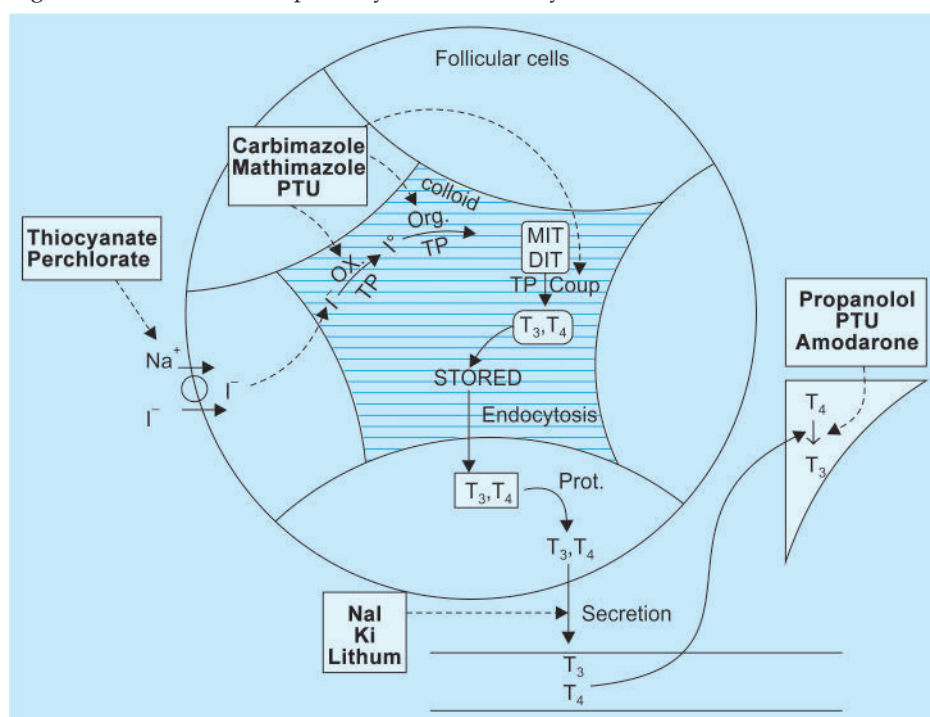
- Thyroid hormones are required for the normal growth and development. Deficiency of thyroid hormones leads to **cretinism** in children and **myxedema** in adults.
- These are **catabolic hormones** and increase the breakdown of fats (to FFA), carbohydrates (cause hyperglycemia) and proteins (cause weight loss).
- These are calorogenic and **increase basal metabolic rate (BMR)**. Heat intolerance occurs in hyperthyroidism whereas hypothyroidism causes cold intolerance. *Brain, gonads and spleen are unresponsive to the calorogenic effect whereas heart is most responsive.*
- Thyroid hormones stimulate the heart (increase rate, contractility and cardiac output). *In hyperthyroidism, atrial fibrillation can occur.*
- Hypothyroidism results in mental retardation whereas hyperthyroidism can result in anxiety, tremors, nervousness and excitability.

INDICATIONS

Main indication of thyroid hormones is **hypothyroidism** (cretinism, myxedema and *myxedema coma*). *Levo-thyroxine (T_4) is preferred for all these indications due to its long half life and requirement of less frequent dosing.* **Myxedema coma** is an emergency situation, in which *liothyronine* (only indication) can also be used (It should be used cautiously in patients with heart diseases like AF).

Drugs Useful for Hyperthyroidism

Drugs can inhibit various steps in thyroid hormone synthesis and release.



Levo-thyroxine (T_4) is preferred over liothyronine (T_3) for treatment of hypothyroidism due to its long half life

Oxi: oxidation, Org: organification, coup: coupling, Prot: Proteolysis, TP: Thyroid peroxidase, PTU: Propylthiouracil

Fig. 7.1: Synthesis and action of thyroid hormones with drug targets

1. INHIBITORS OF $\text{Na}^+\text{-I}^-$ SYMPORTER

Iodine is trapped in the follicular cells with $\text{Na}^+\text{:I}^-$ symporter. Thiocyanate, fluoborate, perchlorate, pertechnate and nitrates inhibit this transporter and thus thyroid hormone synthesis. These drugs are very toxic and are obsolete now. Thiocyanate is produced by cabbage, cigarette smoking and sodium nitroprusside.

2. THYROID PEROXIDASE INHIBITORS

Thyroid peroxidase enzyme catalyzes three reactions (oxidation, organification and coupling) in the process of thyroid hormone synthesis. Carbimazole, methimazole and propylthiouracil act by inhibiting this enzyme. These drugs inhibit the formation of new thyroid hormones but their action manifests only when already stored pool of T_3 and T_4 is utilized. Thus, a lag period of 1-3 weeks is present. These drugs can rarely cause reversible agranulocytosis (most serious adverse effect) whereas most common adverse effect associated with these drugs is maculopapular pruritic rash. Carbimazole is a prodrug and acts after conversion to methimazole. Major differences between carbimazole and propylthiouracil are that the latter:

- Has high Plasma protein binding.
- Can be used in pregnancy (because less transfer across placenta due to high PPB).
- Is less potent.
- Has shorter plasma half-life, so requires multiple daily dosing.
- Also inhibits peripheral conversion of T_4 to T_3 .

Uses

- Thyroid peroxidase inhibitors are used for the control of thyrotoxicosis in patients with Graves' disease and toxic nodular goiter.
- Propylthiouracil is drug of choice for hyperthyroidism in first trimester pregnancy and lactation. For all other patients, methimazole is preferred.
- These are also used in young patients before performing thyroidectomy.
- Another use of antithyroid drugs is to make the patient euthyroid before application of radioactive iodine.

Note: Propylthiouracil has been found to be hepatotoxic and FDA has declared methimazole as preferred drug over propylthiouracil for all patients except in first trimester of pregnancy and lactation.

3. INHIBITORS OF THYROID HORMONE RELEASE

Sodium iodide, potassium iodide and Lugol's solution act as '**thyroid constipating agents**' by inhibiting the release of T_3 and T_4 . These drugs are the **fastest acting anti-thyroid drugs**. These agents make thyroid gland *shrink* in size and *decrease its vascularity*. These properties are utilized in preoperative preparation of thyroid gland. Thyroid storm is another indication of these drugs. **Iodine is also used as an antiseptic and expectorant**. Lithium can cause hypothyroidism by inhibiting the release of thyroid hormones.

In sensitive individuals, acute reaction consisting of swelling of lips, angioedema, fever, joint pain and petechial hemorrhages can occur. Chronic overdose of iodides is called **iodism**. Major symptoms are inflamed mucus membranes, increase in secretions (salivation, lacrimation and rhinorrhoea), headache, rashes and gastrointestinal distress. These drugs may also cause *flaring up of acne* in adolescents.

4. DRUGS CAUSING THE DESTRUCTION OF THYROID GLAND

I^{131} is the most commonly used radioactive iodine with a half-life of 8 DAYS (stable isotope of iodine is I^{127}). When administered (as sodium salts, orally), these are actively taken up by the thyroid gland and stored in the colloid. Here, it emits x-rays and β -particles. Latter can penetrate only 0.5-2mm of tissue and destroy the gland from within. Concentration of radioactive iodine by the thyroid gland is responsible for its *selective thyroid destroying effect*.

Propylthiouracil is drug of choice for hyperthyroidism in first trimester of pregnancy and in lactation. For all other patients, methimazole is preferred.

Iodides are the **fastest acting anti-thyroid drugs**.

I^{131} is the most commonly used radioactive iodine with a half-life of 8 DAYS

I^{131} can be used for the treatment of hyperthyroidism but response is slow (*maximum response may take 3 months*). Thyroid peroxidase inhibitors are administered to make the patient euthyroid. After a gap of 5 days (after stopping anti-thyroid drugs), radioactive iodine is given and thyroid peroxidase inhibitor treatment is resumed till the effect of I^{131} starts. Radioactive iodine therapy is primarily indicated for **patients older than 35 years, those with heart disease** and in the presence of other contra-indications of surgery. These drugs **are not suitable for young children and in the pregnancy**. Another disadvantage of radioactive iodine is that if **hypothyroidism** develops, it is **permanent** (requiring life long T_4 therapy). *Coexisting ophthalmopathy is a relative contra-indication.*

5. DRUGS INHIBITING THE PERIPHERAL CONVERSION OF T_4 TO T_3

Propanolol and propylthiouracil inhibits the generation of more active T_3 from T_4 by inhibiting 5'-deiodinase. These drugs therefore, can be used in the treatment of hyperthyroidism. **Amiodarone** also inhibit this enzyme and thus can result in hypothyroidism.

6. ADJUVANT DRUGS

- **β -blockers** (propanolol, esmolol, atenolol) antagonize the sympathetic effects of thyrotoxicosis like tremors, tachycardia, palpitations and anxiety.
- Calcium channel blockers like **diltiazem** can also be used for this purpose.
- Steroids (i.v. methylprednisolone) are used for Graves's ophthalmopathy. Latter can be aggravated by I^{131} and thiazolidinediones (like pioglitazone and rosiglitazone).

INSULIN AND ORAL HYPOGLYCEMIC AGENTS

Diabetes mellitus (DM) is diagnosed when fasting blood glucose exceeds 126 mg/dl (or postprandial > 200 mg/dl or HbA_{1c} > 6.5g%). Type I DM (IDDM) is treated only by insulin whereas in the treatment of type II DM (NIDDM), orally active drugs are tried first in uncomplicated cases. Insulin is used in all the patients of type I diabetes mellitus and in the patients of type II diabetes who are not controlled with oral hypoglycemic agents (OHA), in pregnancy, to tide over stressful situations (like surgery) and in complications (like ketoacidosis and hyperosmolar coma).

Insulin

It was discovered by Banting and Best in 1921. It consists of 51 amino acids arranged in two chains; A (21 amino acids) and B (30 amino acids). **Pork insulin differs from human insulin by one amino acid only whereas beef insulin has a difference of three amino acids.** Half life of insulin in plasma is about 5-6 minutes. Glucose is the main stimulus for the release of insulin from the β cells of pancreas. Glucose stimulates GLUT-2 and inhibits ATP sensitive K^+ channels; factors that are responsible for the depolarization of β cells and release of insulin. **α_2 receptor stimulation inhibits insulin secretion whereas β_2 agonists and vagal stimulation enhances insulin release.** *Somatostatin inhibits whereas glucagon stimulates the release of insulin.* Adrenergic system regulates insulin release via α_2 (decreases) and β_2 (increases) receptors.

Actions

1. It decreases blood glucose by
 - Stimulating the entry of glucose in muscle and fat (by increasing the synthesis of GLUT 4).
 - Inhibiting glycogenolysis (by inhibiting phosphorylase) and gluconeogenesis (by inhibiting phosphoenol pyruvate carboxykinase). These processes are inhibited at lower concentration of insulin.
 - Increasing glycolysis (by stimulation of glucokinase) and glycogenesis (by stimulating glycogen synthase). These require more concentration of insulin.
2. It inhibits lipolysis and thus favors triglyceride deposition.
3. It increases the synthesis and inhibits the breakdown of proteins.

α_2 receptor stimulation inhibits insulin secretion whereas β_2 agonists and vagal stimulation enhances insulin release.

Advantage of rapid acting insulins (lispro etc) is that their duration of action remain constant (~ 4 hours) irrespective of dose. This contrasts with all other insulins (including regular) where duration of action is prolonged with increase in dose



Lispro, Glulisine and Aspart, all contain letter 's', which means short acting.



Insulin degludec is longest acting insulin and unlike insulin glargine, it can be mixed with other insulins too.



Beta blockers mask all the warning signs of hypoglycemia expect **sweating** (It is mediated by sympathetic cholinergic fibres and not by beta receptors).



Rapid acting insulins (lispro, aspart and glulisine) are preferred for use in CSII (continuous subcutaneous insulin infusion) devices

Preparations

Conventional preparations are obtained from pork and beef. Addition of zinc makes it long acting.

S.No.	Type	Insulin	Onset	Duration	Comment
1	Rapid Acting	Lispro	15-20 min	3-4 hours	Present as monomers
		Aspart	15-20 min	3-4 hours	Most rapidly acting
		Glulisine	15-20 min	3-4 hours	
2	Short Acting	Regular (Crystalline zinc)	30-60 min	5-8 hours	Regular insulin can be given i.v.
		Semi-Lente	1-2 hours	8-12 hours	
3.	Intermediate Acting	NPH or Isophane	2 hours	16-18 hours	
		Lente	2 hours	16-20 hours	
4.	Long Acting	Ultra-Lente	4-6 hours	20-36 hours	
		Glargine	4-6 hours	15-24 hours	Supplied at pH = 4
		Detemir	2-4 hours	20-24 hours	
		Degludec	2-4 hours	24-40 hours	

Human insulin (humulin) is prepared by recombinant DNA technology and has rapid absorption (from s.c. route) and shorter duration of action. Recently ultrashort acting (insulin lispro, glulisine and aspart) and ultralong acting (insulin detemir and glargine) preparations have also been developed.

Note:

- All insulin preparations are supplied at neutral pH (7.2.-7.4) except glargine (supplied at pH 4.0). Therefore, glargine cannot be mixed with any insulin.
- All insulin preparations contain buffer (phosphate or acetate) *except regular, glulisine and glargine*.
- If regular insulin is mixed with lente or ultralente insulin, it can lose its rapidity of action.

Route of administration

- All preparations can be given by s.c. route.
- Only regular (crystalline zinc) insulin can be given i.v.
- Inhalational insulin (exubera) had lead to lung cancers and fibrosis. In June 2014, a new inhalational insulin (Afrezza) was approved by FDA for type-1 DM. It should not be used in patients with chronic lung diseases like asthma.

Factors affecting insulin absorption

- Site* of injection (most rapid from abdomen followed by arm, buttock and thigh).
- Type* of insulin (Fast with regular, aspart, lispro and glulisine)
- Subcutaneous *blood flow* (rate increases with massage, hot bath or exercise).
- Depth* of injection (faster with i.m. than with s.c. route)

Complications of insulin therapy

- Most common complication is hypoglycemia* that can be treated by glucose (oral or i.v.) or glucagon (i.v.).
- Lipodystrophy* at the injection site can occur with conventional preparations and the chances are less with highly purified and recombinant forms of insulin.
- Allergic reactions like lipoatrophy can occur with conventional preparations.
- Sodium and water retention leading to edema has been rarely reported.

Drug interactions

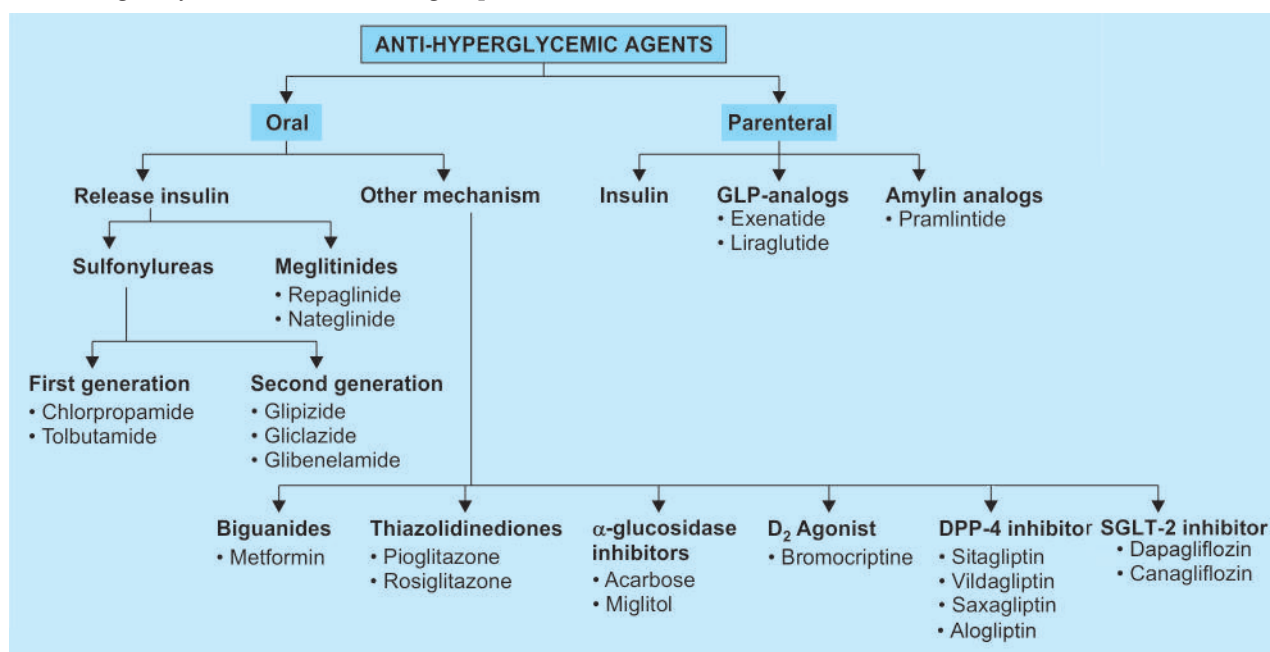
- Use of **non-selective beta blockers** in patient on insulin therapy **delays the recovery from hypoglycemia** (less chances with cardioselective beta blockers). These drugs may also *mask the warning signs of hypoglycemia i.e. palpitations, tremors and anxiety*. All the warning signs may be masked **except sweating** (It is mediated by sympathetic cholinergic fibres and not by beta receptors)
- Acute consumption of **alcohol** can precipitate **hypoglycemia**.
- Drugs elevating blood glucose (diuretics, corticosteroids, oral contraceptives and diazoxide etc.) decrease the effectiveness of insulin.

Indications of insulin therapy

- All cases of IDDM
- NIDDM patients
 - Not controlled on OHA
 - In pregnancy
 - In complications like diabetic ketoacidosis and hyperosmolar coma (regular insulin i.v. is preferred).
 - To tide over stressful conditions like infections and surgery etc.
- Acute hyperkalemia

Oral Anti-Hyper Glycemic Agents

These drugs may be classified into two groups based on the mechanism of action.



1. DRUGS ACTING BY THE RELEASE OF INSULIN [INSULIN SECRETAGOGUES]

This group includes sulfonylureas and meglitinides. These drugs **inhibit ATP sensitive K⁺ channels** and cause depolarization of β cells resulting in the release of insulin. These drugs are **effective only if 30% or more of the β cells** in the pancreas are available. **Major limitation** of these drugs is that like insulin, these can also cause **hypoglycemia**.

Sulfonylureas and meglitinides inhibit ATP sensitive K^+ channels

K^+ cannot go out resulting in more positive charge in β -cells

Depolarization starts

Leads to opening of Ca^{2+} channels and thus entry of Ca^{2+} in β -cells

Release of insulin from granules

Decrease in blood glucose

(a) Sulfonylureas

These may be first generation (*chlorpropamide, tolbutamide, tolazamide and acetohexamide*) or second generation (*glibenclamide* also known as *glyburide, glipizide, gliclazide and glimepiride*) compounds. *Tolbutamide is the shortest acting whereas chlorpropamide is the longest acting sulfonylurea. Second generation drugs are more potent than the first generation agents.* Sulfonylureas can cause weight gain (less chance with glipizide and gliclazide). All these drugs can cause **hypoglycemia** (*maximum with chlorpropamide and with glyburide*) and **chlorpropamide** has additional actions as well. It can cause **dilutional hyponatremia** (ADH like action), **cholestatic jaundice and disulfiram like reaction** (intolerance to alcohol). Gliclazide has additional antiplatelet action also. *Glimepiride exerts beneficial effects with regard to ischemic preconditioning.*

Sulfonylureas (except glyburide) and meglitinides (nateglinide and repaglinide) are safe in renal failure.

(b) Meglitinides

These drugs have similar mechanism to cause release of insulin. *Nateglinide and repaglinide* are the drugs in this group. These drugs are used for the treatment of post prandial hyperglycemia due to their rapid onset and short duration of action. These drugs can also result in **hypoglycemic episodes**.

Note:

- **Glubride** has **maximum insulinotropic potency** whereas tolbutamide has least
- Half-life of glyburide is only 1-2 hours, but its effects persist beyond 24 hours because
 - It produces an active metabolite
 - Apart from binding to sulfonylurea receptor at the membrane, it also **gets sequestered within β -cells** of pancreas (only sulfonylurea with this property)
- **Glimepiride** decreases blood glucose at **lowest dose** among sulfonylureas.
- **Mitiglinde** is another sulfonylurea approved in **Japan**

Metformin is drug of choice for type 2 diabetes mellitus

2. DRUGS ACTING BY OTHER MECHANISMS

These drugs do not cause hypoglycemia because these are not increasing serum insulin concentration.

(a) Biguanides

- *Metformin and phenformin* are biguanides and are preferred agents for obese patients (as these are weight neutral and may even cause weight loss). These drugs decrease blood glucose by activating AMPK (Adenosine Mono Phosphate-activated protein Kinase) that helps in *decreasing the production* (inhibit gluconeogenesis and glycogenolysis) and *increasing the utilization* (stimulation of glycolysis and tissue uptake of glucose). These drugs also inhibit the intestinal absorption of glucose.

M

M – Metformin preferred in
O – Obese patients
S – Sulfonylureas preferred in
T – Thin Patients

Lactic acidosis (more with phenformin) and **megaloblastic anemia** (more with metformin) due to vitamin B₁₂ deficiency are the major adverse effects of these drugs. Biguanides increase the intestinal production of lactate by anaerobic glycolysis. In normal individuals, the lactate produced in the intestine is converted to glucose by gluconeogenesis in the liver. Biguanides put patients at risk of lactic acidosis by inhibiting this very same process of gluconeogenesis.

- Lactic acidosis is more likely to occur in the presence of hepatic and renal impairment or alcohol ingestion. Other contra-indications include cardiac failure, and chronic hypoxic lung disease. Metformin is also useful for **polycystic ovarian disease** (PCOD). **Metformin is the only oral agent** that has been demonstrated to **reduce macrovascular events** in type 2 DM.
- **Metformin is first-line therapy for type 2 diabetes.**

Metformin is the only oral agent that has been demonstrated to **reduce macrovascular events** in type 2 DM.

(b) Thiazolidinediones

- Troglitazone, pioglitazone and rosiglitazone are the drugs in this group that act as agonists of a nuclear receptor ; peroxisome proliferator activated receptor gamma (PPAR γ). It regulates the transcription of genes involved in glucose and lipid metabolism. Important genes that are up regulated by PPAR- γ are:

- Adiponectin
- Fatty acid transport protein
- Insulin receptor substrate
- GLUT - 4

- These drugs are used to reverse insulin resistance in type II DM. These drugs also tend to increase HDL. *Troglitazone was withdrawn* due to serious *hepatotoxicity* and monitoring of hepatic function is recommended for other glitazones also. Glitazones have been reported to cause *weight gain, edema and plasma volume expansion*. Therefore, these should be avoided in CHF patients. (NYHA class III and IV)
- **Rosiglitazone** increases the *risk of angina and MI*. So, pioglitazone is preferred agent from this group.
- **Rosiglitazone** increases *total and LDL cholesterol* as well as HDL-cholesterol whereas pioglitazone increases HDL-cholesterol without affecting total and LDL-cholesterol.
- **Pioglitazone** is associated with **increased risk of bladder cancer** on long term use.
- Both of these can result in:
 - Weight gain
 - Edema
 - Increase in fracture risk in women
 - Anemia

Effect of antidiabetic drugs on weight

- **Increase:**
 - Sulfonylureas
 - Insulin
 - Pioglitazone
- **Decrease:**
 - GLP - I agonists
 - Pramlintide
- **No effect:**
 - DPP-4 inhibitors
 - Metformin

Pioglitazone is associated with possible increase in risk of bladder cancer on long term use.

(c) α -Glucosidase inhibitors

Complex carbohydrates (polysaccharides and sucrose) are absorbed after conversion to simple carbohydrates by α glucosidase. Inhibitors of this enzyme (*acarbose, voglibose and miglitol*) decrease carbohydrate absorption from the GIT. Major adverse effect of these drugs is *flatulence* due to fermentation of unabsorbed carbohydrates. (therefore, contra-indicated in inflammatory bowel disease) If high doses are taken, simple carbohydrates like glucose (not sucrose or other complex carbohydrates) can be used. According to some trials, these drugs can help in restoring β -cell function and prevent new cases of type 2 diabetes in pre-diabetics.

Acarbose can decrease blood glucose in both type 1 as well as type 2 diabetes. However, apart from insulin, **the only drug approved for treatment of both type 1 as well as type 2 diabetes is pramlintide.**



Alogliptin is a new DPP-4 inhibitor recently approved for Type 2 diabetes



Hypoglycemia in the presence of α -glucosidase inhibitors can be reversed by simple carbohydrates like glucose (not sucrose or other complex carbohydrates) can be used.

New Drugs for Diabetes Mellitus

1. INCRETINS

Oral glucose provokes 4 times higher insulin release than intravenous glucose. This is because oral glucose releases GLP-1 (Glucagon like peptide-1), that amplifies the glucose-induced insulin release. GLP-1 secretion is reduced in patients with type 2 diabetes. Incretins like GLP-1 has little stimulatory effect on insulin secretion at normoglycemic concentration (Unlike sulfonylureas and other insulin secretagogues). Thus, GLP-1 has lower risk of causing hypoglycemia. Apart from releasing insulin, GLP-1 has following actions:

- Suppresses glucagon secretion
- Preserves islet cell integrity and decreases apoptosis.
- Delays gastric emptying resulting in reduced appetite

The endogenous GLP-1 is rapidly broken by dipeptidyl peptidase-4 and thus has a half-life of 1-2 minutes only.

So, the two strategies by which incretin effect can be strengthened are:

A. GLP-1 Receptor Agonists:

Exenatide and liraglutide are GLP-1 receptor agonists. These are administered *subcutaneously* and act by mechanism similar to GLP-1 (as discussed above): New drugs of this category, recently approved are **albiglutide** and **dulaglutide**

- These drugs can promote **weight loss**.
- Most common adverse effect of these drugs is **nausea**.
- These can also result in **acute pancreatitis**
- These are contra-indicated in patients with personal or family history of **medullary thyroid cancer or MEN-2**.
- **Liraglutide** is **longer acting** (once daily) as compared to exenatide (twice daily)
- Liraglutide does not require dose adjustment in renal failure whereas exenatide dose should be reduced.
- Recently, **liraglutide** has been approved for **management of obesity**.

B. DPP-4 Inhibitors:

Sitagliptin, vildagliptin, saxagliptin, alogliptin, empagliflozin and linagliptin prolong the action of endogenous GLP-1 by inhibiting its metabolism through DPP-4:

- Unlike incretin-mimetic drugs, these *do not cause nausea or weight loss*.
- **Most common** adverse effect of DPP-4 inhibitors is **nasopharyngitis** and upper respiratory tract infections.
- DPP-4 inhibitors are **effective orally**.
- These drugs require dose adjustment in renal failure except **linagliptin**.
- *Vildagliptin can cause hepatitis*.

2. SODIUM GLUCOSE CO-TRANSPORTER-2 INHIBITORS

Glucose is freely filtered across glomerulus and is reabsorbed in proximal tubules by sodium glucose co-transporter-2 [SGLT-2]. **Dapagliflozin and canagliflozin** act by inhibiting this transporter and cause glucosuria in diabetics. These also result in *weight loss*. These are effective orally.

- Efficacy of these drugs is reduced in renal failure.
- Main adverse effects are **increased incidence of urinary tract infections** and genital infections.
- **Higher rates of breast and bladder cancers** have been reported in patients taking dapagliflozin.

3. AMYLIN ANALOGS

Pramlintide is a synthetic analog of islet amyloid polypeptide (IAPP) also called amylin. It acts by:

- Decreasing glucagon secretion
- Delaying gastric emptying
- Decreasing appetite

Important points about pramlintide are:

- It is administered by **subcutaneous** route.
- It can cause **weight loss**
- It is **approved for treatment of type 2 as well as type 1 diabetes mellitus** (only drug apart from insulin)
- It **can cause hypoglycemia**.

Acarbose can decrease blood glucose in both type 1 as well as type 2 diabetes. However, apart from insulin, the only drug approved for treatment of both type 1 as well as type 2 diabetes is pramlintide

4. BILE ACID BINDING RESINS

Bile acid metabolism is abnormal in patients with type 2 diabetes mellitus and bile acid binding agents have been found to lower blood glucose in these patients. Colesevalam is specifically approved for type 2 diabetes. These drugs can result in hypertriglyceridemia.

5. BROMOCRIPTINE

Recently, FDA has approved bromocriptine mesylate as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes. It has been found that dopamine alter insulin resistance by acting on hypothalamus and bromocriptine targets D₂ receptors.

CORTICOSTEROIDS

Adrenal cortex consists of three layers; *zona glomerulosa*, *zona fasciculata* and *zona reticularis* from outside to within respectively (remembered as GFR). *Mineralocorticoids* are secreted from *zona glomerulosa* whereas inner layers secrete glucocorticoids and sex steroids. Corticosteroids are synthesized from cholesterol. Glucocorticoid secretion is maximum in the early morning.

Actions

MINERALOCORTICOIDS

Major endogenous mineralocorticoid is aldosterone. It acts in DCT of the kidney to cause reabsorption of Na⁺ and excretion of K⁺ and H⁺. Thus, *excess of mineralocorticoids* can lead to retention of sodium and water (hypertension and edema), *hypokalemia* and *alkalosis* whereas Addison's disease (deficiency of adrenal corticoids) is characterized by hyperkalemia, acidosis and hypotension. Aldosterone is also involved in **causing myocardial remodeling** associated with CHF and the drugs blocking this effect [*spironolactone*, *ACE inhibitors*, angiotensin receptor antagonists (*ARBs*) and β blockers] decrease the mortality in patients with CHF.

GLUCOCORTICOIDS

Major endogenous glucocorticoid is hydrocortisone (cortisol). Many of the effects of glucocorticoids are dose-dependent whereas some are permissive effects (without these, many normal functions become deficient) e.g. response of vascular and bronchial smooth muscle to catecholamines is diminished in the absence of cortisol.

- **Effect on metabolism:** Glucocorticoids are *catabolic* in nature and thus cause breakdown of carbohydrates (hyperglycemia), proteins (muscle wasting) and fat. There is *redistribution of fat*; deposition over face (moon face), mouth (fish mouth) and back (buffalo hump) whereas removal from the extremities is seen. Glucocorticoids cause negative Ca²⁺ balance (by inhibiting intestinal absorption, enhancing renal excretion and causing loss of Ca²⁺ from the bones) and can predispose to osteoporosis.

- **Effect on CVS and CNS:** Glucocorticoids *prevent the increase in the permeability of capillaries*. These have *mild euphoric* effect and high doses can lower seizure threshold.
- **Effect on GIT:** These hormones may *aggravate peptic ulcer* by increasing the secretion of HCl and pepsin in stomach.
- **Effect on hematopoietic system:** Glucocorticoids cause *destruction* of T cells and B cells (less sensitive) in malignancies whereas little effect is exerted on normal cells. These drugs cause *sequestration* of lymphocytes, eosinophils, monocytes and basophils in tissues (and thus decrease circulating levels of these cells) whereas circulating neutrophils are increased due to release from bone marrow.
- **Effect on inflammatory response:** Glucocorticoids are *powerful anti-inflammatory* agents. Most important mechanism is the *inhibition of chemotaxis* (recruitment of the cells at the site of inflammation). These hormones also induce the production of **annexins** (previously called, **lipocortins**) that are responsible for the inhibition of phospholipase A₂ (involved in the production of prostaglandins and leukotrienes). They also delay the healing of wounds and scar formation.
- **Effect on immunity:** These hormones suppress cell mediated immunity (CMI) more than humoral immunity. Main effect is **due to inhibition of recruitment of immune cells**, but they also inhibit the release of IL-1 and IL-2. Antibody production is affected at high doses and continuous administration of glucocorticoids *can result in catabolism of IgG*. Immunosuppressive effect of glucocorticoids is the basis of their use in graft rejection and various hypersensitivity reactions.

IMPORTANT PHARMACOKINETIC PROPERTIES

Glucocorticoids		Duration of Action	G Activity	M Activity	Potency (Eq. Dose) in mg
1.	HYDROCORTISONE (CORTISOL)	Short	1	1	20
2.	CORTISONE	Short	Minimum (0.8)	0.8	Least potent G. (25)
3.	PREDNISONE	Intermediate	4	0.5	5
4.	PREDNISOLONE	Intermediate	5	0.5	5
5.	MEPREDNISONE	Intermediate	5	0	4
6.	METHYLPREDNISOLONE	Intermediate	5	0	4
7.	TRIAMCINOLONE	Intermediate	5	0	4
8.	FLUPREDNISOLONE	Intermediate	15	0	1.5
9.	PARAMETHASONE	Long	10	0	2
10.	BETAMETHASONE	Long	25	0	Most potent G.(0.6)
11.	DEXAMETHASONE	Long	Maximum (30)	0	0.75
MINERALOCORTICIDS					
12.	DOCA		0	20	
13.	FLUDROCORTISONE		10	250	Most potent M.
14.	ALDOSTERONE		0.3	3000 (max.)	Not used clinically

G. = Glucocorticoid, M. = Mineralocorticoid

Important Points

Maximum glucocorticoid activity	Dexamethasone
Maximum mineralocorticoid activity	<i>Aldosterone</i>
Glucocorticoid with Maximum mineralocorticoid activity	Hydrocortisone
Least potent glucocorticoid	<i>Cortisone</i>
Most potent glucocorticoid	Betamethasone
Selective mineralocorticoid action (with zero glucocorticoid activity)	<i>DOCA</i>
Selective glucocorticoid action (with zero mineralocorticoid activity)	Methylprednisolone, triamcinolone, paramethasone, dexamethasone, betamethasone
Steroid with maximum topical activity	<i>Triamcinolone acetonide</i>

Uses of Corticosteroids**1. REPLACEMENT USE**

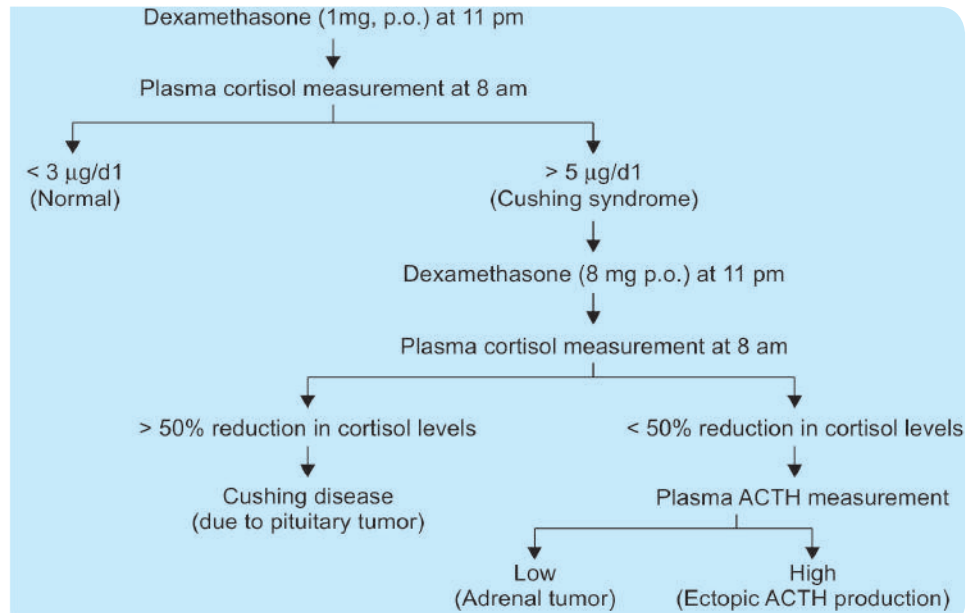
- A) *Acute adrenal insufficiency*: It is an emergency condition and requires immediate management with parenteral administration (i.v.) of hydrocortisone.
- B) *Chronic adrenal insufficiency (Addison's disease)*: It is treated with oral doses of **hydrocortisone**. Mineralocorticoids like fludrocortisone may also be required.
- C) *Congenital adrenal hyperplasia (CAH)*: This disorder is a result of *congenital deficiency of the enzymes* involved in the synthesis of corticosteroids. Due to decreased adrenal steroids, there is no feedback inhibition of pituitary and consequently ACTH secretion increases. ACTH cannot release corticosteroids (because they are not synthesized) but it results in overgrowth of adrenal glands leading to symptoms. Thus, **treatment** of congenital adrenal hyperplasia (adrenogenital syndrome) is **aimed at reducing ACTH secretion**. Exogenous glucocorticoids like hydrocortisone cause feedback inhibition of HPA axis and lead to amelioration of symptoms. **To prevent CAH** (in a pregnant female with history of baby with CAH), **steroids should be administered at 6 weeks period** (i.e. as soon as the pregnancy is diagnosed). The *genotype and sex of the fetus is then determined*. Steroid therapy is stopped if sex is male. If genotyping reveals *female sex*, steroid therapy is *continued till delivery* (to prevent virilization).

2. DIAGNOSTIC USE

Dexamethasone suppression test is used to test the intactness of HPA axis function and diagnosis of Cushing's syndrome. Dexamethasone in a normal person inhibits the release of CRH (feedback inhibition) and it does not interfere with measurement of endogenous corticosteroids in blood or urine. Dexamethasone (1 mg) is given orally at night (11 PM) and plasma cortisol levels are measured in the morning (8 AM). If cortisol levels are less than 3 µg/dl (feedback inhibition is present), it signifies that HPA axis is functioning properly. If cortisol in plasma is more than 5 µg/dl (no feedback inhibition), it indicates that there is excessive secretion of cortisol due to adrenal or pituitary tumor (Cushing syndrome). After confirmation of Cushing syndrome by dexamethasone suppression test, it is possible to differentiate between Cushing's disease (due to pituitary tumor) and other causes (adrenal tumor or ectopic ACTH) by using large dose of dexamethasone. 8 mg of dexamethasone is administered at night and plasma cortisol level is measured in the morning. If Cushing disease is present, cortisol levels will be less than 50% of the previous value. If cortisol levels are still high, ACTH levels are measured. Reduced ACTH levels suggest adrenal tumor whereas elevated ACTH levels suggest ectopic ACTH production.



Dexamethasone suppression test is used to test the intactness of HPA axis function and diagnosis of Cushing's syndrome.

Fig. 7.2: Dexamethasone suppression test**Antenatal Use of Steroids**

- Accelerate fetal lung maturation
- Decrease incidence of PDA
- Decrease risk of intraventricular hemorrhage

3. ANTENATAL USE

Betamethasone can be given to **accelerate the fetal lung maturation**, if delivery is anticipated before 32 weeks of gestation. In selected patients, antenatal steroid therapy decreases the incidence, severity and complications of respiratory distress syndrome, and decreases overall neonatal mortality and morbidity. In addition, antenatal steroids may decrease the incidence of PDA and **periventricular/intraventricular hemorrhage**.

4. NON ADRENAL USES

- Anti-inflammatory uses:** Corticosteroids can be useful in rheumatoid arthritis, osteoarthritis (intra-articular) and acute gouty arthritis when NSAIDs fail to provide pain relief. These are also useful in inflammatory conditions of eye like conjunctivitis, iritis, iridocyclitis and keratitis. However, steroids are **contraindicated in herpes simplex keratitis**.
- Anti-allergic uses:** Corticosteroids are useful in the management of anaphylaxis (*DOC is adrenaline*), urticaria, angioedema and serum sickness. These are used by inhalational route in chronic severe asthma and i.v. (hydrocortisone) route is employed in acute severe asthma (status asthmaticus). Skin conditions like pemphigus vulgaris, exfoliative dermatitis and Steven Johnson syndrome also require systemic steroid therapy.
- Immunosuppressive uses:** High dose corticosteroid therapy is required in the organ transplantation to prevent graft rejection. They are also useful in autoimmune diseases (e.g. myasthenia gravis, hemolytic anemia) and collagen vascular diseases (like SLE, polyarteritis nodosa and nephrotic syndrome). Steroids are also useful in patients with ulcerative colitis and Crohn's disease who are not responding to 5-aminosalicylic acid.
- Anti-cancer uses:** Due to prominent lympholytic action in malignant cells, steroids are essential component of the combination therapy of ALL and lymphomas (both Hodgkin as well as non-Hodgkin). These are also useful in the breast carcinoma. These can also be used with anti-neoplastic agents to *decrease nausea and vomiting*.
- Other uses**

- Steroids with selective glucocorticoid action (without Na⁺ and water retaining activity) like betamethasone and dexamethasone are used to *decrease cerebral edema* due to malignancies or TB.
- Steroids are also useful in severe infective conditions (like TB meningitis and lepra reaction) to tide over the acute crisis. However these are *contra-indicated in intestinal (Ileo-caecal) TB* due to the risk of perforation.
- These can be used as a desperate measure in the septicemic shock.
- Steroids can also be used for treatment of *sarcoidosis*.
- In *thrombocytopenia*, prednisolone is used to decrease bleeding tendency.
- *Autoimmune hemolytic anemia* is treated with prednisolone.
- Significant decrease in neurological defects have been seen in *spinal cord injury* patients treated with large doses of methylprednisolone (within 8 hours).

Points to Remember for Systemic Use of Steroids

- Long term use (for more than 2 weeks) can lead to HPA axis suppression. Steroids should not be withdrawn abruptly because it may precipitate acute adrenal insufficiency. Many patients recover from *HPA-axis suppression* within several weeks to months but **recovery may take one year or longer in some patients**.
- Large single dose is less harmful than small doses given for long periods. Thus 80mg prednisolone for 2 days is much less harmful than 20mg dose for 6 months.
- During condition of stress like infection or trauma, steroid dose should be unchanged or increased (2 to 10 fold). *It should not be reduced*.
- To prevent HPA axis suppression, steroids can be given on alternate days but long acting steroids like betamethasone and dexamethasone cause HPA axis suppression even when administered on alternate days.

Adverse Effects and Contraindications

- *Hypertension, edema (contra-indicated in CHF and hypertension), alkalosis and hypokalemia* can occur due to mineralocorticoid activity.
- *Cushing's habitus* (characteristic appearance due to redistribution of fat) and *striae* can occur.
- *Hyperglycemia* (C/I in DM), *muscular weakness* and resorption of bones (C/I in osteoporosis) can result due to chronic steroid therapy.
- These may cause *posterior subcapsular cataract* (on systemic use) and development of *glaucoma* (topical use) on long term use.
- Due to immunosuppressant action, steroids increase the *susceptibility to infections* and due to anti-inflammatory activity these can *delay wound healing*.
- These are contraindicated in *peptic ulcer disease* because bleeding and perforation can occur.
- Given during pregnancy, steroids can cause fetal abnormalities and given to young children for prolonged periods, these may result in growth retardation.
- Steroids are *contra-indicated in psychosis* (due to CNS stimulatory action) and *epilepsy* (due to lowering of seizure threshold).
- *Osteonecrosis* (avascular necrosis), most commonly of hip can occur with high doses of glucocorticoids.



Adverse effects and contra-indications of steroids:

- G – Glaucoma (on topical use)
- L – Limb muscle atrophy
- U – Ulcer (peptic ulcer)
- C – Cushing syndrome
- O – Osteoporosis
- C – Cataract (on systemic use)
- O – Osteonecrosis (avascular necrosis)
- R – C/I in Renal failure
- T – C/I in Tuberculosis (particularly ileo-caecal)
- I – Impair healing
- C – C/I in CHF
- O – Oedema
- I – Infections (due to immunosuppressant action)
- D – Diabetes mellitus
- S – Suppression of HPA-axis

Glucocorticoid Synthesis Inhibitors

These drugs are useful in the diagnosis of adrenal diseases and in the treatment of Cushing's syndrome.

- **Metirapone** inhibits 11β hydroxylase enzyme (involved in the synthesis of cortisol and cortisone) and results in the reduced glucocorticoid activity. It was used for diagnostic purposes and for the treatment of Cushing's syndrome. It is the only drug in this group which is safe in pregnancy.
- **Aminoglutethimide** inhibits the enzyme *cholesterol side chain cleavage* that helps in the conversion of cholesterol to pregnenolone. Thus, it inhibits the synthesis of all corticosteroids. It also inhibits the enzyme *aromatase* and is useful in breast carcinoma. Glucocorticoids and mineralocorticoids can be given along with this agent in the treatment of breast cancer to prevent the precipitation of acute adrenal insufficiency.
- **Mitotane** causes atrophy of zona fasciculata and reticularis without affecting zona glomerulosa. Thus it causes reduction in glucocorticoids and sex steroids. It can be used for **medical adrenalectomy**.
- **Trilostane** inhibits 3β hydroxysteroid dehydrogenase enzyme, which is involved in the production of adrenal and gonadal hormones. It is also an *aromatase inhibitor*.
- **Ketoconazole** is an antifungal agent that can be used for the treatment of Cushing's syndrome due to the inhibitory actions on 17α hydroxylase and 3β hydroxysteroid dehydrogenase enzymes.

Corticosteroid Receptor Antagonists

- **Mifepristone** is a long acting antagonist at the glucocorticoid and progesterone receptors. It is used for medical termination of pregnancy, as a post-coital contraceptive and rarely for inoperable patients of Cushing's syndrome.
- **Spironolactone and epleronone** are aldosterone receptor antagonists that are used as K^+ sparing diuretics.
- **Drospirenone**, a progestin in an oral contraceptive, also antagonizes the effects of aldosterone.

DRUGS AFFECTING BONE MINERAL HOMEOSTASIS

Calcium and phosphate homeostasis is maintained by the action of vitamin D (active form is **calcitriol**), parathyroid hormone (PTH) and FGF-23 (Fibroblast growth factor-23). Secondary regulators of Ca^{2+} homeostasis include calcitonin, glucocorticoids and estrogens.

	Serum PO_4^{3-}	Serum Ca^{2+}	Mechanism
Vitamin D	↑	↑	↑ intestinal absorption of both Ca^{2+} and PO_4^{3-} ↓ renal excretion of both
PTH	↓	↑	↓ renal excretion of Ca^{2+} and ↑ that of PO_4^{3-} ↑ resorption of Ca^{2+} from bone ↑ intestinal absorption of calcium by increasing calcitriol
FGF-23	↓	-	↓ Ca^{2+} and PO_4^{3-} absorption by intestines ↑ PO_4^{3-} excretion by kidneys

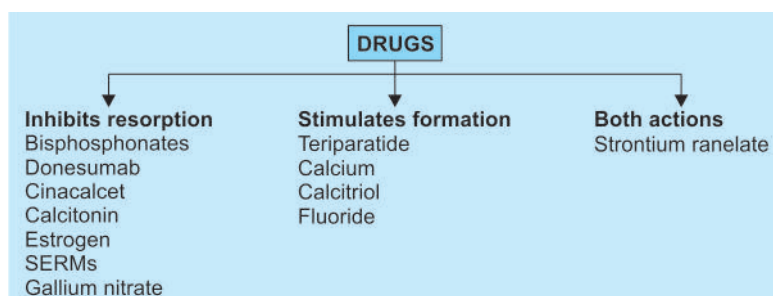
Thus **vitamin D and calcitonin can be used to treat osteoporosis whereas PTH excess can result in osteoporosis.**

- *Plasma Ca^{2+} is the major factor regulating PTH secretion.* Hypocalcemia stimulates PTH secretion whereas hypercalcemia inhibits it. Calcium inhibits PTH secretion by stimulating calcium sensing receptor on parathyroid cells.
- *PTH increases circulating calcitriol by two mechanisms; Directly by stimulating 1α hydroxylase in kidney and indirectly by decreasing serum phosphate.*

- Vitamin D₂ is ergocalciferol whereas D₃ is cholecalciferol.
- Vitamin D is converted to 25-OHD (calcifediol) *in the liver* with the help of 25- α -hydroxylase and then to 1, 25-dihydroxy D₃ (calcitriol) by the action of 1 α -hydroxylase *in kidney*. Calcitriol is inactivated to 1, 24, 25 (OH)₃ D with the help of 24- α -hydroxylase in kidney. **Doxercalciferol and Paricalcitol** have been approved for treatment of secondary hyperparathyroidism in patients with chronic renal disease. These are less likely to cause hypercalcemia than calcitriol.
- Apart from effects on Ca²⁺ and PO₄³⁻, **calcitriol also affects maturation and differentiation of mononuclear cells** (possibility of use in cancers), inhibits epidermal proliferation and promotes epidermal differentiation (potential treatment of psoriasis vulgaris). **Topical calcipotriol (calcipotriene)** has been approved for use in psoriasis. It is slightly more effective than glucocorticoids.
- **Fibroblast growth factor-23** inhibits calcitriol production and phosphate reabsorption in kidney. It is produced by osteoblasts and osteoclasts.

Drugs decreasing bone resorption initially increases bone mineral density (BMD), but it reaches a plateau in 2-3 years because bone formation also decreases. On the other hand, drugs promoting bone formation can increase BMD throughout the period of treatment.

Drugs Useful for the Treatment of Osteoporosis



BISPHOSPHONATES

- These agents are used for the treatment of osteoporosis due to their *inhibitory effect on osteoclast mediated bone resorption*. These drugs accelerate **apoptosis of osteoclasts** and also **suppress differentiation of osteoclast precursors to mature osteoclasts** (by inhibiting IL-6). This results due to reduction in cholesterol synthesis via inhibition of farnesyl pyrophosphate synthase by bisphosphonates.
- Drugs in this group include **first generation** agents (least potent) like *medronate, clodronate and etidronate*, **second generation** drugs like *alendronate, ibadronate* and *pamidronate* and **third generation compounds** like *risedronate and zoledronate* (most potent).
- These are used for the treatment of *post-menopausal and steroid induced osteoporosis, Paget's disease and hypercalcemia of malignancy* (pamidronate and zoledronate by i.v route are preferred).
- Bisphosphonates can also be used in malignancies. **Zoledronate** has been used successfully as an adjunct in treating philadelphia-chromosome positive **CML**.
- Distinctive toxicity of these agents is **esophageal irritation** that can lead to ulceration as well. To prevent this complication, patients taking bisphosphonates are advised to take nothing by mouth except water and not to lie down at least for half an hour. This minimizes the chances of the drug touching the esophagus.
- *Zoledronate* has been associated with *renal toxicity* and *first generation* bisphosphonates can result in *osteomalacia*.
- Recently, **osteonecrosis of jaw** has been noted with use of bisphosphonates particularly zoledronate. Patients receiving bisphosphonates must receive regular dental care and try to avoid dental extraction.

Bisphosphonates are used for the treatment of

- Post-menopausal osteoporosis
- Steroid induced osteoporosis
- Paget's disease
- Hypercalcemia of malignancy

- Long-term use of bisphosphonates increases the risk of **atypical 'chalkstick' fracture of femur (subtrochantric or shaft)**. Risk increases with concurrent high dose steroid therapy.
- Long-term use of bisphosphonates increase the risk of **esophageal cancer**.
- Bisphosphonates **can result in hypocalcemia as well as hypercalcemia**.
- **Half-life of alendronate in bone is 10 years**.

Note:

- Main contraindications of bisphosphonates are renal dysfunction, esophageal motility disorders and peptic ulcer.
- **Zoledronate** infusion of 5mg **once yearly** has been approved for treatment of osteoporosis.

Distinctive toxicity of bisphosphonates is **esophageal irritation** that can lead to ulceration as well

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Estrogens inhibit bone resorption directly by inhibiting osteoclasts and indirectly by modulating paracrine factors. It **increases anti-resorptive [IGF-1 and TGF- β]** and **suppresses pro-resorptive [IL-1, IL-6, TNF- α and osteocalcin]** factor synthesis by osteoblasts.

Estrogen increases bone formation and its deficiency in the old age may result in post-menopausal osteoporosis. Use of hormone replacement therapy for this condition predisposes the patients to the adverse effects of estrogens on breast and endometrium (increased incidence of breast and endometrial carcinoma). **Raloxifene** is a selective estrogen receptor modulator with estrogen agonistic action on bone and antagonistic action on breast and endometrium. It is therefore the preferred drug for the treatment and prevention of *post-menopausal osteoporosis*. Major adverse effect of this agent is increased risk of **thromboembolism**. **Bazedoxifene** is another SERM that has been approved recently for prevention of post menopausal osteoporosis and to treat vasomotor symptoms of menopause.

TERIPARATIDE

Teriparatide and strontium ranelate can stimulate osteoblast whereas most other agents used for osteoporosis act by inhibiting osteoclast

It is **recombinant PTH₁₋₃₄**. It has been noted that PTH in low and pulsatile dose stimulates bone formation whereas in excess it causes resorption of bones. Teriparatide is available for the treatment of osteoporosis by intermittent s.c. administration.

Teriparatide and strontium ranelate can stimulate osteoblast whereas most other agents used for osteoporosis act by inhibiting osteoclast

- Teriparatide stimulates the production of new collagenous bone matrix that must be mineralized. Therefore, patients receiving teriparatide must have sufficient intake of vitamin D and calcium.
- When administered to patients with osteoporosis in doses of 20 mcg/d subcutaneously for 2 years, Teriparatide dramatically improves bone density in most bones **except the distal radius**.
- The recommended dose should not be exceeded, since Teriparatide has caused osteosarcoma in rats when administered in very high doses. Due to **potential risk of osteosarcoma**, teriparatide should be avoided in:
 - *Paget's disease* of bone
 - *Prior radiotherapy* to bone
 - *Past history of osteo or chondrosarcoma*
 - *Unexplained increase in alkaline phosphatase*
- Teriparatide should be used with caution in patients if they also taking corticosteroids and thiazide diuretics along with oral calcium supplementation because **hypercalcemia may develop**.
- Following a course of Teriparatide, a course of bisphosphonates should be considered in order to retain the improved bone density.
- Other adverse effects have included exacerbation of nephrolithiasis and elevation of serum uric acid levels.
- Teriparatide may be **used for healing of chalkstick fractures associated with bisphosphonate therapy**.

DENOSUMAB

Osteoclasts express a receptor called receptor for activated nuclear factor κ B (RANK) on its surface. When this receptor is stimulated by RANK ligand, bone resorption results due to activation of osteoclasts. Denosumab is a monoclonal antibody against this ligand and is useful for the treatment of osteoporosis. Osteoprotegerin acts as a decoy receptor for RANK-ligand (binds it and thus prevents binding of RANK-L to osteoclasts). It can also prevent osteoporosis. It **can decrease serum calcium** therefore *avoided in patients with hypocalcemia*. It has recently been approved for unresectable **giant cell tumor** of bone.



Denosumab has recently been approved for giant cell tumor of bone

CINACALCET

Calcium sensing receptors are present on parathyroid gland that regulates the secretion of PTH. Ca^{2+} activates these receptors and decreases PTH secretion. Hypocalcemia will have opposite effect i.e. increased PTH secretion. Cinacalcet acts as a **calcimimetic drug** by *directly activating calcium sensing receptors on parathyroid gland*. It has been *approved* for the treatment of *secondary hyperparathyroidism* (due to chronic renal disease) and for patients with hypercalcemia associated with *parathyroid carcinoma*.



Cinacalcet acts as a **cal-cimi-metic drug** by *directly activating calcium sensing receptors on parathyroid gland*. It has been *approved* for the treatment of *secondary hyper-parathyroidism*

STRONTIUM RANELATE

It has a novel mechanism of action as it inhibits bone resorption as well as stimulates bone formation. Strontium is incorporated into hydroxyapatite, replacing calcium. Small increased risk of venous thrombosis, seizures and abnormal cognition have been seen and require further studies.



Strontium ranelate inhibits bone resorption as well as stimulates bone formation.

OTHER DRUGS

- **Calcium and calcitriol** (vitamin D) can be used in the *prophylaxis and treatment of osteoporosis*. Calcium can be life saving in *extreme hyperkalemia* ($> 7 \text{ mEq/L}$). It can reverse some of the cardiotoxic effects of K^+ . Calcium is also approved for *i.v. treatment of black widow spider envenomation and magnesium toxicity*.
- **Gallium nitrate** inhibits bone resorption and is useful in the management of Paget's disease and hypercalcemia of malignancy but *nephrotoxicity* limits its use for this indication.
- **Fluorides** are used to prevent dental caries but their usefulness in osteoporosis is uncertain.
- **Thiazides** inhibit the renal excretion of Ca^{2+} and thus can be used for the treatment of osteoporosis (apart from their use in recurrent calcium stones due to hypercalciurea).
- **Calcitonin** inhibits resorption of bone and thus can be used for the treatment of osteoporosis. It can be administered by *nasal route* for this indication. Calcitonin possess **analgesic effects** on bone pain from fractures.

GONADAL HORMONES

Estrogen, progesterone and testosterone are principal gonadal hormones. Estrogen and progesterone are produced by ovaries whereas testosterone is mainly formed by testes.

Estrogens

- Natural estrogens include **estradiol (principal and most potent estrogen)**, estrone and estrinol (weakest). *Major site of estrogen production in premenopausal female is ovary whereas in post menopausal female, estrogen is produced mainly by peripheral organs like liver, kidney, brain and adipose tissue*. Ethinyl estradiol, mestranol (both steroidal), diethylstilbesterol and genistein (non-steroidal) also possess estrogenic activity.
- Estrogen stimulates synthesis of progesterone receptors whereas progesterone inhibits the synthesis of estrogen receptors.

- **Natural estrogens** are ineffective orally due to **extensive first pass metabolism**. Estrogens *undergo enterohepatic circulation* that is also responsible for hepatic adverse effects (hepatic adenoma and thromboembolism).

Actions

- Growth and development of female reproductive system.
- Increased risk of breast, endometrial and cervical carcinoma.
- Feedback inhibition of gonadotropin (LH/FSH) secretion.
- Stimulation of CTZ to cause nausea and vomiting.
- *Increased predisposition to deep vein thrombosis and pulmonary embolism* due to increased synthesis of factor VII, VIII, IX and X and decreased production of antithrombin III by the liver. *Favourable effect on lipid profile* by decreasing LDL-C and LP (a) and increasing HDL-C. Slight increase in triglycerides may also occur.
- *Glucose intolerance* and sodium and water retention.
- *Maintain bone mass by decreasing the bone resorption.*
- Increased risk of gall bladder stones and *cholestatic jaundice*.
- Can result in *hepatic adenoma* on prolonged use.
- *Vasodilation* by increasing the production of NO.

Indications

Deficiency of this hormone as seen in postmenopausal females may result in osteoporosis, hot flushes, urogenital atrophy and increased risk of cardiovascular diseases. *Major use* of estrogen is for hormone replacement therapy (HRT) in post menopausal females. **Progesterone is added to HRT to decrease the risk of endometrial carcinoma.** Estrogens can reverse all the features of its deficiency.

- Another important use of estrogens is as a *component of oral contraceptives*.
- These can be used in the treatment of dysfunctional uterine bleeding (DUB), *if it is due to estrogen withdrawal*.
- Estrogens reduce testosterone production due to feed back inhibition of LH secretion. This property has been utilized for the treatment of *testosterone dependent tumors like prostatic carcinoma*. But now a days, GnRH agonists and antagonists are preferred for this indication.

Adverse effects and interactions

- Treatment with estrogen can result in *feminization, gynaecomastia and decreased libido in males and nausea, migraine and increased risk of carcinomas (endometrial and breast) in females*.
- *Diabetes, fluid retention, hepatic adenoma, cholelithiasis and predisposition to thromboembolism* can be seen in both the sexes.
- Increased incidence of *vaginal and cervical adenocarcinoma* was noted in the *female offsprings* of mothers who have taken *diethylstilbesterol (DES)* during first trimester of pregnancy. Intake of DES during pregnancy has also been associated with development of hypospadias in new born babies.
- Antimicrobials like *ampicillin* and enzyme inducers like *rifampicin* *decrease the effect of estrogen*; former by inhibiting enterohepatic cycling and latter by increasing the metabolism of estrogen.

Selective Estrogen Receptor Modulators (SERMs)

These are the agents that act as estrogen agonists in some tissues and antagonists in other tissues. *Agonistic action is beneficial in tissues like bone (decreased resorption) and blood (better lipid profile) whereas it is deleterious in endometrium, breast (increased risk of carcinoma) and liver (predisposition to thromboembolism).*



Progesterone is added to hormone replacement to decrease the risk of endometrial carcinoma.



Ospemifene is a new SERM indicated for dyspareunia due to menopause

- SERMs are targeted to provide beneficial effect of estrogen as well as to antagonize its adverse effects. **Clomiphene, tamoxifen, doloxifene, toremifene, fulvestrant, raloxifene, bazedoxifene, ospemifene and ormeloxifene** are now classified as SERMs.
- In humans **clomiphene** has *estrogen antagonistic action in hypothalamus* (reduces feedback inhibition of GnRH secretion). It is used for the treatment of **anovulatory infertility** by increasing GnRH release. Major adverse effect is *hyperstimulation syndrome (polycystic ovarian disease) and multiple pregnancy*.
- Tamoxifen, doloxifene and toremifene** possess estrogen antagonistic activity in the breast and blood whereas agonistic activity in bone, uterus and liver. Their major indication is in the treatment of **breast carcinoma**. *These have beneficial effect on bone and lipid profile but increase the risk of endometrial carcinoma and thromboembolism.*
- Raloxifene and bazedoxifene** are used for **osteoporosis**. Raloxifene also possesses beneficial effects on lipid profile, breast and endometrium. *Major adverse effect is increased predisposition to thromboembolism.*
- Selective tissue estrogen activity regulators (**STEAR**) are the compounds with estrogenic activity, tissue-selective mode of action and particular metabolism that regulates ligand levels. **Tibolone** belongs to this group. It is considered as a designer HRT and is used for preventing vasomotor symptoms and osteoporosis in menopause.
- Centchroman (ormeloxifene)** is used as a **non hormonal oral contraceptive (Saheli)**. It is also approved for the treatment of DUB.
- Fulvestrant** is the first FDA approved agent in the new class of drugs that are called **selective estrogen-receptor downregulators (SERDs)**. These have an *improved safety profile, faster onset, and longer duration of action than the SERMs* due to their pure ER antagonist activity. It was approved for postmenopausal women with **hormone receptor-positive metastatic breast cancer that has progressed despite antiestrogen therapy**. It binds to the estrogen receptor (ER) with an affinity more than 100 times that of tamoxifen, inhibits its dimerization, and increases its degradation. As a consequence of this ER "downregulation," ER-mediated transcription is abolished, completely suppressing the expression of estrogen-dependent genes. This difference in the activity of fulvestrant likely explains why fulvestrant **demonstrates efficacy against tamoxifen-resistant breast cancer**. Fulvestrant is administered *intramuscularly at monthly intervals*. Most common adverse effects of this drug include *nausea, asthenia, pain, vasodilation (hot flushes), and headache*.

Tamoxifen has
Beneficial effect on three B
Bone (↓ resorption)
Breast (↓ carcinoma)
Blood (↑ HDL & ↓ LDL)

Fulvestrant is a selective estrogen-receptor downregulator (SERD). It has *improved safety profile, faster onset, and longer duration of action than the SERMs* due to its pure ER antagonist activity.

Aromatase Inhibitors

Androgens are converted to estrogen in the peripheral tissue of post-menopausal females with the help of an enzyme, aromatase. The drugs inhibiting this enzyme will *decrease the formation of estrogen and are beneficial in the treatment of breast carcinoma*. Aromatase inhibitors are divided into first and second generation compounds. **First generation drugs include aminoglutethimide and second generation agents are letrozole, anastrozole, fadrozole, formestane, vorozole and exemestane**. These can also be classified as **steroidal or type I** (formestane, exemestane) and **nonsteroidal or type II** (letrozole, anastrozole, vorozole) inhibitors. *Type I are irreversible (suicide) whereas type II are reversible inhibitors of aromatase*. These are useful for the treatment of **tamoxifen resistant breast carcinoma**. Common side effects of these drugs include bone pain, hot flushes and thromboembolism.

Progestins

Progesterone is the most important progestin in humans. It is primarily secreted by corpus luteum. Synthetic progestins may be classified as:

Generation	Examples	Properties
1st Generation (Estranes)	Norethindrone Norethinodrel Lynestrenol	- Have weak estrogenic, androgenic and anabolic action - Potent antioviulatory properties
2nd Generation (Gonanes)	Norgestrel Levonorgestrel	- More potent than 1st generation - Have reduced androgenic activity - Levonorgestrel is more potent than norgestrel
3rd Generation	Desogestrel Norgestimate Gestodene	- Very potent - strong antioviulatory properties - Reduced androgenic effects; thus ↓ risk of acne ↓ hirsutism
4th Generation	Nomegestrol Drospirenone	- Weak anti-androgenic property - Less anti-ovulatory - Strong antiestrogenic effects on endometrium - Donot cause adverse effect on lipid profile or glucose tolerance Drospirenone possess aldosterone receptor antagonistic activity; preferred in woman who have fluid retention after taking OCPs

Actions

- Progesterone increases basal insulin levels and the insulin response to glucose.
- These can act as competitors of aldosterone causing decrease in Na⁺ reabsorption.
- Progesterone increases LDL and opposes beneficial effect of estrogen on lipid profile.
- It has depressant effect on the brain.
- It causes growth of breast tissue and also participates in LH surge.
- Progestins decrease the chances of endometrial carcinoma and are added to HRT to decrease this adverse effect of estrogens.**
- Third generation agents are also known as impeded androgens because they lack androgenic activity.

Uses

Major indications of progesterone are for **oral contraception** and **hormone replacement therapy**, for which these are combined with estrogens. Progestins are **added to decrease the risk of endometrial and ovarian carcinoma**. Progestins are also used for secondary amenorrhea, abnormal uterine bleeding, premature labour and luteal phase support to treat infertility.

Selective Progesterone Receptor Modulator (SPRM)

Mifepristone, onapristone, ulipristal and asoprisnil are the drugs affecting progesterone receptors.

- Mifepristone** is a SPRM with mainly antagonistic activity and some agonistic activity on progesterone receptors. It also has **glucocorticoid and androgen receptor blocking activity**. It has a long $t_{1/2}$ of 20 hours. Its uses are:
 - Medical termination of pregnancy:** Oral dose of 600 mg mifepristone with oral misoprostol (400 µg) effectively terminates pregnancy upto 49 days in 95% of patients. Most severe adverse effect is vaginal bleeding. *Recently, low dose mifepristone (200 mg) with oral misoprostol (800 µg) is indicated for termination of pregnancy upto 63 days.*
 - Single 600 mg dose is an effective **emergency contraceptive**.
 - It is recommended for treatment of **Cushing's syndrome** for patients with ectopic ACTH secretion or adrenal inoperable carcinoma who failed to respond to other treatments.
 - Other potential uses include **endometriosis, breast cancer, meningioma** (containing glucocorticoid or progesterone receptors), and **fibroids**.
- Onapristone** is a pure progesterone antagonist in contrast to mifepristone.

Contd...

M

Uses of mifepristone

- M** – Morning after pill
- I** – Induction of abortion
- F** – Fibroid
- E** – Endometriosis
- P** } Progesterone receptor
- R** } +ve breast cancer and meningioma
- I** } Increased Steroids
- S** } (Cushing)
- TONE**

Contd...

- **Ulipristal** acts as partial agonist on progesterone receptors. It does not block glucocorticoid receptors. It acts by inhibiting ovulation. A 30 mg dose is used as **emergency contraceptive** that can be taken within 120 hours (5 days) after unprotected intercourse. If taken within 72 hours, it is as effective as levonorgestrel whereas it is more effective than levonorgestrel if taken within 72-120 hours of unprotected intercourse. Most severe adverse are headache and abdominal pain.
- **Asoprisnil** is an investigational SPRM, tested for treatment of progesterone sensitive myomata. Clinical trials were discontinued due to endometrial changes in patients.

Hormonal Contraceptives

Hormonal contraceptives can be used *orally* (combined oral contraceptive or progestin only pills) or by implants.

COMBINED ORAL CONTRACEPTIVES

- These contain both estrogen and progestin. Most commonly used estrogen in combined OCPs is ethinyl estradiol. On the basis of amount of estrogen, combined OCPs can be classified as

Type of OCP	Amount of ethinyl estradiol
Standard dose	0.05 mg (50 µg)
Low dose	0.03 – 0.035 mg (30-35 µg)
Very low dose	0.02 mg (20 µg)

Chances of breast and cervical carcinoma are increased whereas endometrial and ovarian carcinomas are decreased by OCP use.

- Most commonly used progesterone in combined OCPs is levonorgestrel (LNG)
- Combined OCPs may be
 - *Monophasic*: Content of estrogen and progesterone remain same in all the pills (for 21 days).
 - *Biphasic*: Content of progesterone is different in pills for first 10 days and that for 11-21 days
 - *Triphasic*: Content of progesterone is gradually increased. It is lowest in first phase (1-6 days), moderate in second phase (7-11 days) and further increased in third phase (12-21 days).
- **Biphasic and triphasic pills** permit reduction in progesterone content without compromising efficacy. These pills **decrease the risk of breakthrough bleeding**.
- Main mechanism of combined OCPs is to cause **feedback inhibition of pituitary** (causing abolition of LH surge) *resulting in inhibition of ovulation*. Other mechanisms include *thickening of cervical mucus, decreased motility and secretions of the fallopian tubes and making endometrium unfavourable for implantation*.
- Combined OCPs are started on first day of menstrual cycle and given for 21 days. To allow withdrawal bleeding, iron tablets are given (without hormones) for next seven days.
- Ovulation returns within 3 months of stopping OCP use in 90% of cases
- OCPs are contraceptives of choice for
 - Newly married couples
 - After evacuation of molar pregnancy

Main mechanism

Combined OCP	Inhibit ovulation
Mini-pills	Cervical mucus thickening
Emergency Contraceptive	Inhibit implantation

PROGESTERONE ONLY PILLS (MINIPILLS)

- These contain low dose of progestin without any estrogen. These are less effective than combined OCPs.
- Minipills are preferred in women where estrogen is contra-indicated e.g.
 - Smokers
 - >35 years of age
 - Risk factors of thromboembolism
- Minipills are oral contraceptives of choice for

- Lactating women
- Sickle cell anemia
- Seizure disorder
- Progesterone only pills are given daily without any break.
- Thickening of cervical mucus is major mechanism of minipills.

	Estrogen (dose in μg)	Progesterone (dose in mg)	Trade name
1. Combined pills			
A. Monophasic			
Standard dose	EE (50)	Norgestrel (0.5)	
Low dose	EE (30)	Norgestrel (0.3)	MALA-D and MALA-N
Very low dose	EE (20)	Levonorgestrel (0.1)	
B. Biphasic			
Day 1-10	EE (35)	Norethindrone (0.5)	
Day 11-21	EE (35)	Norethindrone (1)	
C. Triphasic			
Day 1-6	EE (30)	Levonorgestrel (0.05)	
Day 7-11	EE (40)	Levonorgestrel (0.075)	
Day 12-21	EE (30)	Levonorgestrel (0.125)	
2. Mini pills		Norethindrone (0.35)	
		Norgestrel (0.75)	

PARENTERAL CONTRACEPTIVES

- These can be used in females with contra-indication to estrogens.
- Major problem with these methods is prolonged infertility after their use.
- Most common adverse effects of parenteral contraceptives is irregular bleeding.

Name	Drug	Route	Frequency	Special points
• DMPA	Medroxy progesterone acetate	i.m	once in 3 months	
• NET-EN	Norethindrone enanthate	i.m	once in 2 months	
• NORPLANT	Levonorgestrel	S.C. on upper arm	Replaced after 5 years	
• IMPLANON	3-keto desogestrel (Etonorgestrel)	S.C.	Replaced after 3 years	Most popular implant these days
• UNIPLANT	nomegestrol	S.C.	Replaced after 1 year	Single rod implant system
• CAPRANOR	Levonorgestrel	S.C.	Capsule begins to disappear after 1 year	Biodegradable implant

Adverse Effects

- Nausea, mastalgia, breakthrough bleeding and edema are related to the amount of estrogen in the preparation.
- Migraine is made worse with the use of OCPs.
- Failure of withdrawal bleeding is another important adverse effect.
- Breakthrough bleeding is the most common problem with the use of progesterone

- only pills.** Chances of this bleeding decrease with biphasic and triphasic pills.
- Weight gain can occur *with* the use of progestins containing androgenic properties. **Desogestrel and norgestimate cause less weight gain.**
 - **Acne and hirsutism may worsen by progestins containing androgenic properties.**
 - **Risk of venous thromboembolism**, MI and stroke is increased with the use of OCPs because estrogen increases the clotting factors (VII, VIII, IX and X) and decreases anticlotting factors (antithrombin III).
 - *Cholestatic jaundice, gall bladder disease and incidence of hepatic adenomas* are increased with OCP use.
 - Chances of **breast and cervical carcinoma** are **increased whereas endometrial and ovarian carcinomas** are **decreased** by OCP use. *Progesterone is responsible for decreasing the risk of these cancers.*

Biphasic and triphasic pills decrease the breakthrough bleeding without increasing the total hormone content.

Contraindications (According to WHO)

Absolute contraindications	Relative contraindications
1. Coronary artery diseases, cerebrovascular accident, deep vein thrombosis or pulmonary embolism or history of these.	1. Postpartum < 21 days.
2. Structural heart disease complicated by pulmonary hypertension, atrial fibrillation or history of subacute bacterial endocarditis.	2. Lactation (6 weeks to 6 months).
3. Diabetes mellitus with nephropathy, neuropathy, retinopathy or any other vascular complication.	3. Undiagnosed abnormal vaginal or uterine bleeding.
4. Diabetes mellitus of more than 20 year duration.	4. Migraine without aura.
5. Breast cancer.	5. Diabetes mellitus without vascular disease.
6. Pregnancy	6. Controlled hypertension.
7. Lactation (<6 weeks postpartum)	7. Age above 35 years and light smoker (<20 cigarettes per day)
8. Known hepatic adenoma or carcinoma or history of these.	8. Past h/o breast carcinoma but no evidence of recurrence for 5 years
9. Active viral hepatitis or severe cirrhosis.	9. Gall Bladder disease (medically treated and current biliary tract disease)
10. Major surgery with prolonged immobilization	10. Use of drugs that affect liver enzymes like rifampicin and anticonvulsants
11. Any surgery on legs.	
12. >35 years old and heavy smoker (> 20 cigarettes per day).	
13. Uncontrolled hypertension (> 160/100 mmHg) or with vascular disease.	
14. Migraine with aura or headache with focal neurological symptoms	

M

Non-contraceptive benefits of OCP

Decrease risk of:

Other – Ovarian cyst
B – Benign breast disease
E – Ectopic pregnancy
N – Neoplasia (Ovarian, Endometrial, Colon cancer)
E – Endometriosis
F – Fibroid
I – Iron deficiency anemia
T – Tension (Pre-menstrual tension syndrome)
S – Skeletal (RA and Osteoporosis)

Non-Contraceptive Benefits of OCPs

- Reduction in endometrial cancer by 50% (when used for at least 12 months, greatest benefit with > 3 years use).
- Reduction in ovarian cancer by 40%, most notable after 3 years, use, but present after

as little as 3-6 months of use.

- Reduction in benign breast disease.
- Reduction in blood loss, anemia, and dysmenorrhea.
- Protection against pelvic inflammatory disease.
- Decreased risk of ectopic pregnancy.
- Possible reduction in risk of colon cancer.
- Possible decrease in uterine leiomyoma.
- Reduction in acne.
- Possible protection against rheumatoid arthritis.
- Protection against osteoporosis.

EMERGENCY CONTRACEPTIVES

Method	Use within time of unprotected intercourse	Dose and Duration	Failure	Comments
1. Levonorgestrel (LNG)	72 hours	1.5 mg (oral) single dose	1%	Can be used upto 120 hours however less efficacious
2. OC pills	72 hours	2 tablets followed by another 2 within 12 hours	3%	
3. Mifepristone	72 hours	600 mg oral single dose	1%	
4. Ulipristal	120 hours	30 mg oral single dose	–	More effective than LNG if used between 72-120 hours
5. IUD	5 days	–	–	

Androgens

Most important androgens are *testosterone* and *dihydrotestosterone (DHT)*. Less potent androgens include androstenidione and dehydroepiandrostenidione (DHEA). **Testosterone is converted to DHT by 5- α reductase and to estradiol by aromatase.**

Actions

Actions of DHT	Actions of testosterone	Actions of both testosterone and DHT
• Development and maturation of external genitalia (scrotum, penis, urethra etc.) in male	F – Feedback inhibition of LH I – Internal genitalia development S – Spermatogenesis H – Hematopoiesis	• Increase in mass and strength of skeletal muscle and bone • Epiphyseal fusion
• Male behaviour and changes of puberty		
• Growth and hypertrophy of prostate in the elderly.		
• Growth of hair follicles (pubic, axillary and beard) during puberty		
• Loss of scalp hair in adults.		
• Activation of sebaceous glands.		

Most of the actions of androgens are mediated by DHT whereas testosterone is itself active at few sites.

Pharmacokinetics

Testosterone is inactive orally due to high first pass metabolism. **17-alkylated derivatives like methyltestosterone and fluoxymestrane are effective orally.**

Uses

- Long acting derivatives like testosterone enanthate (i.m.) are indicated for *hypogonadal men* to compensate for the decreased endogenous secretion. Long term oral therapy is associated with liver adenomas and carcinomas. It can also be administered by *transdermal route*. *Polycythemia and hypertension* (due to erythropoietic action) may be a problem.
- These can also be used to *reduce breast engorgement* during postpartum period.
- Sometimes, these are used for *chemotherapy of breast tumors* in premenopausal females.
- These are frequently *abused by athletes* due to their anabolic properties.
- These agents have been used to *stimulate growth in boys with delayed puberty*.
- Androgens have been used in the *treatment of osteoporosis*.

Adverse Effects

- *Masculinising* actions (hirsutism, amenorrhoea, clitoral enlargement and deepening of voice) in females.
- *Increased risk of atherosclerosis* due to decrease in HDL and increase in LDL cholesterol.
- Use of androgens during pregnancy may result in masculinization of the female fetus and under-masculinization of the male fetus.
- *Sodium retention and edema* can occur rarely, so caution is advised in patients with heart and kidney disease.
- 17-alkyl substituted compounds (**methyltestosterone and fluoxymestrane**) are more likely to cause **cholestatic jaundice and peliosis hepatica**.
- Increased chances of *acne, erythrocytosis, gynaecomastia and azoospermia*.
- Androgens are contraindicated in pregnant females, infants, carcinoma of the male breast and prostate and patients with cardiac and renal diseases.

DANAZOL

It is a compound with **weak androgenic, progestational and glucocorticoid activities**. It decreases the secretion of gonadotropins from the pituitary by causing feedback inhibition. Its major use is in the **treatment of endometriosis**. Other uses include fibrocystic disease of breast, hemophilia, Christmas disease, ITP and angioneurotic edema. *Weight gain, edema, acne, increased hair growth, hot flushes and changes in libido are the major adverse effects* of this drug. *It can also produce mild to moderate hepatocellular damage.*

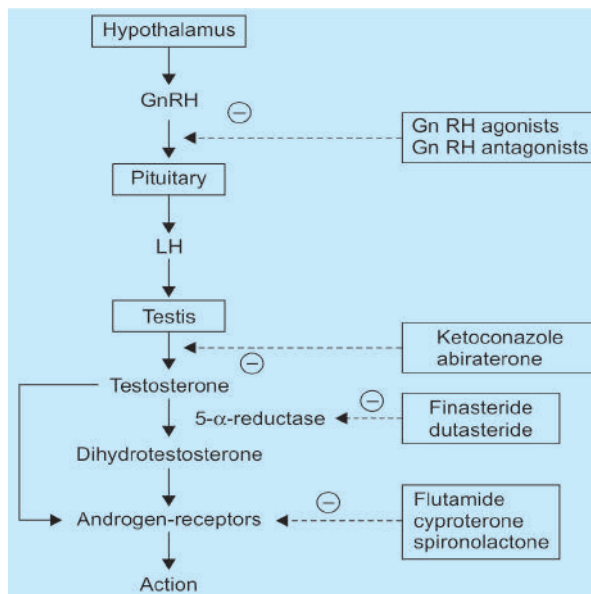
Danazol is a compound with **weak androgenic, progestational and glucocorticoid activities**. It decreases the secretion of gonadotropins from the pituitary by causing feedback inhibition. Its major use is in the **treatment of endometriosis**.

Anti-Androgens

Drugs in this group can act by **inhibiting the synthesis, activation or action of androgens**.

- **Steroid synthesis inhibitors:** **Ketoconazole** inhibits the synthesis of adrenal and gonadal hormones but its usefulness in the treatment of prostatic carcinoma is limited by serious toxicity on prolonged use. It can cause *gynaecomastia* due to increase in estradiol: testosterone ratio. **Abiraterone** is an *orally active prodrug* that acts by inhibiting 17- α -hydroxylase and 17, 20-lyase. It reduces the synthesis of cortisol and androgens, and is approved for castration resistant refractory *prostate cancer*.
- **5- α reductase inhibitors:** Most of the actions of testosterone are mediated by its conversion to DHT by 5- α reductase. Important amongst these are growth of prostate, male pattern baldness and hirsutism in females. **Finasteride and dutasteride** are 5- α reductase inhibitors useful in the *treatment of BHP, male pattern baldness and hirsutism* by reducing the production of DHT.

- **Androgen receptor inhibitors:** Cyproterone and cyproterone acetate act as antagonists of androgen receptors. Latter compound has marked progestational activity that inhibits feedback enhancement of LH and FSH. These drugs are useful in the **treatment of hirsutism** and as a component of **contraceptive pills**. **Flutamide, bicalutamide, enzalutamide and nilutamide** are other anti-androgens that act by same mechanism. These are useful for the treatment of *prostatic carcinoma*. *Flutamide can cause gynecomastia and reversible liver damage*. These drugs can also be combined with GnRH agonists (like leuprolide) to reduce the initial flare up reaction.
- **Spironolactone:** It is an aldosterone antagonist that also competes with DHT for its receptor. It can be used for the *treatment of hirsutism*.



UTERINE STIMULANTS

These drugs increase uterine contractions and are known as **oxytocics or ecbolics**.

Oxytocin

It is secreted by *posterior pituitary* along with ADH. It *increases the uterine contractions with complete relaxation in between*. It *increases the contraction of upper segment (fundus and body) of uterus whereas lower segment is relaxed* facilitating the expulsion of the fetus. *Estrogen increases whereas progesterone decreases the sensitivity of uterus to oxytocin*.

- Oxytocin is involved in milk ejection reflex whereas prolactin causes milk secretion.
- High doses of oxytocin cause fall in BP (due to *vasodilation*) resulting in reflex tachycardia.
- It also has ADH like action in high dose and can result in fluid retention.

Uses

It is used for the **induction of labor** in post-maturity and uterine inertia. It can also be used for the *treatment of postpartum hemorrhage* but **methyergometrine is preferred** for this indication. *Oxytocin challenge test* is performed to know the adequacy of uteroplacental circulation in high risk pregnancies.

Adverse effects

Injudicious use may result in *rupture of uterus* due to powerful uterine contractions. It may also cause *water intoxication* due to ADH like action. Oxytocin **should not be used** in cases of *contracted pelvis, obstructed labour, malpresentation, history of LSCS, hypovolemic states and cardiac disease*.

Ergot Derivatives

Ergometrine is derived from *Claviceps purpurea* and is used as an oxytocic agent. It produces uterine contractions in the upper as well as lower segment and is used to control postpartum hemorrhage. Its derivative, **methylergometrine** is more potent oxytocic and is preferred for this indication. Latter is administered at the delivery of anterior shoulder. These drugs are preferred over oxytocin for this indication. Hypertension and sepsis are contraindications for their use.

UTERINE RELAXANTS

These drugs decrease uterine contractions and are known as **tocolytics**. These are mainly used to delay labour when premature contractions are present.

BETA AGONISTS

Ritodrine, **isoxsuprine** and **terbutaline** are the selective β_2 agonists useful as tocolytic agents. These drugs should not be used in mother having heart disease or diabetes mellitus. **Pulmonary edema** is a serious complication of these drugs at high doses. β_2 agonists can also produce tachycardia, palpitations, tremors, hyperglycemia and hypokalemia.

MAGNESIUM SULPHATE

It is mainly used to control convulsions in eclampsia. It also possesses tocolytic activity and can be used. It is preferred over β_2 agonists in patients with cardiac problems, diabetes, hyperthyroidism and hypertension. Toxicity is manifested initially as loss of patellar reflex followed by respiratory depression and finally cardiac arrhythmias and arrest. Magnesium sulphate by i.v. or inhalational route has also been utilized in the treatment of acute severe asthma.

OTHER DRUGS

Calcium channel blockers like nifedipine and **oxytocin antagonist 'atosiban'** can also be used to delay premature labour. Ethyl alcohol (i.v. infusion), NSAIDs and progesterone also suppress uterine contractions but are rarely used for this indication. 'Halothane' is an efficacious tocolytic agent and is the anaesthetic of choice for version (external or internal). **Hydroxyprogesterone** has been used prophylactically to prevent pre-term labour; however, teratogenic potential limits its use. Calcium channel blockers and atosiban provides the best balance of successful delayed delivery with lesser risk to mother and baby.



Toxicity of magnesium sulfate manifests initially as loss of patellar reflex followed by respiratory depression and finally cardiac arrhythmias and arrest.

DRUG OF CHOICE	
Condition	Drug
• Infantile spasms	ACTH
• Hypothyroidism	Levo-thyroxine
• Myxedema coma	Levo-thyroxine
• Hyperthyroidism	Carbimazole or methimazole
– In lactation	Propylthiouracil
– In 1st trimester of pregnancy	Propylthiouracil
– In 2nd and 3rd trimester of pregnancy	Carbimazole or methimazole
– Graves' ophthalmopathy	Methylprednisolone
• Thyroid storm	Propanolol (life saving)+ Iodides
• Diabetes mellitus	
Type 1 (IDDM)	Insulin
Type 2 (NIDDM)	Metformin
– In obese	Metformin
– Uncontrolled	Insulin
– Pregnancy	Insulin
– To tide over stress	Insulin
• Diabetic ketoacidosis	Insulin (Regular)
• Post prandial hyperglycemia	Nateglinide
• Acute hyperkalemia	Calcium gluconate
• Beta blocker poisoning	Glucagon
• Hypoglycemia	Glucose (oral or i.v.)
• Adrenal insufficiency	
– Acute	Hydrocortisone
– Chronic (Addison's disease)	Hydrocortisone
• Erectile dysfunction	Sildenafil
• Contraceptive	
– Newly married	Combined oral contraceptives
– In lactation	Mini pills
– Emergency contraceptive	Levonorgestrel
• Anovulatory infertility	Clomiphene
• Osteoporosis	
– Post menopausal	Alendronate
– Steroid-induced	Alendronate
– In women with risk factors for breast cancer	Raloxifene
• Hypercalcemia of malignancy	Bisphosphonates
• Paget's disease of bone	Bisphosphonates
• Tetany	Calcium
• Induction of labour	Oxytocin
• Post partum hemorrhage	Oxytocin
• Acromegaly	Cabergoline
• Esophageal varices	Terlipressin (if not available, octreotide)

Contd...

Contd...

• Hyperprolactinemia	Cabergoline
• Androgenital alopecia	Finasteride
• Dysfunctional uterine bleeding	
– Light bleeding	Medroxyprogesterone acetate
– Heavy bleeding	Combined oral contraceptives
– Intractable bleeding	Leuprolide
• Endometriosis	Combined oral contraceptives
• Ectopic pregnancy	Methotrexate

MULTIPLE CHOICE QUESTIONS

PITUITARY AND HYPOTHALAMUS

- Which of the following is not an adverse effect of growth hormone therapy? (AIIMS May 2012)
 - Carpal tunnel syndrome
 - Hypoglycemia
 - Intracranial hypertension
 - Slipped femoral epiphysis
- Which of the following is used in the treatment of hyperprolactinemia? (AIIMS May 2012)
 - Cimetidine
 - Methysergide
 - Bromocriptine
 - Ondansetron
- A 22 year old female, Neeta presented to you with complaints of headache and vomiting since 2 months. She is having amenorrhea but urine pregnancy test is negative. She also complained of secretion of milk from the breasts. A provisional diagnosis of hyperprolactinemia was made and MRI was suggested. MRI confirmed the presence of a large pituitary adenoma. Neeta was advised surgery, however, she is not willing to undergo surgery. Which of the following medications is most likely to be prescribed? (AI 2011)
 - Sumatriptan
 - Bromocriptine
 - Ergotamine
 - Allopurinol
- Ocaterotide is used in all except: (AIIMS May 2011)
 - Glucagonoma
 - Insulinoma
 - Carcinoid syndrome
 - Glioma
- All of the following statements about octreotide are true EXCEPT: (AI 2007)
 - It is effective orally
 - It is used for the treatment of acromegaly
 - It can be used for the management of secretory diarrhoea
 - It can be used in portal hypertension
- Octreotide is useful in esophageal varices. It is a synthetic analogue of somatostatin. The true statement regarding this drug is:
 - It can be given orally
 - It is longer acting than somatostatin
 - Its major adverse effect is secretory diarrhea
 - All of the above
- All of the following agents are useful in acromegaly EXCEPT:
 - Bromocriptine
 - Somatostatin
 - Octreotide
 - Nafarelin
- Mechanism of action of bromocriptine is:
 - Agonism at D_2 receptors
 - Antagonism at D_2 receptors
 - Antagonism at D_1 receptors
 - Antagonism at α receptors
- Important difference between leuprolide and ganirelix is that ganirelix:
 - Can be given orally
 - Immediately reduces gonadotropin secretion
 - Must be given in a pulsatile fashion
 - Initially stimulates release of LH and FSH
- Which of the following drugs DO NOT cause hyperprolactinemia?
 - Bromocriptine
 - Haloperidol
 - Reserpine
 - Chlorpromazine
- A young female, Rama with amenorrhea, infertility and galactorrhoea was treated with a drug that successfully restored ovulation and menstruation. Before being given the drug, the woman was carefully questioned about previous mental health problems, which she did not have. She was advised to take the drug orally. The drug used to treat this patient was probably:
 - Bromocriptine
 - Desmopressin
 - Human gonadotropin hormone
 - Leuprolide
- A 47-year old male, Kishore exhibited signs and symptoms of acromegaly. Radiologic studies showed the presence of a large pituitary tumor. Surgical treatment of the tumor was only partially effective in controlling the disease. At this point, which of the following drugs is most likely to be used as pharmacological therapy?
 - Desmopressin
 - Leuprolide
 - Octreotide
 - Somatropin
- A 7-year old boy, Manoj underwent successful chemotherapy and cranial radiation for the treatment of acute lymphocytic leukemia. One month after the

completion of therapy, the patient presented with excessive thirst and urination plus hypernatremia. Laboratory testing revealed pituitary diabetes insipidus. To correct these problems, this patient is likely to be treated with:

- (a) Corticotropin
- (b) Desmopressin
- (c) hCG
- (d) Menotropins

14. Long acting dopamine agonist is: (TN 2007)

- (a) Bromocriptine
- (b) Lisuride
- (c) Cabergoline
- (d) Apomorphine

15. Bromocriptine is useful in all except: (RJ 2001)

- (a) Parkinsonism
- (b) Prolactinoma
- (c) Endogenous depression
- (d) Infertility

16. Drugs used for treatment of acute variceal bleeding are all except: (MH 2000)

- (a) Octreotide
- (b) Somatostatin
- (c) Desmopressin
- (d) Terlipressin

17. GnRH analogue used in hormonal treatment of carcinoma prostate is? (MH 2007)

- (a) Goserelin
- (b) Nilutamide
- (c) Cyproterone acetate
- (d) Finasteride

18. Which of the following is given at intervals as a pulsatile therapy? (AP 1997) (MH 2007)

- (a) GnRH
- (b) GH
- (c) FSH
- (d) Estrogen

19. True regarding use of bromocriptine for suppression of lactation includes: (Kolkata 2007)

- (a) It can cause deep vein thrombosis
- (b) It can cause hypotension
- (c) Metoclopramide potentiates the action of bromocriptine
- (d) It is given for 1 week only

20. The clinical use of leuprolide include all the following EXCEPT: (Karnataka 2008)

- (a) Endometriosis
- (b) Osteoporosis
- (c) Prostate cancer
- (d) Precocious puberty

THYROID

21. Which of the following statements about iodine is false? (AIIMS Nov 2013)

- (a) Contraindicated in hyperthyroidism
- (b) Causes iodism
- (c) Inhibits the release of thyroxine
- (d) Inhibits the synthesis of iodo thyroxine and iodo thyronine

22. Conversion of T_4 to T_3 is inhibited by all except: (AIIMS Nov 2011)

- (a) Propanolol
- (b) Propylthiouracil
- (c) Amiodarone
- (d) Methimazole

23. A pregnant female is taking carbimazole. Which of the following is not seen in the neonate? (AIIMS May, 2007)

- (a) Choanal atresia
- (b) Scalp defects
- (c) Cleft lip/palate
- (d) Fetal goiter

24. The drug of choice for the treatment of thyrotoxicosis during pregnancy is: (AIIMS Nov, 2003)

- (a) Carbimazole
- (b) Iodine therapy
- (c) Propylthiouracil
- (d) Methimazole

25. The antithyroid drug with the most rapid onset of antithyroid action is:

- (a) I^{131}
- (b) Sodium iodide
- (c) Methimazole
- (d) Propylthiouracil

26. Triiodothyronine (T_3) as compared to T_4 :

- (a) Is more plasma protein bound
- (b) Is shorter acting
- (c) Is less potent
- (d) Has delayed action

27. Mechanism of action of propylthiouracil in hyperthyroidism is:

- (a) Inhibition of organification of iodine
- (b) Inhibition of oxidation of iodine
- (c) Inhibition of coupling of two DIT residues
- (d) All of the above

28. Which of the following drugs inhibit 5'-deiodinase?

- (a) Propylthiouracil
- (b) Methimazole
- (c) Lugol's iodine
- (d) Radioactive iodine

29. Carbimazole as compared to propylthiouracil:

- (a) Is less potent
- (b) Is shorter acting

- (c) Does not produce an active metabolite
- (d) Does not inhibit peripheral conversion of T_4 to T_3

30. Fastest acting anti-thyroid drug is:

- (a) Lugol's iodine
- (b) Radioactive iodine
- (c) Propylthiouracil
- (d) Sodium thiocyanate

31. The physical half life of radioactive I^{131} is:

- (a) 8 hrs
- (b) 8 days
- (c) 16 days
- (d) 60 days

32. Beta blockers are used in hyperthyroidism:

- (a) As short term symptomatic therapy till effect of carbimazole develops
- (b) As long term therapy after subtotal thyroidectomy
- (c) In patient not responding to carbimazole
- (d) To potentiate the effect of radioactive iodine

33. I^{131} is the preferred treatment for:

- (a) Children
- (b) Young adults with recent onset Graves' disease
- (c) Elderly patients with ischemic heart disease
- (d) Pregnant women

34. In the treatment of hypothyroidism, thyroxine is preferred over liothyronine because thyroxine:

- (a) Is faster acting
- (b) Has higher affinity for thyroid hormone receptors
- (c) Has a longer half life
- (d) Can be made more easily by recombinant DNA technology

35. A pregnant female Salma with thyrotoxicosis is planned for surgery. Before surgery can be done, her gland should be reduced in size and vascularity by administering:

- (a) Iodide ion
- (b) Propanolol
- (c) Propylthiouracil
- (d) Radioactive iodine

36. Manish, a patient of hypothyroidism was prescribed lthyroxine. Which of the following is the most reliable guide for adjustment of thyroxine dose in him?

- (a) Pulse rate
- (b) Body weight
- (c) Serum thyroxine level
- (d) Serum TSH level

37. Which of the following is not used in the management of thyroid storm? (DPG 2010)

- (a) Potassium iodide
- (b) Reserpine
- (c) Propanolol
- (d) Calcium channel blockers

38. Plasma half life of carbimazole is: (DPG 2006)

- (a) 4 hours
- (b) 8 hours
- (c) 16 hours
- (d) 24 hours

39. All are antithyroid drugs except: (UP 2006)

- (a) Propylthiouracil
- (b) Methimazole
- (c) Carbimazole
- (d) Carbamazepine

40. L-Thyroxine is used in: (UP 2006)

- (a) Thyroid storm
- (b) Cretinism
- (c) Endemic goiter
- (d) Grave's disease

41. Safest treatment of hyperthyroidism in pregnant women is: (Karnataka 2004, SGPGI 2002, MH 2002)

- (a) Radioactive iodine
- (b) Methimazole
- (c) Carbimazole
- (d) Propylthiouracil

42. All are causing hypothyroidism except: (Bihar 2005)

- (a) PAS
- (b) Captopril
- (c) Lithium
- (d) Amiodarone

43. Conversion of T_4 to T_3 inhibition is associated with:

- (a) Propylthiouracil (AP 2001)
- (b) Ampicillin
- (c) Lithium
- (d) Carbimazole

PANCREAS AND DIABETES MELLITUS

44. Which of the following anti-diabetic drugs can cause vitamin B_{12} deficiency? (AI 2012)

- (a) Glipizide
- (b) Acarbose
- (c) Metformin
- (d) Pioglitazone

45. Which of the following drugs does not cause hypoglycemia: (AIIMS May 2011)

- (a) Acarbose
- (b) Insulin
- (c) Glimepride
- (d) Nateglinide

46. A patient is receiving insulin and acarbose for diabetes mellitus and developed hypoglycemia. Which of the following should be used for treatment of hypoglycemia in this patient? (AIIMS May 2011)

- (a) Sucrose
- (b) Galactose

- (c) Glucose
(d) Starch
47. True about pioglitazone are all except: *(AIIMS May 2011)*
- (a) Metabolized in the liver by CYP3A4
(b) Selective agonist for the nuclear peroxisome proliferator activated receptor gamma
(c) It causes transcription of gene for carbohydrate and fat metabolism in the absence of insulin
(d) It should be avoided in a patient with cardio-vascular disease
48. All of the statements about exenatide are true except: *(AIIMS May 2011)*
- (a) It is a GLP -1 analogue
(b) It can be used for treatment of Type 1 diabetes mellitus
(c) It is given subcutaneously
(d) It decreases glucagon
49. All of the following statements about nateglinide are true except? *(AI 2011)*
- (a) Decreases post-prandial hyperglycemia
(b) Hypoglycemia is less common than with sulfonylureas
(c) It decreases insulin resistance
(d) It acts by releasing insulin
50. Insulin causes all of the following except: *(AIIMS May, 2010)*
- (a) Glycogenesis
(b) Glycolysis
(c) Lipogenesis
(d) Ketogenesis
51. What will happen if insulin alone is given rapidly in Diabetic Ketoacidosis? *(AI 2009) (AIIMS May, 2010)*
- (a) Hypokalemia
(b) Hyponatremia
(c) Hyperkalemia
(d) Hypocalcemia
52. Which of the following statements regarding acarbose is FALSE? *(DNB 2008, AIIMS Nov, 2008)*
- (a) It acts by inhibiting the enzyme alpha-glucosidase
(b) It reduces post-prandial hyperglycemia
(c) It decreases the progression of impaired glucose tolerance to overt diabetes mellitus
(d) It can cause hypoglycemia
53. All of the following preparations of insulin are rapid and short acting EXCEPT: *(AI 2007)*
- (a) Lispro
(b) Aspart
(c) Glargine
(d) NPH
54. Which of the following statements about biguanides is NOT true? *(AI 2004)*
- (a) Do not stimulate insulin release
(b) Decrease hepatic glucose production
(c) Renal dysfunction is not a contraindication for their use
(d) Can be combined with sulfonylureas
55. All the following statements about alpha-glucosidase inhibitors are true EXCEPT: *(AI 2004)*
- (a) Reduces intestinal absorption of carbohydrates
(b) Effective in both type 1 and 2 diabetes
(c) Hypoglycemia is a common and serious side effect
(d) Can be used with other oral hypoglycemic agents
56. If a diabetic patient being treated with an oral hypoglycemic agent develops dilutional hyponatremia, which one of the following could be responsible for this effect? *(AIIMS Nov, 2003)*
- (a) Chlorpropamide
(b) Tolbutamide
(c) Glyburide
(d) Glimepiride
57. All of the following are true about metformin EXCEPT: *(AIIMS May, 2002)*
- (a) Causes little or no hypoglycemia in non diabetic patients
(b) Acts by increased insulin secretion
(c) Increases peripheral utilization of glucose and decreases absorption of glucose from intestine
(d) When given with alcohol, increases risk of lactic acidosis
58. True about lispro-insulin is: *(PGI Dec 2004)*
- (a) Action is faster and short in duration than regular insulin
(b) It is given 15 minutes prior to meal
(c) Source is lamb
(d) Action is faster and of longer duration than regular insulin
59. Antidiabetic drugs that can be used safely in renal failure are: *(PGI Dec 2002)*
- (a) Metformin
(b) Glimepiride
(c) Phenformin
(d) Rosiglitazone
(e) Repaglinide
60. The most likely complication of insulin therapy in ketoacidosis is:
- (a) Dilutional hyponatremia
(b) Hypoglycemia
(c) Increased bleeding tendency
(d) Pancreatitis
61. Which of the following drugs promotes the release of endogenous insulin?
- (a) Acarbose
(b) Glipizide
(c) Metformin
(d) Pioglitazone

62. Which of the following drugs is taken during the first part of the meal for the purpose of delaying absorption of dietary carbohydrates?
- Acarbose
 - Glipizide
 - Nateglinide
 - Pioglitazone
63. Which of the following patients is most likely to be treated with intravenous glucagon?
- A young man who took cocaine and has a blood pressure of 190/110 mm Hg
 - A middle aged man with type II diabetes who has not taken his regular dose of glipizide for last 4 days
 - An old man with severe bradycardia and hypotension resulting from ingestion of overdose of atenolol
 - An old woman with lactic acidosis as a complication of severe infection and shock
64. Insulin acts by stimulation of:
- Ionotropic receptor
 - Enzymatic receptor
 - Metabotropic receptor
 - Nuclear receptor
65. The most common route of administration of insulin is:
- Intradermal
 - Subcutaneous
 - Intramuscular
 - Intravenous
66. Human insulin as compared to pork/beef insulin is:
- More potent
 - Rapidly absorbed
 - Longer acting
 - More antigenic
67. Glipizide differs from chlorpropamide in that it:
- Is more potent
 - Is longer acting
 - Does not lower blood sugar in nondiabetic subjects
 - Is less prone to cause hypoglycemic reaction
68. Which of the following characteristics make metformin a preferred biguanide than phenformin?
- It is more potent
 - It is less liable to cause lactic acidosis
 - It does not interfere with vitamin B₁₂ absorption
 - It is not contraindicated in patients with kidney disease
69. Glibenclamide reduces blood glucose in all of the following EXCEPT:
- Non diabetics
 - Type 1 diabetics
 - Type 2 diabetics
 - Obese diabetics
70. Glibenclamide is preferred over chlorpropamide in the treatment of DM because the latter is more likely to cause:
- Hypoglycemia
 - Alcohol intolerance
 - Cholestatic jaundice
 - All of the above
71. Metformin is NOT effective in lowering of blood sugar level in which of the following patients?
- Non diabetics
 - Obese diabetics
 - Type 2 diabetics
 - Diabetics not responding to sulfonylureas
72. Which of the following statements about nateglinide is TRUE?
- It is a long acting oral hypoglycemic drug
 - Taken just before a meal, it limits post prandial hyperglycemia in type 2 diabetes mellitus
 - It lowers blood glucose in both type 1 and type 2 diabetes mellitus
 - It acts by opening K⁺ channels in myocytes and adipocytes
73. The correct statement regarding the present status of oral hypoglycemics in diabetes mellitus is:
- They are the first choice drug in all cases
 - They should be prescribed only if the patient refuse insulin injections
 - They are used in type 1 diabetes mellitus
 - They are used first in most cases of uncomplicated mild to moderate type 2 diabetes
74. Which of the following drugs is most likely to cause hypoglycemia when used as a monotherapy in the treatment of type 2 diabetes?
- Acarbose
 - Glipizide
 - Metformin
 - Rosiglitazone
75. A 15 year old girl with type 1 diabetes is brought to emergency complaining of dizziness. Laboratory findings include severe hyperglycemia, ketoacidosis and blood pH of 7.15. To achieve rapid control of severe ketoacidosis, appropriate drug is:
- Crystalline zinc insulin
 - NPH insulin
 - Tolbutamide
 - Ultra lente insulin
76. A 54-year old obese patient with type 2 diabetes mellitus and a history of alcoholism probably should not receive metformin because it can increase the risk of:
- Disulfiram like reaction
 - Hypoglycemia
 - Lactic acidosis
 - Severe hepatic toxicity
77. Insulin causes:
- Na⁺ entry into cells
 - K⁺ exit from cells

(DPG 2010)

- (c) Na^+ exit/ K^+ entry
(d) K^+ entry into cells
78. Indications of newer insulins include all EXCEPT: (DPG 2008)
(a) Insulin resistance
(b) Lipodystrophy
(c) Pregnancy
(d) Diabetic kidney disease
79. Which of the following is not used for the treatment of insulin induced hypoglycemia? (DPG 2007)
(a) Intravenous glucose
(b) Glucagon
(c) Adrenaline
(d) Oral carbohydrates
80. Sulfonylureas act by: (DPG 2006)
(a) Decreasing glucagon secretion from pancreas
(b) Decreasing insulin secretion from pancreas
(c) Increasing gluconeogenesis
(d) Increasing insulin secretion from pancreas
81. Flushing is common in patient taking which of the following oral hypoglycemic drug with alcohol: (DPG 2005)
(a) Chlorpromamide
(b) Phenformin
(c) Glibenclamide
(d) Tolazamide
82. Anti-diabetic effect of sulfonylureas is by reducing: (MPPG 2002)
(a) Glucagon production
(b) Insulin secretion
(c) Tissue sensitivity to insulin
(d) Tissue sensitivity to glycogen
83. Lactic acidosis is common in: (UP 2005)
(a) Metformin
(b) Phenformin
(c) Repaglinide
(d) Rosiglitazone
84. Tolbutamide acts by increasing: (All India 1993)(TN 2000)
(a) Insulin receptors
(b) Glucose entry
(c) Glucose absorption
(d) Insulin secretion
85. Adverse effects of insulin include all of the following except: (TN 2004, DNB 2002 & 2005)
(a) Edema
(b) Hyperglycaemia
(c) Lipodystrophy
(d) Allergy
86. Long acting insulin is: (RJ 2000)
(a) Lente
(b) Semilente
(c) Ultralente
(d) Lispro insulin
87. 2nd generation sulfonylurea drugs are all except: (RJ 2005)
(a) Glipizide
(b) Gliclazide
(c) Tolbutamide
(d) Glibenclamide
88. Monocomponent insulin has all the following advantages except: (MH 2003)
(a) Can be used in pregnancy
(b) Less hypoglycemic episodes
(c) Longer duration of action
(d) Less chances of lipodystrophy
89. Which of the following drug is alpha-glucosidase inhibitor? (MH 2005)
(a) Pioglitazone
(b) Miglitol
(c) Metformin
(d) Nateglinide
90. Monotherapy with which of the following antidiabetic drug can cause hypoglycemia? (MH 2007)
(a) Metformin
(b) Glibenclamide
(c) Pioglitazone
(d) All of the above
91. Insulin having longest duration of action is: (Bihar 2004)
(a) Isophane insulin
(b) Protamine zinc insulin
(c) Insulin zinc suspension
(d) Plain insulin
92. Which of the following is not a starting criteria for sulfonylurea therapy? (Bihar 2004)
(a) Total pancreatectomy
(b) NIDDM
(c) Diabetes after 60 years
(d) None
93. Oral hypoglycemic drug that is less likely to cause hypoglycemia is: (Kolkata 2008)
(a) Repaglinide
(b) Gliclazide
(c) Rosiglitazone
(d) Glimipiride
94. All of the following are true regarding chlorpropamide except: (Kolkata 2005)
(a) It is short acting
(b) It can cause hypoglycemia in elderly
(c) Causes weight gain
(d) Associated with alcoholic flush
95. Common side effect of thiazolidinediones is: (Kolkata 2006)
(a) Dysguesia
(b) Hypoglycemia
(c) Water retention with weight gain
(d) Anemia
96. Long acting insulin preparations are frequently administered by: (Karnataka 2002)
(a) Oral route
(b) Intramuscular route
(c) Intradermal route
(d) Subcutaneous route

CORTICOSTEROIDS

97. **Drug of choice for pregnant female suspected of having a baby with congenital adrenal hyperplasia is:** (AIIMS Nov 2011)
 (a) Dexamethasone
 (b) Betamethasone
 (c) Hydrocortisone
 (d) Prednisolone
98. **Mineralocorticoid receptors are present in all except:** (AI 2011) (AIIMS Nov 2008)
 (a) Hippocampus
 (b) Colon
 (c) Liver
 (d) Kidney
99. **Hyperaldosteronism causes all except:** (AI 2009) (AIIMS May, 2010)
 (a) Hyponatremia
 (b) Hypokalemia
 (c) Hypertension
 (d) Metabolic acidosis
100. **Which of the following is an indication for the use of corticosteroids?** (DPG 2011)
 (a) Psychosis
 (b) Herpes simplex
 (c) Loeffler's syndrome
 (d) Subacute thyroiditis
101. **At same concentration of steroid which of the following is most potent?** (AI 2010)
 (a) Ointment
 (b) Cream
 (c) Lotion
 (d) Gel
102. **The most potent topical corticosteroid is:** (DPG 2009)
 (a) Hydrocortisone butyrate cream 0.1%
 (b) Betamethasone valerate cream 0.5%
 (c) Clobetasol propionate cream 0.5%
 (d) Clobetasone butyrate cream 0.5%
103. **Steroids are indicated in all of the following forms of tuberculosis except:** (DPG 2009)
 (a) Meningitis
 (b) Pericarditis
 (c) Ileo-caecal tuberculosis
 (d) Adrenal involvement
104. **Which of the following is TRUE of adrenal suppression due to steroid therapy?** (AI 2005)
 (a) It is not associated with atrophy of the adrenal glands
 (b) It is less likely to occur in patients receiving inhaled steroids
 (c) It should be expected in anyone receiving >5 mg prednisolone daily
 (d) Following cessation, the stress response normalizes after 8 weeks
105. **All of the following are correct about steroids EXCEPT:** (AI 2001)
 (a) Inhibit the release of arachidonic acid from vessel wall through action on phospholipase A
 (b) Binds to the plasma membrane receptors and following internalization influence nuclear changes
 (c) Inhibit vascular membrane permeability
 (d) Increase glucose synthesis in liver
106. **Glucocorticoids act in inflammation by:** (PGI June, 2006)
 (a) ↓ Lipocortin
 (b) ↑ IL-2
 (c) ↑ Lipocortin
 (d) ↑ CRP
 (e) ↑ LTs
107. **Drugs causing Addison's disease are:** (PGI June, 2006)
 (a) Ketoconazole
 (b) Aminoglutethimide
 (c) Cyclosporine
 (d) Glucocorticoids
 (e) ACTH
108. **Glucocorticoids have proved useful in the treatment of:**
 (a) Chemotherapy induced vomiting
 (b) Hyperprolactinemia
 (c) Parkinson's disease
 (d) Type II diabetes
109. **Aldosterone is known to cause sodium retention. Its Na⁺ retaining action is exerted on which part of the nephron?**
 (a) Proximal convoluted tubule
 (b) Ascending limb of loop of Henle
 (c) Collecting ducts
 (d) Early distal convoluted tubule
110. **Which of the following is NOT an adverse effect of excessive mineralocorticoid action?**
 (a) Na⁺ and water retention
 (b) Acidosis
 (c) Aggravation of CHF associated myocardial fibrosis
 (d) Rise in blood pressure
111. **The drug prednisolone is known to be a powerful anti-inflammatory agent. This is true due to the action of the drug on which of the following enzymes?**
 (a) Cyclooxygenase
 (b) Lipoxygenase
 (c) Phospholipase A
 (d) Phosphodiesterase
112. **Hydrocortisone acts as an anti-inflammatory agent because of induction of the synthesis of which of the following protein?**
 (a) Heat shock protein 90
 (b) Inhibin
 (c) Transcortin
 (d) Lipocortin

113. Which of the following steroids is preferred for high dose intravenous corticosteroid pulse therapy?
- Cortisone
 - Hydrocortisone
 - Triamcinolone
 - Methyl-prednisolone
114. Select the regime of corticosteroids which has the maximum adverse effect potential?
- Prednisolone 20 mg/day oral for one year
 - Prednisolone 60 mg/day oral for 7 days
 - Dexamethasone 4 mg intravenous daily for 3 days
 - Methyl-prednisolone 1000 mg intravenous twice single dose
115. Which of the following disorders is NOT aggravated by corticosteroid therapy?
- Congenital adrenal hyperplasia
 - Diabetes mellitus
 - Hypertension
 - Peptic ulcer
116. In the treatment of congenital adrenal hyperplasia due to lack of 21 β -hydroxylase, the purpose of administration of a synthetic glucocorticoid is:
- Inhibition of aldosterone synthesis
 - Prevention of hypoglycemia
 - Recovery of normal immune function
 - Suppression of ACTH secretion
117. Toxic effects of long term administration of a glucocorticoid include:
- Hepatotoxicity
 - Osteoporosis
 - Precocious puberty
 - Lupus like syndrome
118. A patient Dharampal has been diagnosed to have bronchial asthma and is maintained on oral prednisolone 20 mg daily and inhaled salbutamol as required. The patient develops chest infection. Which of the following measures would you like to take?
- Stop prednisolone
 - Reduce prednisolone dose to 5 mg/day
 - No change/increase in prednisolone dose
 - Substitute prednisolone with inhaled budesonide
119. Shanti has been diagnosed to have brain tumor. You would prefer to give her betamethasone/dexamethasone over hydrocortisone as steroids to decrease her cerebral edema because:
- They do not cause Na^+ and water retention
 - They are more potent
 - They can be administered intravenously
 - They inhibit brain tumours
120. A 50 year old man with advanced tuberculosis has developed signs of severe acute adrenal insufficiency. The patient should be treated immediately with a combination of:
- Aldosterone and fludrocortisone
 - Triamcinolone and dexamethasone
 - Cortisol and fludrocortisone
 - Dexamethasone and metyrapone
121. Long term steroid therapy can lead to suppression of hypothalamic-pituitary-adrenal axis. It can be overcome by using alternate day therapy with corticosteroids. Which of the following steroids are unsuitable for alternate day therapy for such purpose?
- Cortisol
 - Prednisolone
 - Betamethasone
 - Hydrocortisone
122. Which is not true about beclomethasone? (DPG 2010)
- Indicated for chronic use
 - Inhalational steroid
 - Effective in acute asthma
 - Predispose to fungal infections
123. Most potent mineralocorticoid is: (TN 2000, DPG 2008)
- Aldosterone
 - DOCA
 - Fludrocortisone
 - Triamcinolone
124. All are side effects of steroids EXCEPT: (DG 2008)
- Skin atrophy
 - Telengectasia
 - Folliculitis
 - Photosensitivity
125. Systemic steroids can cause all of the following EXCEPT: (DPG 2004)
- Hypertension
 - Glaucoma
 - Cataract
 - Osteoporosis
126. Compared to hydrocortisone maximum glucocorticoid action is found in: (DPG 2004)
- Dexamethasone
 - Prednisolone
 - Methyl prednisolone
 - Cortisone
127. Steroids are contraindicated in all, EXCEPT: (DPG 2003)
- Diabetes mellitus
 - Hypertension
 - Eczematous skin disease
 - Peptic ulcer disease
128. Oral contraceptive failure can occur with: (UP 2007, MH 2000, DPG 2003)
- Insulin
 - Rifampicin

- (c) Cimetidine
(d) Omeprazole
129. In Addison's disease drug to be given is: (DBN 2006, DNB 2003, MPPG 2003)
(a) Hydrocortisone
(b) Betamethasone
(c) Prednisolone
(d) DOCA
130. Corticosteroids cause all EXCEPT: (MPPG 2001)
(a) Muscular hypertrophy
(b) Peptic ulceration
(c) Psychosis
(d) Suppression of pituitary-adrenal axis
131. Glucocorticoids with mineralocorticoids activity is seen in: (UP 2006) (UP 2007)
(a) Triamcinolone
(b) Betamethasone
(c) Cortisol
(d) Dexamethasone
132. Which of the following antifungal drug can be used in the treatment of Cushing syndrome? (UP 2005)
(a) Ketoconazole
(b) Fluconazole
(c) Itraconazole
(d) Miconazole
133. All of the following glucocorticoids lack mineralocorticoid activity, except: (TN 2007)
(a) Beclomethasone
(b) Triamcinolone
(c) Prednisolone
(d) Dexamethasone
134. All of the following are side effects of steroids except: (RJ 2000)
(a) Hyperglycemia
(b) Infection
(c) Osteomalacia
(d) Peptic ulcer
135. All are side effects of steroids except: (RJ 2002)
(a) Diabetes
(b) Osteoporosis
(c) Fragile skin
(d) Hypotension
136. Anti-inflammatory action of corticosteroids is due to blocking of: (RJ 2006)
(a) 15 lipoxygenase
(b) Prostaglandin synthetase
(c) Thromboxane synthetase
(d) Break down of phospholipids
137. Which of the following is used for medical adrenalectomy? (RJ 2009)
(a) Mitotane
(b) Methotrate
(c) Doxorubicin
(d) 5-Fluorouracil
138. Which of the following is the side effect of steroids due to its mineralocorticoid component? (MH 2003)
(a) Skin striae
(b) Hypertension
(c) Osteoporosis
(d) Moon face
139. Side effect of steroids are all except: (Bihar 2004)
(a) Hypoglycemia
(b) Hypertension
(c) Psychosis
(d) Growth retardation
140. Which one has least mineralocorticoid activity? (Kolkata 2005)
(a) Cortisol
(b) Prednisolone
(c) Fludrocortisone
(d) Methyl prednisolone
141. Steroids cause: (Kolkata 2005)
(a) Increased TSH
(b) Increased FSH
(c) Prevent de-iodination
(d) All of the above
142. In which of the following disease is corticosteroids indicated? (Karnataka 2006)
(a) Osteoporosis
(b) Peptic ulcer
(c) Collagen vascular diseases
(d) Tuberculosis

■ OSTEOPOROSIS AND CALCIUM METABOLISM

143. All of the following decrease bone resorption in osteoporosis except: (AI 2011)
(a) Alendronate
(b) Etidronate
(c) Strontium
(d) Teriparatide
144. Which of the following drug is a SERM useful for treatment of osteoporosis? (AIIMS Nov, 2010)
(a) Raloxifene
(b) Bisphosphonate
(c) Strontium
(d) Estradiol
145. Both decreased bone resorption and increased bone formation is caused by: (AIIMS May, 2010) (AIIMS Nov, 2008)
(a) Strontium ranelate
(b) Ibadronate
(c) Teriparatide
(d) Calcitonin
146. Which of the following is a serious adverse effect seen with zoledronate? (DPG 2011)
(a) Acute renal failure
(b) Ventricular fibrillation
(c) Peptic ulcer
(d) Anterior uveitis

- 147. Bisphosphonates act by:** (AI 2006)
- Increasing the osteoid formation
 - Increasing the mineralization of osteoid
 - Decreasing the osteoclast mediated resorption of bone
 - Decreasing the parathyroid hormone secretion
- 148. All of the following are advantages of using raloxifene over estrogen in post-menopausal women EXCEPT:** (AI 2004)
- Reduces fracture rates
 - Avoids endometrial hyperplasia
 - Reduces incidence of venous thrombosis
 - No increase in incidence of breast carcinoma
- 149. Bisphosphonates are used in all EXCEPT:** (AIIMS Nov, 2007)
- Paget's disease
 - Vitamin D excess
 - Postmenopausal osteoporosis
 - Hypercalcemia of malignancy
- 150. Which of the following is an indication for the use of raloxifene?**
- Chronic renal failure
 - Hypoparathyroidism
 - Renal osteodystrophy
 - Post-menopausal osteoporosis
- 151. Chronic use of which of the following medications is most likely to cause osteoporosis?**
- Lovastatin
 - Propanolol
 - Warfarin
 - Prednisone
- 152. Regarding raloxifene, which of the following statements is INCORRECT?**
- It acts as an estrogen agonist in bone
 - It exerts estrogen antagonistic action on endometrium
 - It increases risk of developing breast cancer
 - It can induce/aggravate menopausal hot flushes
- 153. A child Mahesh has been diagnosed to be having vitamin D dependent rickets. The most appropriate vitamin D preparation for him is:**
- Calciferol
 - Cholecalciferol
 - Calcifediol
 - Calcitriol
- 154. The unique property of SERMs is that they:**
- Have both estrogenic and progestational agonistic activity
 - Inhibits the aromatase enzyme that is required for estrogen synthesis
 - Produces estrogenic effect without binding to estrogen receptors
 - Act as agonist in some tissues and antagonist in other tissues
- 155. All of these drugs can be used in the treatment of post menopausal osteoporosis EXCEPT:**
- Alendronate
 - Teriparatide
 - Calcium
 - Thyroxine
- 156. A 52 year-old postmenopausal patient has evidence of low bone mineral density. She and her physician are considering therapy with raloxifene or a combination of conjugated estrogens and medroxyprogesterone acetate. Which of the following patient characteristics is MOST likely to lead them to select raloxifene?**
- Previous hysterectomy
 - Recurrent vaginitis
 - Strong family history of breast cancer
 - Troublesome hot flushes
- 157. A patient Geeta began taking alendronate and she was advised to take large amount of water and remain in the standing position for at least half an hour till she had the first meal of the day. These instructions were given to reduce the risk of:**
- Cholelithiasis
 - Constipation
 - Erosive esophagitis
 - Osteonecrosis
- 158. Bone resorption is enhanced by:** (DPG 2010)
- PGD₂
 - PDF₂
 - PGE₂
 - PGL₂
- 159. Calcitonin causes hypocalcemia by:** (MPPG 2002)
- Inhibiting bone resorption
 - Promoting osteolysis
 - Decreasing renal tubular reabsorption of calcium
 - Decreasing absorption of phosphorus
- 160. Correct statement about mode of administration of pamidronate:** (RJ 2009)
- IV
 - Orally
 - IM
 - SC
- 161. Bisphosphonates act by:** (RJ 2009)
- Increasing the osteoid formation
 - Increasing the mineralization of osteoid
 - Decreasing the osteoclast mediated resorption of bone
 - Decreasing the parathyroid hormone secretion
- 162. Which is the fastest calcium lowering agents?** (Jharkhand 2003)
- Calcitonin
 - Plicamycin
 - Etidronate
 - Zoledronate

163. Prevention or treatment of osteoporosis in postmenopausal women may be achieved by all EXCEPT:
- Estrogen and progesterone hormone replacement therapy (DPG 2008)
 - Calcium and vitamin D supplementation
 - Bisphosphonates
 - Multivitamins

GONADAL HORMONES AND CONTRACEPTIVES

164. Hormone replacement therapy is beneficial for all of the following conditions except: (AIIMS May 2013)
- Vaginal atrophy
 - Flushing
 - Osteoporosis
 - Coronary heart disease
165. All are true regarding selective estrogen receptor down-regulator (SERD), Fulvestrant except: (AI 2011)
- Used for treatment of advanced breast cancer
 - Is a selective estrogen antagonist
 - Is slower and short acting and less safer than SERMs
 - Administered as once a month i.m. dose
166. Contraceptive that should be avoided in epilepsy is: (AI 2009) (AI 2011)
- Oral contraceptives
 - Condoms
 - Intrauterine contraceptive devices
 - Post-coital pills
167. Major use of mifepristone in obstetrics and gynaecology is for management of: (AI 2011)
- Ectopic pregnancy
 - Molar pregnancy
 - Fibroid uterus
 - Threatened abortion
168. Prolonged testosterone treatment to a man results in:
- Increased spermatogenesis (AIIMS Nov, 2010)
 - Increased sperm motility
 - Azoospermia
 - Increased gonadotropins
169. Use of tamoxifen in carcinoma of breast patients does not lead to the following side effects: (DPG 2011)
- Thromboembolic events
 - Endometrial carcinoma
 - Cataract
 - Cancer in opposite breast
170. Failure of oral contraceptives occur when used with any of these except: (AIIMS Nov, 2009, AI 2009)
- Aspirin
 - Tetracycline
 - Phenytoin
 - Rifampicin
171. Which of the following progesterone is used in emergency contraception? (AIIMS May, Nov 2009)
- Levonorgestrel
 - Micronised Progesterone
 - Norgestrel
 - Depot Medroxyprogesterone acetate
172. All of the following statements about estrogen are TRUE EXCEPT: (AI 2009)
- Decreases HDL
 - Increases triglycerides
 - Increases turnover of LDL receptors
 - Increases apolipoprotein A
173. Which of the following is a selective estrogen receptor modulator? (DPG 2009)
- Raloxifene
 - Mifepristone
 - Danazol
 - Anastrozole
174. Finasteride acts by blocking: (AI 2007)
- α -receptors
 - 5- α reductase enzyme
 - Androgen receptors
 - β -receptors
175. The following statements regarding finasteride are true EXCEPT: (AI 2005)
- It is used in the treatment of benign prostatic hyperplasia
 - Impotence is well documented after its use
 - It blocks the conversion of dihydrotestosterone to testosterone
 - It is a 5 α reductase inhibitor
176. In a patient taking oral contraceptive, the chance of pregnancy increases after taking any of the following drugs EXCEPT: (AI 2002)
- Phenytoin
 - Griseofulvin
 - Ampicillin
 - Cimetidine
177. Oral contraceptives are not given with: (AIIMS Nov, 2007)
- Streptomycin
 - Rifampicin
 - Pyrazinamide
 - Ethambutol
178. Hormone replacement therapy is helpful in all of the following conditions EXCEPT: (AIIMS May, 2007)
- Vaginal atrophy
 - Flushing
 - Coronary heart disease
 - Osteoporosis
179. Which of the following is an aromatase inhibitor? (AIIMS May, 2006)
- Tamoxifen
 - Letrozole
 - Danazol
 - Taxane

180. Women receiving estrogen therapy have an increased risk of development of all of the following EXCEPT:
(a) Breast cancer (AIIMS Nov, 2004)
(b) Endometrial cancer
(c) Carcinoma of the gall bladder
(d) Hepatocellular carcinoma
181. Which of the following substances is most potent androgen? (AIIMS Nov, 2003, May, 2004, DPG 2004)
(a) Dehydroepiandrosteridione
(b) Dihydrotestosterone
(c) Androstenidione
(d) Testosterone
182. Emergency contraceptive drugs are: (PGI Dec 2007)
(a) Levo-norgestrel
(b) Estrogen + progesterone
(c) Mifepristone
(d) DMPA
(e) Norplant
183. Hormonal therapy used in breast cancer are: (PGI Dec 2002)
(a) Danazol
(b) Cyproterone acetate
(c) Tamoxifen
(d) LHRH analogue
(e) Methotrexate
184. Androgen receptor antagonists include: (PGI Dec. 2001)
(a) Cyproterone
(b) Spironolactone
(c) Cimetidine
(d) Progesterone
(e) Flutamide
185. The estrogen that is used in most combined hormonal contraceptives is:
(a) Clomiphene
(b) Ethinyl estradiol
(c) Estrone
(d) Norgestrel
186. Diethylstilbesterol should never be used in pregnant women because it is associated with:
(a) Development of deep vein thrombosis in the pregnant woman
(b) Feminization of the external genitalia of male offspring
(c) Infertility and development of vaginal cancer in female offspring
(d) Virilization of the external genitalia of female offspring
187. Finasteride has efficacy in the prevention of male pattern baldness by virtue of its ability to:
(a) Competitively antagonize androgen receptors
(b) Decrease the release of gonadotropins
(c) Inhibit the synthesis of testosterone
(d) Reduce the production of DHT
188. The enzyme 5α reductase mediated conversion of testosterone to dihydrotestosterone is NOT required for which of the following actions?
(a) Formation of male external genitalia in the fetus
(b) Prostatic hypertrophy in elderly males
(c) Pubertal changes in the male adolescent
(d) Spermatogenesis
189. An endocrinologist decided to give a 7 yr old boy testosterone therapy and continued it till puberty. This therapy is likely to:
(a) Increase adult stature
(b) Reduce adult stature
(c) Have no effect on adult stature
(d) Cause hypertrophy of penis
190. The 5α reductase inhibitor that has been found to be effective both in benign prostatic hypertrophy and male pattern baldness is:
(a) Flutamide
(b) Finasteride
(c) Prazosin
(d) Minoxidil
191. Dr Neelam decides to give estrogen therapy in a postmenopausal woman. The risk of which of the following will not be increased?
(a) Gall stones
(b) Osteoporosis
(c) Endometrial carcinoma
(d) Breast cancer
192. Clomiphene citrate is not known to produce which of the following effects in a young female of 30 years of age (child bearing age group)?
(a) Hot flushes
(b) Ovulation
(c) Decreased FSH and LH secretion
(d) Polycystic ovaries
193. The combined estrogen-progestin oral contraceptive pill act mainly by:
(a) Production of cervical mucus hostile to sperm penetration
(b) Suppression of FSH and LH release
(c) Making endometrium unsuitable for implantation
(d) Enhancing uterine contraction to dislodge the fertilized ovum
194. One of the health benefits of the use of combined oral contraceptives in pre-menopausal women is that these contraceptives reduce the risk of:
(a) Deep vein thrombosis
(b) Migraine

- (c) Ovarian cancer
- (d) Ischemic stroke

195. A 23-year old woman desires a combined oral contraceptive for pregnancy protection. A factor that would lead a health professional to recommend an alternative form of contraception is that the woman:
- (a) Has an evidence of hirsutism
 - (b) Has a history of gastroesophageal reflux disease and is currently taking omeprazole
 - (c) Has a history of pelvic inflammatory disease
 - (d) Has a history of migraine headache that is well controlled by sumatriptan
196. A drug 'X' primarily reduces the static component of urinary obstruction in benign hypertrophy of prostate and takes more than 3 months to exert its beneficial effect. Which of the following is 'X'?
- (a) Tamsulosin
 - (b) Terazosin
 - (c) Finasteride
 - (d) Amphetamine
197. Dr. Shweta decided to add a progestin for 10-12 days each month to estrogen replacement therapy in menopausal women in the gynaecology OPD. Addition of progestin is recommended because the progestin:
- (a) Blocks the increased risk of myocardial infarction due to estrogen
 - (b) Blocks the increased risk of endometrial carcinoma due to estrogen
 - (c) Reverses vulval atrophy occurring in post menopausal women
 - (d) Enhances the metabolic benefits of estrogen treatment
198. A young female Shagun comes to you in the gynaecology OPD and gives the history that she had intercourse with her boyfriend 5 hours back. Select the drug that can act as a single dose postcoital contraceptive for her:
- (a) Clomiphene citrate
 - (b) Mifepristone
 - (c) Danazol
 - (d) Medroxyprogesterone acetate
199. A patient Parul gives you the history that she has missed a single dose of her combined oral contraceptive pill. Which of the following will you advise her?
- (a) Continue with the course without regard to the missed dose
 - (b) Take 2 pills the next day and continue with the course
 - (c) Take 2 pills everyday for the remaining part of the course
 - (d) Discontinue the course and use alternative method of contraception
200. Oral contraceptive pills can cause all except: (DPG 2010)
- (a) Mastalgia
 - (b) Dysmenorrhea
 - (c) Chloasma
 - (d) Breakthrough bleeding
201. Side effects of oral contraceptives are all EXCEPT: (DPG 2007)
- (a) Irregular bleeding
 - (b) Headache
 - (c) Thrombosis
 - (d) Increased risk of ovarian cancer
202. All of the following are natural estrogens EXCEPT: (RJ 2008, DPG 2006)
- (a) Estradiol
 - (b) Ethinylestradiol
 - (c) Estriol
 - (d) Estrone
203. Mechanism of action of tamoxifen is: (DPG 2000)
- (a) Has androgenic receptor blocking action
 - (b) Inhibits enzyme 5 α -reductase
 - (c) Has partial agonist and antagonist action on estrogen receptors
 - (d) Inhibition of FSH and LH release from the pituitary
204. The progestogenic emergency contraceptive pills act by: (MPPG 2007)
- (a) Altered cervical secretion
 - (b) Inhibition of ovulation
 - (c) Anti-implantation effect
 - (d) Inhibition of LH secretion
205. Which one of the following agents inhibits spermatogenesis? (MPPG 2002, DPG 2001)
- (a) Gelusil
 - (b) Gemcadiol
 - (c) Gestodene
 - (d) Gossypol
206. Which one of the following has both estrogenic and anti-estrogenic property: (MPPG 2002)
- (a) Chlorpromazine
 - (b) Clofibrate
 - (c) Clomiphene
 - (d) Clonidine
207. Tamoxifen is useful in: (MPPG 2001)
- (a) Carcinoma prostate
 - (b) Carcinoma ovary
 - (c) Estrogen receptor positive breast carcinoma
 - (d) Seminoma
208. Thromboembolism is due to which component of oral contraceptive pills: (MPPG 2001)
- (a) Progesterone
 - (b) Estrogen
 - (c) Iron
 - (d) FSH
209. An example of antiprogestosterone is: (TN 2002)
- (a) Gossypol
 - (b) Atosiban

- (c) Clomiphene
(d) Mifepristone (RU 486)
210. The drug used for first trimester abortion is: (TN 2002)
(a) Oral mifepristone
(b) Intra-amniotic saline
(c) Extra-amniotic ethacrydine lactate
(d) Oxytocin infusion
211. "Oral contraceptive pills" protect against: (TN 2002)
(a) Thrombosis
(b) Ovarian cancer
(c) Cancer cervix
(d) Hepatocellular adenoma
212. Mifepristone is a: (TN 2003, RJ 2000)
(a) Progesterone antagonist
(b) Oestrogen antagonist
(c) Both
(d) None
213. All are anti-androgens except: (TN 2006)
(a) Finasteride
(b) Flutamide
(c) Cyproterone acetate
(d) Dihydrotestosterone
214. Oral contraceptive pill is useful in preventing all of the following except: (TN 2007)
(a) Carcinoma breast
(b) Carcinoma ovary
(c) Pelvic inflammatory disease
(d) Anaemia
215. Oral contraceptive failure occurs with: (RJ 2000)
(a) Phenytoin
(b) Phenobarbitone
(c) Rifampicin
(d) All
216. Clomiphene citrate is used for: (RJ 2002)
(a) Mania
(b) Induction of ovulation
(c) Depression
(d) Psychosis
217. Which of the following is role of progestogens? (MH 2003)
(a) Inhibits ovulation
(b) Protects against endometrial cancer
(c) Causes prompt withdrawal bleeding
(d) All
218. Which of the following is anti-androgenic drug? (MH 2006)
(a) Bicalutamide
(b) Oxymetholone
(c) Raloxifene
(d) Stanozolol
219. Which among the following is not a SERM? (Bihar 2006)
(a) Flutamide
(b) Ormeloxifen
(c) Tamoxifen
(d) Raloxifen
220. Which among the following is not an androgen receptor blocker? (Bihar 2006)
(a) Finasteride
(b) Cyproterone
(c) Flutamide
(d) None
221. Flutamide is an: (Karnataka 2007)
(a) Anti-convulsant
(b) Anti-androgen
(c) Anti-progestin
(d) Anti-oestrogen
222. Following are the adverse effects of estrogens except:
(a) Suppression of libido
(b) Fusion of epiphyses
(c) Hot flushes
(d) Gynaecomastia in males
223. All of the following are recognized effects of combined oral contraceptive except: (Karnataka 2005)
(a) Breakthrough bleeding
(b) Decreased risk of endometrial cancer
(c) Increased risk of ischemic stroke
(d) Increased risk of ovarian cancer

DRUGS ACTING ON UTERUS AND MISCELLANEOUS

224. All of these hormones use cAMP as second messenger except: (AIIMS Nov 2009)
(a) Corticotropin
(b) Dopamine
(c) Glucagon
(d) Vasopressin
225. Hypospadias in the baby is caused by maternal use of which of the following drug? (AI 2012)
(a) Diethylstilbestrol
(b) Tolbutamide
(c) Clomiphene
(d) Clobazam
226. All are used in the treatment of hot flushes except: (AI 2011)
(a) Tamoxifen
(b) Venlafaxine
(c) Gabapentin
(d) Clonidine
227. In spider nevi, dilatation of blood vessels is due to: (AIIMS May, 2010)
(a) Testosterone
(b) Estrogen
(c) Hepatotoxins
(d) FSH
228. Receptor for which of the following is present intracellularly? (AI 2003)
(a) Insulin
(b) Corticosteroid
(c) Epinephrine
(d) Glucagon

- 229. All of the following belong to the steroid receptor superfamily EXCEPT:** (AI 2002)
- Vitamin D₃ receptor
 - Thyroid receptor
 - Retinoid receptor
 - Epinephrine receptor
- 230. Male gynaecomastia is seen with:** (AIIMS May, 2007)
- Clomiphene
 - Testosterone
 - Spironolactone
 - Tamoxifen
- 231. Regarding oxytocin, true statements are:** (PGI June, 2002)
- Secreted by anterior pituitary
 - Acts on myoepithelial cells of breast
 - Causes contraction of uterus during labour
 - May cause retention of water
 - Has sympatholytic activity
- 232. The mechanism by which ergometrine stops postpartum hemorrhage is that it:**
- Causes vasoconstriction of uterine arteries
 - Increases tone of uterine muscle
 - Promotes coagulation
 - Induces platelet aggregation
- 233. Which of the following is an adrenergic drug preferred for arresting labour?**
- Ritodrine
 - Isoprenaline
 - Salbutamol
 - Terbutaline
- 234. Exenatide is a newer drug proposed to be used in the treatment of:**
- Osteoporosis
 - Diabetes mellitus
 - Hyperparathyroidism
 - Anovulatory infertility
- 235. Teriparatide can be used for the treatment of:**
- Osteoporosis
 - Hormone responsive breast carcinoma
 - Polycystic ovarian disease
 - Hyperparathyroidism
- 236. All of the following agents act through nuclear receptors EXCEPT:**
- Thyroxine
 - Rosiglitazone
 - Prednisolone
 - Estrogen
- 237. A 62-year-old female, Phoolwati presents to the emergency with acute severe low back pain after too quickly sitting down onto a chair. She has a history of rheumatoid arthritis and bronchial asthma. She reports that she was on many medications for several years. X-ray shows a fracture of the fifth lumbar vertebra. Which of the following drugs are likely responsible for the patient's complaints?**
- Methotrexate
 - Prednisolone
 - Indomethacin
 - Salbutamol
- 238. Oxytocin causes all except:** (DPG 2010)
- Lactogenesis
 - Milk ejection
 - Contraction of uterine muscle
 - Myoepithelial cell contraction
- 239. Drug of choice for polycystic ovarian disease is:** (DPG 2007)
- Metformin
 - Estrogen
 - Estrogen and progesterone combination pill
 - Dopamine antagonist
- 240. Which of the following is not administered by intradermal route?** (DPG 2007)
- BCG
 - Insulin
 - Mantoux
 - Drug sensitivity injection
- 241. Which of the following is not an indication for oxytocin:** (DPG 2001)
- Spontaneous premature labour
 - Post partum haemorrhage
 - Uterine inertia
 - Breast engorgement due to inefficient milk ejection reflex
- 242. Hirsutism producing drugs include all except:** (TN 2000)
- Methyldopa
 - Corticosteroids
 - Phenytoin
 - Minoxidil
- 243. Hypoglycemia is caused by:** (TN 2000)
- Alcohol intoxication
 - Thiazide
 - Diazoxide
 - Metoclopramide
- 244. All of the following drugs are oxytocics except:** (RJ 2000)
- Oxytocin
 - Ergometrine
 - Prostaglandin
 - Orciprenaline
- 245. Norplant contains how many capsule of levonorgestrel:** (RJ 2005)
- 4
 - 6
 - 8
 - 10

246. Mechanism of Calcitriol is: (RJ 2009)
 (a) Decreased calcium resorption calcium from bone
 (b) Increase calcium absorption from intestine
 (c) Decreased calcium absorption from kidney
 (d) Decrease calcium absorption from intestine
247. What is the action of oxytocin in small doses, when used as intravenous infusion in a full term uterus? (MH 2006)
 (a) Relaxes uterus
 (b) Induces uterine contractions
 (c) Causes cervical dilatation
 (d) All
248. True about atosiban is that it: (MH 2006)
 (a) Is an oxytocin receptor antagonist
 (b) Is an progesterone receptor antagonist
 (c) Is least effective in inhibiting preterm uterine contractions
 (d) Is a anti-tocolytic drug
249. Beta agonist which is used for stopping premature labor is: (Jharkhand 2004)
 (a) Carvedilol
 (b) Terbutaline
 (c) Pindolol
 (d) Nadolol
250. Which one of the following drugs is not a uterine relaxant? (Karnataka 2006)
 (a) Isoxsuprine
 (b) Dopamine
 (c) Salbutamol
 (d) Terbutaline
251. A 46-years-old male patient has Cushing's syndrome that is due to the presence of adrenal tumor. Which of the following drugs would be expected to reduce the signs and symptoms of the man's disease? (Karnataka 2005)
 (a) Betamethasone
 (b) Cortisol
 (c) Fludrocortisone
 (d) Ketoconazole
3. LHRH analogue used in breast cancer is
 (a) Cetrorelix
 (b) Anastrozole
 (c) Leuprolide
 (d) Tamoxifen
4. Long-term ingestion of steroids lead to all of the following except:
 (a) Avascular necrosis of head of femur
 (b) Cataract
 (c) Glaucoma
 (d) Growth retardation
5. Which of the following drug is a dopamine receptor agonist ?
 (a) Methyl dopa
 (b) Bromocriptine
 (c) Haloperidol
 (d) Morphine
6. Combined oral contraceptive pills act mainly by:
 (a) Production of cervical mucus hostile to sperm penetration
 (b) Inhibition of ovulation
 (c) Making endometrium unsuitable for implantation
 (d) Enhancing uterine contractions to dislodge the fertilized ovum.
7. Which of the following is an anabolic steroid ?
 (a) Methyltestosterone
 (b) Fluoxymesterone
 (c) Nandrolone
 (d) Danazol
8. Tibolone is a :
 (a) SSRI
 (b) SPRM
 (c) STEAR
 (d) SERM
9. Drug which inhibits conversion of T_4 to T_3 is:
 (a) Carbimazole
 (b) Methimazole
 (c) Propylthiouracil
 (d) Lugol's iodine
10. Which of the following agents has the least glucocorticoid action?
 (a) Fludrocortisone
 (b) Cortisone
 (c) Dexamethasone
 (d) Betamethasone
11. Which is an intermediate acting insulin?
 (a) Insulin lispro
 (b) Regular insulin
 (c) NPH insulin
 (d) Insulin glargine
12. Side effects of oxytocin are all except:
 (a) Placental abruption
 (b) Fetal distress
 (c) Peripheral vascular disease
 (d) Water intoxication

RECENT QUESTIONS ASKED BY NATIONAL BOARD

1. Which of the following is a selective progesterone receptor modulator?
 (a) Tamoxifen
 (b) Ulipristal
 (c) Nomegestrol
 (d) Toremifene
2. Glipizide, the oral hypoglycaemic drug acts by:
 (a) Improving insulin resistance
 (b) Inhibiting brush border enzyme
 (c) Helps in insulin secretion
 (d) Increased glucose uptake by fat cells

13. Steroid with 12-36 hrs half life is:
 - (a) Betamethasone
 - (b) Prednisolone
 - (c) Hydrocortisone
 - (d) Dexamethasone
14. Adverse effects of diethylstilbesterol when used in pregnant woman is
 - (a) Deep vein thrombosis in pregnant woman
 - (b) Feminization of external genitalia of male offspring
 - (c) Development of vaginal carcinoma in female offspring
 - (d) Virilization of the external genitalia of female offspring
15. Which of the following is a topical vitamin D analogue?
 - (a) Cholecalciferol
 - (b) Doxercalciferol
 - (c) Calcipotriol
 - (d) Paricalcitol
16. Which of the following does not cause insulin release?
 - (a) Rosiglitazone
 - (b) Nateglinide
 - (c) Glimipiride
 - (d) Tolbutamide
17. Which of the following is a synthetic estrogen?
 - (a) Estrone
 - (b) Estriol
 - (c) Estradiol
 - (d) Diethylstilbestrol
18. Which of the following can cause lactic acidosis?
 - (a) Biguanides
 - (b) Glibenclamide
 - (c) Tolbutamide
 - (d) Chlorpropamide
19. All are true statements regarding octreotide except:
 - (a) Somatostatin analogue
 - (b) Used in refractory diarrhea in AIDS
 - (c) Used in carcinoid syndrome
 - (d) An absorbent
20. cAMP is second messenger for the following except:
 - (a) TSH
 - (b) Insulin
 - (c) LH
 - (d) FSH
21. rPTH used in osteoporosis is:
 - (a) Teriparatide
 - (b) Denosumab
 - (c) Calcitriol
 - (d) Calcipotriol
22. Which of the following is preferred for infertility treatment of a female with increased prolactin levels?
 - (a) Dopamine
 - (b) Carbidopa
 - (c) Cabergoline
 - (d) Bromocriptine
23. Glucagon is most effective for which of the following conditions?
 - (a) Cocaine intake with BP of 180/110 mmHg
 - (b) Old man with decreased BP/decreased heart rate due to atenolol
 - (c) Old man with type 2 diabetes mellitus and no glipizide for 4 days
 - (d) Female with lactic acidosis due to shock
24. Female with secondary amenorrhea with serum prolactin level 75ng/ml is to be treated with:
 - (a) Cabergoline
 - (b) Ganirelix
 - (c) Clomiphene
 - (d) Estradiol
25. Compared to hydrocortisone, maximum glucocorticoid activity is seen in:
 - (a) Cortisone
 - (b) Prednisolone
 - (c) Dexamethasone
 - (d) Methylprednisolone
26. Which of the following decreases thyroid hormone on a long term basis?
 - (a) T₄
 - (b) I¹³¹
 - (c) Calcitriol
 - (d) Fluorouracil
27. Intranasal calcitonin is used for?
 - (a) Paget's disease
 - (b) MEN Syndrome
 - (c) Hypercalcemia
 - (d) Postmenopausal osteoporosis
28. Parathormone is useful in which of the following?
 - (a) Hyperparathyroidism
 - (b) Paget's disease
 - (c) Osteoporosis
 - (d) Osteomalacia
29. Which insulin is never mixed with other insulins?
 - (a) Lente
 - (b) Aspart
 - (c) Lispro
 - (d) Glargine
30. Drug of choice for acute adrenal insufficiency is?
 - (a) Oral prednisone
 - (b) IV hydrocortisone
 - (c) IV betamethasone
 - (d) IV dexamethasone
31. Insulin release due to closure of K⁺ channels is seen with:
 - (a) Nateglinide
 - (b) Acarbose
 - (c) Exenatide
 - (d) Sitagliptin

- 32. Drug used to control postprandial hyperglycemia is:**
- Acarbose
 - Biguanides
 - Sulfonylurea
 - Repaglinide
- 33. Long acting insulin is?**
- Insulin glargine
 - Insulin lispro
 - Insulin aspart
 - Insulin glulisine
- 34. All are true about estrogen except:**
- Causes cholestasis
 - Used in treatment of gynaecomastia
 - Used in hormone replacement therapy
 - Increased risk of breast cancer
- 35. Fastest acting antithyroid drug is:**
- Potassium iodide
 - Propylthiouracil
 - Carbimazole
 - Cholestyramine
- 36. All of the following are topical steroids except:**
- Hydrocortisone valerate
 - Fluticasone propionate
 - Triamcinolone
 - Prednisolone
- 37. Bisphosphonates are not used in?**
- Paget's disease
 - Osteoporosis
 - Cancer induced osteolysis
 - Vitamin D intoxication
- 38. Corticosteroid with maximum sodium retaining potential is:**
- Dexamethasone
 - Prednisolone
 - Aldosterone
 - Betamethasone
- 39. Lugol's Iodine contains:**
- 5% iodine & 10% KI
 - 10% iodine & 20% KI
 - 10% iodine & 15% KI
 - 5% iodine & 15% KI
- 40. Which of the following is not an insulin analogue?**
- Insulin glargine
 - Insulin lispro
 - Actrapid
 - Insulin aspart
- 41. Which of the following is a tocolytic agent?**
- Prazosin
 - Ritodrine
 - Yohimbine
 - Propranolol
- 42. Which of the following is an oxytocin antagonist?**
- Ritodrine
 - Atosiban
 - Isoxsuprine
 - Methergine
- 43. All of the following are uses of mifepristone EXCEPT:**
- Termination of pregnancy
 - Post coital contraception
 - Post partum hemorrhage
 - Cushing's syndrome
- 44. Bisphosphonate-induced osteomalacia is commonly seen with:**
- Alendronate
 - Pamidronate
 - Zoledronate
 - Etidronate
- 45. Bicalutamide is a specific inhibitor of:**
- 5-alpha reductase
 - Androgen receptors
 - Aromatase
 - Estrogen receptor
- 46. Long term administration of glucocorticoids can cause all of the following except:**
- Proximal myopathy
 - Hyperkalemia
 - Hypertension
 - Cataract
- 47. The primary goal of glucocorticoid treatment in rheumatoid arthritis is:**
- Suppression of inflammation and improvement in functional capacity
 - Reversal of the degenerative process
 - Development of a sense of well-being in the patient
 - Prevention of suppression of the hypothalamic-pituitary-adrenal axis
- 48. An old man has enlarged prostate. Which of the following may be used to suppress his prostatic growth:**
- Spironolactone
 - Ketoconazole
 - Finasteride
 - Flutamide
- 49. Absolute contraindication of combined oral contraceptive pill is:**
- Epilepsy
 - Obesity
 - Smoking 10 cigars/day
 - Active liver disease
- 50. On which of the following does aldosterone exert its greatest effect:**
- Glomerulus
 - Proximal tubule

- (c) Cortical collecting duct
(d) Thick portion of loop of Henle
51. Which of the following drugs causes osteoporosis on long term use:
(a) Etidronate
(b) Prednisolone
(c) Phenytoin
(d) Calcitriol
52. Thyroid gland function is best monitored by which of the following:
(a) Basal metabolic rate (BMR)
(b) Thyroxine and tri-iodothyronine uptake
(c) Level of thyroid stimulating hormone
(d) Level of protein bound iodine
53. Which of the following does not cause hypoglycemia?
(a) Insulin
(b) Glimepiride
(c) Metformin
(d) Gliclazide
54. The management of thyrotoxic crisis includes all the following except:
(a) Propranolol
(b) Hydrocortisone
(c) Oral I^{131}
(d) Propylthiouracil
55. Which of the following is the principle disadvantage of depot progestin
(a) Weight gain
(b) Breast tenderness
(c) Depression
(d) Irregular menstrual bleeding and prolonged anovulation
56. Combined oral pill reduces the risk of:
(a) Breast cancer
(b) Ovarian cancer
(c) Cervical cancer
(d) Vaginal cancer
57. All of the following therapeutic uses of corticosteroids are appropriate except:
(a) Beclomethasone in bronchial asthma
(b) Cortisone for Cushing's syndrome
(c) Prednisolone for Rheumatoid arthritis
(d) Dexamethasone for reducing intracranial pressure
58. Which one of the following is an adverse effect associated with combined oral contraceptives:
(a) Cerebral stroke
(b) Aggravation of asthma
(c) Peripheral neuropathy
(d) Nephrotic syndrome
59. Which of the following drugs is used to control tachycardia and palpitations in persons with acute symptoms of hyperthyroidism?
(a) Liothyronine
(b) Propranolol
(c) Methimazole
(d) Potassium iodide solution
60. Mifepristone (RU-486) is:
(a) Anti-androgen
(b) Anti-estrogen
(c) Anti-progestin
(d) Androgen
61. Sulphonylureas act by:
(a) Reducing the absorption of carbohydrate from the gut
(b) Stimulating the beta islet cells of pancreas to release insulin
(c) Increasing the uptake of glucose in peripheral tissue
(d) Reducing the hepatic gluconeogenesis
62. Which of the following is not a steroid?
(a) 17α Hydroxyprogesterone
(b) Estrone
(c) Pregnenolone
(d) Relaxin
63. Bromocriptine is indicated in the following conditions except:
(a) Prolactin-secreting adenomas
(b) Prolactin deficiency
(c) Amenorrhea-Galactorrhea
(d) Acromegaly
64. A 35 years old male with long standing disseminated TB presents in a emaciated state with following features:
• BP = 85/60 mmHg
• Low volume pulse of 100 BPM
• Diffuse hyperpigmentation that involves hand creases
• Serum $Na^+ = 120\text{meq/L}$ ($N = 136-146\text{ meq/L}$)
• Serum $K^+ = 6.6\text{ meq/L}$
Your most immediate response would be:
(a) To suspect secondary hyperaldosteronism and start IV steroids
(b) To suspect gram negative sepsis and start IV antibiotics
(c) To suspect adrenocortical insufficiency and start IV steroids
(d) To suspect massive pulmonary thromboembolism and start IV Heparin
65. All of the following drugs used in the management of diabetes mellitus cause hypoglycemia except:
(a) Metformin
(b) Tolbutamide
(c) Glibenclamide
(d) Glipizide
66. Which of the following drugs used to treat type II diabetes mellitus causes weight loss:
(a) Metformin

- (b) Glimepiride
(c) Repaglinide
(d) Gliclazide
67. **Most important step in management of diabetic ketoacidosis is administration of:**
(a) Insulin
(b) Intravenous fluids (saline)
(c) Soda-bicarbonate
(d) Potassium
68. **The most potent topical corticosteroid is:**
(a) Betamethasone valerate
(b) Triamcinolone acetonide
(c) Hydrocortisone acetate
(d) Clobetasol butyrate
69. **Vitamin beneficial in osteoporosis in combination with Vitamin D is:**
(a) Vitamin E
(b) Vitamin A
(c) Vitamin K
(d) Vitamin B
70. **The following drugs are used in the management of Postpartum Hemorrhage, except:**
(a) Oxytocin
(b) Methyl ergometrine
(c) Mifepristone
(d) Carboprost
71. **Deaths from lactic acidosis in diabetes mellitus is associated with therapy with which one of the following:**
(a) Metformin
(b) Tolbutamide
(c) Phenformin
(d) Glipizide
72. **Hormone replacement therapy in postmenopausal women can aggravate:**
(a) Osteoporosis
(b) Migraine
(c) Hot flushes
(d) All of the above
73. **Bromocriptine:**
(a) Inhibits prolactin release
(b) Inhibits adrenalin synthesis
(c) Inhibits insulin synthesis
(d) Inhibits thyroid synthesis
74. **Lugol's iodine is given to the patient:**
(a) Before surgery
(b) After surgery
(c) During surgery
(d) Adjuvant therapy
75. **Which of the following is not a treatment of osteoporosis?**
(a) Calcitriol
(b) Androgen
(c) Estrogen
(d) Vitamin D
76. **Somatostatin secreted by which type of cells in pancreas?**
(a) Gamma cells
(b) Delta cells
(c) Alpha cells
(d) Beta cells
77. **The following insulin can be given intravenously:**
(a) Protamine zinc insulin
(b) Ultra lente insulin
(c) Semi lente insulin
(d) Regular insulin
78. **Bromocriptine is indicated in the following except:**
(a) Parkinsonism
(b) Galactorrhoea
(c) Acromegaly
(d) Hypothyroidism
79. **Orally active hormone is:**
(a) TSH
(b) Thyroxine
(c) GH
(d) Prolactin
80. **Longest acting glucocorticoids is:**
(a) Prednisone
(b) Prednisolone
(c) Cortisone
(d) Dexamethasone
81. **Drug of choice for the treatment of hyperthyroidism in pregnancy is:**
(a) Propylthiouracil
(b) Radio iodine
(c) Carbimazole
(d) Iodides
82. **What is the correct administration of oral pills for post coital contraception?**
(a) Combined pills 2 immediately and 2 after 12 hrs
(b) Combined pills 2 immediately and 2 after 48 hrs
(c) Progesterone pills 2 immediately and 2 after 12 hrs
(d) Progesterone pills 2 immediately and 2 after 48 hrs
83. **Mifepristone used for medical abortion is:**
(a) Anti estrogen
(b) Anti progesterone
(c) Anti folate
(d) Prostaglandin derivative
84. **Octreotide is given in all the following conditions except:**
(a) Bleeding esophageal varices
(b) Secretory diarrhea
(c) Infective diarrhea
(d) Acromegaly

85. Thyroxine is used in the treatment of which thyroid cancer:

- (a) Medullary
- (b) Radiation induced
- (c) Anaplastic
- (d) Papillary

86. Drug of choice for bleeding oesophageal varices is:

- (a) Ethanolamine oleate
- (b) Octreotide

- (c) Propanolol
- (d) Phytonadione

87. All of the following reduce T_4 absorption except:

- (a) Metformin
- (b) Iron salts
- (c) Raloxifene
- (d) Colsevelam

EXPLANATIONS

1. **Ans. (b) Hypoglycemia** (Ref: Goodman and Gilman 12/e p1116-1117)

Growth hormone therapy commonly leads to hyperglycemia (not hypoglycaemia)

2. **Ans. (c) Bromocriptine** (Ref: KDT 6/e p236)

It is an ergot alkaloid and is a dopamine agonist. Dopamine acts as prolactin inhibiting hormone in the brain. Agonism of dopamine receptors by bromocriptine is responsible for its use in hyperprolactinemia.

3. **Ans. (b) Bromocriptine** (Ref: KK Sharma 2/e p550)

Bromocriptine is a D_2 agonist and is useful in hyperprolactinemia by its action to inhibit the release of prolactin.

4. **Ans. (d) Glioma** (Ref: Katzung 11/e p650, 1081-1082)

- **Octreotide** is a long acting **somatostatin analog**. It can be used:
- To decrease **secretory diarrhea** and other symptoms of carcinoid syndrome and VIPoma.
- For the treatment of diarrhea due to vagotomy, short bowel syndrome and AIDS.
- For treatment and prophylaxis of **acute pancreatitis**.
- For the management of acromegaly
- For the treatment of islet cell tumors
- For controlling acute bleeding due to esophageal varices

5. **Ans. (a) It is effective orally** (Ref: Katzung 9/e p1048, KDT 6/e p35)

- Octreotide is the long acting and more potent synthetic analog of somatostatin.
- It can be administered by i.v., s.c. or i.m. routes. It is not effective orally.
- It can be used for
 - Acromegaly
 - Secretory diarrhea associated with carcinoids and AIDS
 - Islet cell tumors
 - Esophageal varices (seen in cases of portal hypertension).

6. **Ans. (b) It is longer acting than somatostatin** (Ref: KDT 6/e p235)

For details, see text

7. **Ans. (d) Nafarelin** (Ref: KDT 6/e p239)

Nafarelin is a GnRH agonist. It has no role in acromegaly.

8. **Ans. (a) Agonism at D_2 receptors** (Ref: KDT 6/e p236)

9. **Ans. (b) Immediately reduces gonadotropin secretion** (Ref: KDT 6/e p239)

- GnRH **agonists** like leuprolide, goserelin and nafarelin etc. are used by parenteral route. Continuous administration of these agents decreases gonadotropin secretion whereas pulsatile administration increases the secretion. When used continuously even then first few doses cause increased secretion of gonadotropins (LH and FSH) leading to flare up reaction in prostatic carcinoma.
- GnRH antagonists like cetrorelix and ganirelix are also used by parenteral route but these drugs immediately reduce gonadotropin secretion.

10. **Ans. (a) Bromocriptine** (Ref: KDT 6/e p236)

Hyperprolactinemia is caused by D_2 blockers. All the drugs listed are D_2 blockers except bromocriptine which is a D_2 receptor agonist. It is used in the treatment of hyperprolactinemia.

11. **Ans. (a) Bromocriptine** (Ref: KDT 6/e p236)

- Symptoms of the patient (amenorrhea, galactorrhea and infertility) points towards the diagnosis of hyperprolactinemia.
- Bromocriptine is a D_2 receptor agonist that can be used in the treatment of hyperprolactinemia (dopamine acts as prolactin release inhibiting hormone in the hypothalamus).
- Psychosis occurs due to excessive stimulation of D_2 receptors (D_2 blockers are used as typical antipsychotic drugs) and bromocriptine can precipitate the symptoms in predisposed patients.

12. Ans. (c) Octreotide (Ref: KDT 6/e p235)

Drugs useful in acromegaly are:

- Bromocriptine and cabergoline
- Somatostatin
- Octreotide (long acting somatostatin analogue)
- Pegvisomant (growth hormone receptor antagonist)

13. Ans. (b) Desmopressin (Ref: KDT 6/e p577)

• **Drugs used for the treatment of central (pituitary) diabetes insipidus are:**

- Desmopressin (selective V_2 agonist)
- Thiazides
- Chlorpropamide
- Carbamazepine

• **Drugs used for the treatment of nephrogenic (renal) diabetes insipidus are:**

- Thiazides
- Amiloride (for lithium induced)

- Thiazides are useful for the treatment of both central as well as nephrogenic diabetes insipidus.
- Desmopressin is not effective in nephrogenic diabetes insipidus.

14. Ans. (c) Cabergoline (Ref: KDT 6/e p236)

15. Ans. (c) Endogenous depression (Ref: KDT 6/e p236)

16. Ans. (c) Desmopressin (Ref: KDT 6/e p235, 577)

17. Ans. (a) Goserelin (Ref: KDT 6/e p239)

18. Ans. (a) GnRH (Ref: KDT 6/e p239)

19. Ans. (b) It can cause hypotension (Ref: KDT 6/e p236)

- For suppression of lactation, D_2 agonists like bromocriptine can be used. In hyperprolactinemia, these are given for long periods.
- Metoclopramide being a D_2 antagonist will stop the action of bromocriptine.
- Adverse effects of bromocriptine include nausea, vomiting, postural hypotension, digital vasospasm and CNS effects like hallucinations, psychosis etc.

20. Ans. (b) Osteoporosis (Ref: KDT 6/e p239)

GnRH agonists as well as antagonists can cause *hot flushes, loss of libido and osteoporosis* as adverse effects

21. Ans. (a) Contra-indicated in hyperthyroidism (Ref: KDT 7/e p254-255)

Iodine and iodides are useful in Graves' disease and make the gland shrink, firm and less vascular. These can inhibit all facets of thyroid function. Chronic iodine overdose is called iodism.

22. Ans. (d) Methimazole (Ref: KDT 6/e p250)

Methimazole inhibits only thyroid peroxidase whereas propylthiouracil inhibits thyroid peroxidase as well as 5'-deiodinase. Later is involved in peripheral conversion of T_4 to T_3 . (Katzung 12/e p688, Goodman Gilman 12/e p1150)

23. Ans. (c) Cleft lip/palate (Ref: KDT 6/e p251; Katzung 12/e p688, Goodman Gilman 12/e p1150)

- Use of antithyroid drugs in pregnancy may result in:

- Fetal hypothyroidism
- Aplasia cutis
- Scalp or patchy hair defect
- Choanal atresia
- Esophageal atresia
- Tracheo-esophageal fistula
- Minor facial anomalies
- Hypoplastic or absent phalanges
- Psychomotor delay

24. Ans. (c) Propylthiouracil (Ref: KDT 6/e p250)

- Propylthiouracil *does not* cross placenta and is therefore, the *drug of choice in first trimester pregnancy*.

25. Ans. (b) Sodium iodide (Ref: KDT 6/e p251)

- Iodides inhibit the secretion of thyroid hormones in the circulation and therefore are the fastest acting antithyroid drugs.
- Thyroid peroxidase inhibitors are delayed acting because their action manifests only when already stored pool of thyroid hormones is utilized.
- I^{131} takes more than 3 weeks to manifest their action.

26. Ans. (b) Is shorter acting (Ref: KDT 6/e p247)

- T_3 is the main active thyroid hormone. It is more potent (less plasma protein bound) and faster acting than T_4 . However, short duration of action limits its use for the treatment of hypothyroidism (requires life long treatment).
- T_3 is indicated for the treatment of myxedema coma.

27. Ans. (d) All of the above (Ref: KDT 6/e p248)

Propylthiouracil, carbimazole and methimazole act by inhibiting the enzyme, thyroid peroxidase. It catalyses:

- Oxidation of iodine
- Organification
- Coupling

28. Ans. (a) Propylthiouracil (Ref: KDT 6/e p249, 250)

For the peripheral conversion of T_4 to T_3 , the enzyme needed is 5'-deiodinase. It is inhibited by

- Propylthiouracil,
- Propanolol,
- Amiodarone.

29. Ans. (d) Does not inhibit peripheral conversion of T_4 to T_3 (Ref: KDT 6/e p250)

Carbimazole	Propylthiouracil
Produces an active metabolite, methimazole	No active metabolite
Less plasma protein binding (PPB)	More PPB
Crosses placenta	Does not cross placenta
More potent	Less potent
Does not inhibit 5'-deiodinase	Inhibits 5'-deiodinase

30. Ans. (a) Lugol's iodine (Ref: KDT 6/e p251, 252)

31. Ans. (b) 8 days (Ref: KDT 6/e p252)

32. Ans. (a) As short term symptomatic therapy till effect of carbimazole develops (Ref: KDT 6/e p253)

33. Ans. (c) Elderly patients with ischemic heart disease (Ref: KDT 6/e p253)

- I^{131} is contra-indicated in children and young adults because if hypothyroidism develops in response to radioactive iodine, it is permanent.
- Use of radioactive iodine is contra-indicated in pregnancy.
- In ischemic heart disease patients, surgery should be avoided. I^{131} therapy is a good alternative in such patients.

34. Ans. (c) Has a longer half life (Ref: KDT 6/e p247)

Liothyronine (T_3) as compared to thyroxine (T_4) is:

- Fast acting
- More potent
- Short half life

Indication of liothyronine includes myxedema coma and for most of the indications thyroxine is used because it has a long half life thus can be used less frequently than T_3 .

35. Ans. (c) Propylthiouracil (Ref: KDT 6/e p250)

- Iodides are commonly used to decrease the size and vascularity of thyroid gland before surgery.
- As this patient is pregnant, iodides and radioactive iodine is contra-indicated.
- Propylthiouracil is safe in pregnancy and is used for this purpose.

36. Ans. (d) Serum TSH level (*See below*)

- TSH levels are elevated in a hypothyroid patient (because feedback inhibition by thyroid hormones is not present).
- Administration of thyroid hormones (T_3 and T_4) decreases TSH by contributing to feedback inhibition.
- If TSH levels are less than normal, it signifies overtreatment whereas high TSH level suggests inadequate treatment.

37. Ans. (b) Reserpine (*Ref: Katzung 11/e p677, CMDT-2010/1015*)

Thyroid storm is an extreme form of thyrotoxicosis. The drugs used in thyroid storm are:

- Propranolol to control severe cardiovascular manifestations.
- Calcium channel blockers like diltiazem are used if β -blockers are contra-indicated as in asthmatics.
- Iodides (NaI, KI, Lugol's iodine) to inhibit the release of thyroid hormones from the gland.
- Propylthiouracil or methimazole to reduce the synthesis of thyroid hormones.
- Hydrocortisone to protect the patient against shock.

Note: Aspirin should be avoided as it may displace T_4 from thyroid binding globulin resulting in elevated levels of free T_4 .

38. Ans. (b) 8 hours (*Ref: KDT 6/e p250*)

Half-life of carbimazole is around 8 hours whereas propylthiouracil has $t_{1/2}$ of 2 hours.

39. Ans. (d) Carbamazepine (*Ref: Katzung 11/e p671-673*)**40. Ans. (b) Cretinism** (*Ref: CMDT 2010/1005*)**41. Ans. (d) Propylthiouracil** (*Ref: KDT 6/e p250*)**42. Ans. (b) Captopril** (*Ref: KDT 6/e p484*)**43. Ans. (a) Propylthiouracil** (*Ref: KDT 6/e p250*)**44. Ans. (c) Metformin** (*Ref: Goodman Gilman 12/e p1259*)

- **Lactic acidosis** (more with phenformin) and **megaloblastic anemia** (more with metformin) due to vitamin B_{12} deficiency are the major adverse effects of these drugs. Lactic acidosis is more likely to occur in the presence of hepatic and renal impairment or alcohol ingestion.

45. Ans. (a) Acarbose (*Ref: Katzung 11/e p743-744*)

Drugs that act by release of insulin can cause hypoglycemia. Therefore, glimepride (a sulfonylurea) and nateglinide that blocks ATP sensitive potassium channels and release insulin will cause hypoglycemia as an adverse effect whereas use of acarbose alone is not associated with hypoglycemia.

46. Ans. (c) Glucose (*Ref: Katzung 11/e p743-744*)

- Complex carbohydrates (polysaccharides and sucrose) are absorbed after conversion to simple carbohydrates by α -glucosidase. Inhibitors of this enzyme (*acarbose and miglitol*) decrease carbohydrate absorption from the GIT. Although these drugs themselves do not cause hypoglycemia but blood sugar may decrease if these are combined with insulin or other drugs releasing insulin. In such a case of hypoglycemia, simple carbohydrates like glucose (not sucrose or other complex carbohydrates) should be used.

47. Ans. (c) It causes transcription of gene for carbohydrate and fat metabolism in the absence of insulin (*Ref: Goodman and Gilman 12/e p1260, Katzung 12/e p758*)

- Thiazolidinediones require the presence of insulin for pharmacological activity and are not indicated to treat type 1 diabetes.
- Thiazolidinediones (glitazones) sensitize peripheral tissues to insulin. They bind a nuclear receptor called peroxisome proliferator-activated receptor gamma (PPAR-gamma) and affect the expression of a number of genes.
- Two drugs of this class, rosiglitazone and pioglitazone are available for clinical use. Rosiglitazone is primarily metabolized by the CYP 2C8 isoenzyme and pioglitazone is metabolized by CYP 2C8 and CYP 3A4.
- Edema occurs in about 3–4% of patients receiving monotherapy with rosiglitazone or pioglitazone. The edema occurs more frequently (10–15%) in patients receiving concomitant insulin therapy and may result in congestive heart failure. The drugs are contraindicated in diabetic individuals with New York Heart Association class III and IV cardiac status.

48. Ans. (b) It can be used for treatment of Type 1 diabetes mellitus (*Ref: CMDT 2010 p1095*)

- Exenatide (Exendin 4) is a GLP-1 receptor agonist that is more resistant to DPP-4 action and cleared by the kidney.

- When this drug is given to patients with type 2 diabetes by subcutaneous injection twice daily, it lowers blood glucose and HbA_{1c} levels. It is not indicated in type 1 diabetes.
 - Exenatide appears to have the same effects as GLP-1 on glucagon suppression and gastric emptying.
 - *Only drugs approved for treatment of type 1 diabetes are insulin and pramlintide.*
49. **Ans. (c) It decreases insulin resistance** (Ref: Goodman and Gilman, 12/e p1258-1259)
- Sulfonylureas, nateglinide and repaglinide act by inhibiting ATP sensitive K channels and thus resulting in release of insulin.
 - Like insulin, all of these drugs can cause hypoglycemia.
 - However, nateglinide therapy produce fewer episodes of hypoglycemia as compared to other oral insulin secretagogue.
 - Nateglinide and repaglinide are short acting and thus can reduce post-prandial hyperglycemia.
50. **Ans. (d) Ketogenesis** (Ref: Katzung 11/e p731)
Insulin inhibits the formation of ketone bodies, therefore its deficiency can result in diabetic ketoacidosis.
51. **Ans. (a) Hypokalemia** (Ref: CMDT 2010/1114)
Insulin result in shift of potassium into the cells and thus can result in hypokalemia.
52. **Ans. (b) It can cause hypoglycemia** (Ref: Katzung 12/e p759, Goodman 12/e p1264-1265)
- Alpha-glucosidase inhibitors (acarbose and miglitol) reduce postprandial hyperglycemia by delaying glucose absorption.
 - This class of agents is unique because it reduces the postprandial glucose rise even in individuals with type 1 DM.
 - Acarbose could be used, either as an alternative or in addition to changes in lifestyle, to delay development of type 2 diabetes in patients with impaired glucose tolerance.
 - These drugs do not cause hypoglycemia.
53. **Ans. (c) Glargine** (Ref: Harrison's 16/e p2173; KDT 6/e p261)
- Insulin glargine and insulin detemir are ultra long acting insulins.
 - Insulin aspart and insulin lispro are ultra short acting insulins.
54. **Ans. (c) Renal dysfunction is not a contra-indication for their use** (Ref: KDT 6/e p269)
- Metformin is a biguanide. It does not increase the release of insulin but acts by decreasing the production (by inhibiting gluconeogenesis and glycogenolysis) and increasing the utilization (by stimulating glycolysis and glycogenesis) of glucose. It also decreases the absorption of glucose from the intestine.
 - As biguanides do not increase the release of insulin, there is very little risk of hypoglycemia with their use.
 - Major adverse effects of biguanides are lactic acidosis and megaloblastic anemia. Risk of lactic acidosis increases in patients with hepatic and renal insufficiency and in chronic alcoholics.
55. **Ans. (c) Hypoglycemia is a common and serious side effect** (Ref: KDT 6/e p270)
- Hypoglycemia is caused by the drugs stimulating the release of insulin, e.g. insulin, sulfonylureas and meglitinides.
 - Biguanides, α -glucosidase inhibitors and thiazolidinediones act by other mechanisms and thus are less likely to cause hypoglycemia.
56. **Ans. (a) Chlorpropamide** (Ref: KDT 6/e p267)
- Chlorpropamide is a first generation sulfonylurea. It increases the risk of hypoglycemia (like other sulfonylureas and meglitinides).
 - **Other adverse effects of chlorpropamide are:**
 - *ADH like action leading to dilutional hyponatremia.
 - *Cholestatic jaundice.
 - *Disulfiram like reaction.
57. **Ans. (b) Acts by increased insulin secretion** (Ref: KDT 6/e p269)
58. **Ans. (a) Action is faster and short in duration than regular insulin; (b) It is given 15 minutes prior to meal** (Ref: KDT 6/e p261)
- Lispro insulin is an insulin analogue, produced by recombinant technology.
 - Its onset of action is rapid (within 15 minutes of s/c injection), peaks at 30-90 minutes and last only 3-4 hrs.
 - So meal should be taken 15-20 minutes after insulin injection whereas in case of regular insulin patient have to wait for about 60 minutes after taking insulin.
 - Patient must be taught to ingest adequate carbohydrate diet early in the meal to avoid hypoglycaemia during meal.
 - Duration of action remains upto about 4 hrs irrespective of dosage; but in case of regular insulin duration of action is prolonged when larger dose is used.

59. Ans. (b) Glimepiride; (d) Rosiglitazone; (e) Repaglinide (Ref: KDT 6/e p269-270;CMDT 2010/1092)

- Metformin (a biguanide) being excreted unchanged by kidneys is contraindicated in renal failure. Its excretion is impaired in renal failure resulting in raised plasma level. It can block hepatic uptake of lactate to provoke lactic acidosis. Renal failure affects not only lactate removal by kidneys but also metformin excretion.
- Glimepiride (All sulfonylurease except chlorpropamide) is completely metabolized by the liver to relatively inactive metabolic products.
- **Repaglinide** undergoes complete metabolism in liver to inactive biliary products. It is useful in **patients with renal impairment or elderly**.
- Rosiglitazone is primarily metabolized by CYP. It is less likely to cause hepatotoxicity than troglitazone. It is contraindicated in liver disease and CHF.

60. Ans. (b) Hypoglycemia (Ref: KDT 6/e p262)

61. Ans. (b) Glipizide (Ref: KDT 6/e p266)

62. Ans. (a) Acarbose (Ref: KDT 6/e p270)

- It is an alpha-glucosidase inhibitor.
- It inhibits the breakdown of complex carbohydrates to simple carbohydrates and thus decreases their absorption.

63. Ans. (c) An old man with severe bradycardia and hypotension resulting from ingestion of overdose of atenolol

(Ref: KDT 6/e p274)

- Glucagon is the antidote of β -blocker poisoning. It acts by increasing cAMP in the heart via stimulation of glucagon receptors. Cyclic AMP stimulates the heart.
- Calcium gluconate can also be used for the treatment of β -blocker poisoning.

64. Ans. (b) Enzymatic receptor (Ref: KDT 6/e p258)

Insulin acts by stimulation of tyrosine kinase receptors.

65. Ans. (b) Subcutaneous (Ref: KDT 6/e p259)

66. Ans. (b) Rapidly absorbed (Ref: KDT 6/e p261)

Human insulin has rapid absorption and shorter duration of action than pork or beef insulin.

67. Ans. (a) Is more potent (Ref: KDT 6/e p266)

Second generation (like glipizide) sulfonylureas are more potent than first generation agents (like chlorpropamide).

- Chlorpropamide is the longest acting sulfonylurea.
- Sulfonylureas can cause hypoglycemia (even in non-diabetics) due to release of insulin.

68. Ans. (b) It is less liable to cause lactic acidosis (Ref: KDT 6/e p269)

Incidence of lactic acidosis is more with phenformin and that of megaloblastic anemia (due to interference with vitamin B₁₂ absorption) is more with metformin.

69. Ans. (b) Type 1 diabetics (Ref: KDT 6/e p266)

- Sulfonylureas decrease blood glucose in diabetics as well as non-diabetics.
- It requires at least 30% of functional beta cells for their action.
- Insulin is the only treatment for type 1 diabetes.

70. Ans. (d) All of the above (Ref: KDT 6/e p267)

71. Ans. (a) Non-diabetics (Ref: KDT 6/e p269)

- Metformin is the drug of choice for the treatment of obese diabetic patients, as it causes weight loss.
- It does not cause release of insulin, therefore less chances of hypoglycemia.

72. Ans. (b) Taken just before a meal, it limits post-prandial hyperglycemia in type 2 diabetes mellitus (Ref: KDT 6/e p269)

- Nateglinide and repaglinide are short acting oral hypoglycemic agents.
- These are used to limit the post-prandial hyperglycemia.
- Like sulfonylureas, these drugs also act by blocking K⁺ channels in the β -cells of pancreas that lead to depolarization and release of insulin.

73. Ans. (d) They are used first in most cases of uncomplicated mild to moderate type 2 diabetes (Ref: KDT 6/e p271)

74. Ans. (b) Glipizide (Ref: KDT 6/e p266, 267)

Hypoglycemia is caused by the drugs that cause release of insulin. Two group of such drugs are sulfonylureas (like chlorpropamide, glipizide etc) and meglitinides (e.g. Repaglinide)

75. **Ans. (a) Crystalline zinc insulin** (Ref: KDT 6/e p263)

Diabetic ketoacidosis must be managed by fast acting insulin preparations like

- Regular insulin [crystalline zinc insulin]
- Insulin lispro
- Insulin aspart.

76. **Ans. (c) Lactic acidosis** (Ref: KDT 6/e p269)

Biguanides like metformin and phenformin increase the risk of lactic acidosis particularly in the patients with hepatic or renal disease. Both these drugs can cause lactic acidosis although phenformin has more potential to cause this adverse effect than metformin. Metformin is more likely to cause megaloblastic anemia than phenformin.

77. **Ans. (d) K⁺ entry into cells** (Ref: CMDT-2010/798)

- Insulin, bicarbonate and β -agonists shift K⁺ intracellularly within minutes of administration. Thus, these drugs can be used for treatment of acute hyperkalemia

78. **Ans. (d) Diabetic kidney disease** (Ref: KDT 6/e p261)

- Human insulins are less antigenic (because contaminants are not there) than pork or beef insulin. These are used to prevent insulin resistance and lipodystrophy (atrophy or hypertrophy). These are also favored in pregnant patients.

79. **Ans. (c) Adrenaline** (Ref: Harrison 16/e p2185)

- Hypoglycemia is treated urgently by oral glucose.
- It neuroglucopenia precludes oral feeding, i.v. glucose (25 g) should be given.
- If i.v. therapy is not practical, s.c. or i.m. glucagon should be given. Because glucagon primarily acts by glycogenolysis, it is ineffective in glycogen depletion states (e.g. alcohol induced hypoglycemia).

80. **Ans. (d) Increasing insulin secretion from pancreas** (Ref: KDT 6/e p266)

- Sulfonylureas stimulate the release of insulin by the β cells of the islets of Langerhans by blocking K⁺ channels. Glucagon secretion is also reduced by sulfonylureas, but it is a minor action.

81. **Ans. (a) Chlorpropamide** (Ref: KDT 6/e p267)

- Intolerance to alcohol with flushing (disulfiram like reaction) occurs with chlorpropamide.
- Chlorpropamide, tolbutamide, tolazamide and acetohexamide are first generation sulfonylureas.

82. **Ans. (a) Glucagon production** (Ref: KDT 6/e p266)

Sulfonylureas act by

- Increasing insulin release from pancreas (not by decreasing insulin secretion), so 'option b' ruled out.
- A minor action reducing glucagon and increasing somatostatin release has been demonstrated.

83. **Ans. (b) Phenformin** (Ref: Katzung 11/e p741)

84. **Ans. (d) Insulin secretion** (Ref: KDT 6/e p266)

85. **Ans. (b) Hyperglycemia** (Ref: KDT 6/e p262)

86. **Ans. (c) Ultralente** (Ref: KDT 6/e p259)

87. **Ans. (c) Tolbutamide** (Ref: KDT 6/e p266)

88. **Ans. (c) Longer duration of action** (Ref: KDT 6/e p261)

89. **Ans. (b) Miglitol** (Ref: KDT 6/e p266)

90. **Ans. (b) Glibenclamide** (Ref: KDT 6/e p267)

91. **Ans. (b) Protamine zinc insulin** (Ref: KDT 6/e p259)

92. **Ans. (a) Total pancreatectomy** (Ref: KDT 6/e p266)

93. **Ans. (c) Rosiglitazone** (Ref: Katzung 11/e p739-740)

94. **Ans. (a) It is short acting** (Ref: KDT 6/e p567-568)

95. **Ans. (c) Water retention with weight gain** (Ref: Katzung 11/e p743)

96. **Ans. (d) Subcutaneous route** (Ref: KDT 6/e p261)

97. Ans. (a) **Dexamethasone** (Ref: Goodman and Gilman 12/e p123-29-1230)

To suppress fetal androgen production effectively and consequent virilization, dexamethasone must be initiated before 10 weeks of gestation.

Note: To treat congenital adrenal hyperplasia in baby hydrocortisone is used.

98. Ans. (c) **Liver** (Ref: Internet)

- MR is expressed in many tissues, such as the kidney, colon, heart, central nervous system (hippocampus), brown adipose tissue and sweat glands.

99. Ans (d) **Metabolic acidosis** (Ref: CMDT 2010/1056)

- Aldosterone causes retention of Na^+ and water and removal of K^+ and H^+ . Therefore, excess of aldosterone may result in hypernatremia, hypertension (due to retention of Na^+) and hypokalemia (due to removal of K^+) and metabolic alkalosis (due to removal of H^+).

100. Ans. (c) **Löffler's syndrome** (Ref: CMDT 2010/266, 1018)

- Corticosteroids are contra-indicated in psychosis and herpes simplex.
- Treatment of choice for subacute thyroiditis is aspirin. Thyrotoxic symptoms are treated with propranolol. Transient hypothyroidism, if symptomatic, can be treated with thyroxine.
- Prednisolone produce dramatic relief in eosinophilic pulmonary syndromes like Loeffler syndrome.

101. Ans. (a) **Ointment** (Ref: Katzung 11/e p1048,1060)

'Ointment bases tend to give better activity to the corticosteroids than do cream or lotion vehicles'.

Ability of the vehicle to retard evaporation from the surface of skin varies as

Tinctures (least) < wet dressings < Lotions < Gels < Aerosols < Powders < Pastes < Creams < Foams < Ointments (Maximum).

102. Ans. (b) **Betamethasone valerate cream 0.5%** (Ref: Katzung 10/e p102; KDT 6/e p282)

Betamethasone is most potent and hydrocortisone is least potent topical steroid.

103. Ans. (c) **Ileo-caecal tuberculosis** (Ref: Katzung 10/e p1263; KDT 6/e p287)

- If used in intestinal tuberculosis, steroids can result in silent perforation, therefore are contra-indicated in ileo-caecal tuberculosis.

104. Ans. (b) **It is less likely to occur in patients receiving inhaled steroids** (Ref KDT 6/e p286)

- HPA-axis suppression is associated with adrenal atrophy.
- It occurs when hydrocortisone (>20-25 mg/day) or equivalent is given for more than 2-3 weeks. In the question, there is no mention of time.
- Patients developing HPA axis suppression must be provided with steroids for stressful situations for ONE YEAR after withdrawal.
- Chances of HPA-axis suppression is minimum with inhaled route as compared to oral route.

105. Ans. (b) **Binds to the plasma membrane receptors and following internalization influence nuclear changes** (Ref: KDT 6/e p232)

- Steroids act by binding to intracellular receptors.

106. Ans. (c) **↑ Lipocortin** (Ref: KDT 6/e p279)

The mechanism of anti-inflammatory and immunosuppressive action of glucocorticoids are:

- Induction of Lipocortins (now known as annexins) in macrophages, endothelium, and fibroblasts that result in inhibition of PLP.A_2
- Decrease in cytokine production, e.g. IL-1, IL-2, IL-3, IL-6, TNF-alpha, GM-CSF and gamma-interferon by macrophages, lymphocytes and endothelium.
- Inhibit IgE mediated histamine and LTC_4 release from the basophils.
- Decreased production of ELAM-I, ICAM-I in endothelial cells.
- Decreased production of collagenase.
- Decreased production of acute phase reactants from macrophages and endothelial cells.

107. Ans. (a) **Ketoconazole**; (b) **Aminoglutethimide** (Ref: Harrison's 16/e p2141, KDT 6/e p287)

Drugs causing Addison's disease are:

- Metirapone
- Ketoconazole
- Aminoglutethimide
- Mitotane

108. **Ans. (a) Chemotherapy induced vomiting** (Ref: KDT 6/e p647)

109. **Ans. (c) Collecting ducts** (Ref: Katzung 10/e p240)

- Aldosterone is the principal mineralocorticoid. It stimulates the reabsorption of Na^+ and excretion of K^+ and H^+ by its action on late distal tubules and collecting ducts.

110. **Ans. (b) Acidosis** (Ref: KDT 6/e p277)

111. **Ans. (c) Phospholipase A** (Ref: KDT 6/e p279)

112. **Ans. (d) Lipocortin** (Ref: KDT 6/e p279)

Corticosteroids induce the synthesis of lipocortins that inhibit the enzyme phospholipase A2.

113. **Ans. (d) Methylprednisolone** (Ref: KDT 6/e p281)

114. **Ans. (a) Prednisolone 20 mg/day oral for one year** (Ref: KDT 6/e p286)

- If used for more than two weeks, corticosteroids can lead to HPA-axis suppression. If discontinued abruptly, precipitation of acute adrenal insufficiency can result. This is the most serious adverse effect seen with the use of corticosteroids that can cause death of the patient.

115. **Ans. (a) Congenital adrenal hyperplasia** (Ref: KDT 6/e p283)

- Corticosteroids are used for the management of congenital adrenal hyperplasia.
- Corticosteroids can result in hyperglycemia and thus may vitiate the control of blood glucose in diabetics.
- Due to retention of Na^+ and water, corticosteroids can worsen the hypertension.
- By inhibiting the production of gastroprotective prostaglandins, corticosteroids increase the risk of peptic ulcer disease.

116. **Ans. (d) Suppression of ACTH secretion** (Ref: KDT 6/e p283)

In congenital adrenal hyperplasia, due to decreased formation of steroids, there is decreased feedback inhibition of ACTH. Thus more ACTH is formed which leads to adrenal hyperplasia. Thus exogenous steroids are given to suppress ACTH secretion.

117. **Ans. (b) Osteoporosis** (Ref: KDT 6/e p286)

Glucocorticoids have lot of adverse effects on long term use. These can lead to Cushing syndrome, hyperglycemia, osteoporosis, delayed wound healing, increased susceptibility to infections, cataract, glaucoma and many other adverse effects.

118. **Ans. (c) No change/increase in prednisolone dose** (Ref: KDT 6/e p283)

- During conditions of stress or infection, dose of steroids should not be decreased. Rather, increase in dose may be required.

119. **Ans. (a) They do not cause Na^+ and water retention** (Ref: KDT 6/e p285)

- Triamcinolone, betamethasone, dexamethasone and paramethasone are selective glucocorticoids (have zero mineralocorticoid action).
- These are preferred for cerebral edema because they lack salt and water retaining potential (mineralocorticoid action).

120. **Ans. (c) Cortisol and fludrocortisone** (Ref: KDT 6/e p282)

Patient should be given both mineralocorticoids as well as glucocorticoid.

Max. mineralocorticoid activity – Aldosterone

Max. glucocorticoid activity – Dexamethasone

121. **Ans. (c) Betamethasone** (Ref: KDT 6/e p282, 287)

Steroids with long half life like betamethasone and dexamethasone cannot be used for alternate day therapy because even in alternate day therapy there will be sufficient blood levels of these steroids to cause suppression of HPA axis.

122. Ans. (c) Effective in acute asthma (Ref: Katzung 11/e p348)

- Beclomethasone is an inhalational steroid useful in prophylaxis of asthma. Like other inhalational steroids, it can also cause oropharyngeal candidiasis.
- For acute attack of asthma, bronchodilators are used. Steroids are slow to act, therefore are not effective in acute attack. Prednisolone or hydrocortisone can be used along with bronchodilators for acute severe asthma.

123. Ans. (a) Aldosterone (Ref: KDT 6/e p282)

Aldosterone is most potent mineralocorticoid whereas betamethasone is most potent glucocorticoid.

124. Ans. (d) Photosensitivity (Ref: KDT 6/e p855)

- Steroids are used for treatment of photosensitivity.
- Other effects i.e. skin atrophy, telangiectasia and folliculitis can be caused by steroids.

125. Ans. (b) Glaucoma (Ref: KDT 6/e p286)

- Glaucoma occurs after the use of prolonged **topical** therapy in susceptible individuals.

126. Ans. (a) Dexamethasone (Ref: KDT 6/e p282)

For details, refer to text.

127. Ans. (c) Eczematous skin disease (Ref: KDT 6/e p286)

Hypertension and diabetes are aggravated by steroids. In peptic ulcer, bleeding and silent perforation may occur. Thus, steroids are contraindicated in these conditions. However, since steroids may have to be used as a life saving measure, all of these are relative contraindications. Topical corticosteroids are highly effective in eczematous skin diseases.

128. Ans. (b) Rifampicin (Ref: KDT 6/e p317)

- Oral contraceptive failure can occur with patients taking rifampicin because rifampicin is a microsomal enzyme inducer and induces the metabolism of OCPs.

129. Ans. (a) Hydrocortisone (Ref: KDT 6/e p283, CMDT 2014/1116)

- In chronic adrenal insufficiency or Addison's disease, hydrocortisone given orally is the drug of choice.
- Hydrocortisone is a glucocorticoid with maximum mineralocorticoid action.

130. Ans. (a) Muscular hypertrophy (Ref: KDT 6/e p286)

"Muscle weakness occurs in both hypo or hypercorticism"

131. Ans. (c) Cortisol (Ref: KDT 6/e p282)

132. Ans. (a) Ketoconazole (Ref: Katzung 11/e p693)

133. Ans. (c) Prednisolone (Ref: KDT 6/e p282)

134. Ans. (c) Osteomalacia (Ref: KDT 6/e p286)

135. Ans. (d) Hypotension (Ref: KDT 6/e p2002)

136. Ans. (d) Break down of phospholipids (Ref: KDT 6/e p279)

137. Ans. (a) Mitotane (Ref: Katzung 11/e p695)

138. Ans. (b) Hypertension (Ref: KDT 6/e p285)

139. Ans. (a) Hypoglycemia (Ref: KDT 6/e p286)

140. Ans. (d) Methyl prednisolone (Ref: KDT 6/e p282)

141. Ans. (c) Prevent de-iodination (Ref: Katzung 11/e p670, 686)

Glucocorticoids on long term use suppress the release of ACTH, GH, TSH and LH. These also inhibit the activity of 5'-deiodinase and thus inhibit the peripheral conversion of T4 to T3. These also decrease thyroid binding globulin.

142. Ans. (c) Collagen vascular diseases (Ref: KDT 6/e p284)

143. Ans. (d) Teriparatide (Ref: CMDT 2010/1041)

- Teriparatide acts by stimulating the formation of bone whereas bisphosphonates act by inhibiting the resorption of bone. Strontium ranelate has both of these properties.

144. Ans (a) Raloxifene (Ref: Katzung, 11/e p759, Goodman and Gilman, 11/e p1557)

Raloxifene is a selective estrogen receptor modulator with estrogen agonistic action on bone and antagonistic action on breast and endometrium. It is therefore the preferred drug for the treatment and prevention of *post-menopausal osteoporosis*. Major adverse effect of this agent is increased risk of **thromboembolism**.

145. Ans (a) **Strontium ranelate** (Ref: *Katzung 11/e p761*)

146. Ans (a) **Acute renal failure** (Ref: *Goodman and Gilman 12/e p1296*)

- The serious adverse effect noted with most of bisphosphonates is osteonecrosis of Jaw bone.
- Zoledronate can cause serious side-effects as nephrotoxicity and renal failure.

147. Ans. (c) **Decreasing the osteoclast mediated resorption of bone** (Ref: *KDT 6/e p333, 334*)

148. Ans. (c) **Reduces incidence of venous thrombosis** (Ref: *KDT 6/e p305*)

- Raloxifene is a SERM. It has agonistic activity on estrogen receptors in some tissues (bone, blood and liver) and antagonistic activity on other tissues (breast, endometrium).
- Estrogen therapy can result in
 - Increased bone formation
 - Increased risk of endometrial carcinoma
 - Increased risk of breast carcinoma
 - Increased production of clotting factors predisposing to thromboembolism
 - Increase in HDL and decrease in LDL cholesterol
- Raloxifene thus produces all the beneficial effects except on liver. Thromboembolism is its major adverse effect.

149. Ans. (b) **Vitamin D excess** (Ref: *Katzung 10/e p713; KDT 6/e p334*)

BISPHOSPHONATES are used for the treatment of post menopausal osteoporosis, steroid induced osteoporosis, Paget's disease and hypercalcemia of malignancy (pamidronate and zoledronate by i.v route are preferred).

150. Ans. (d) **Post-menopausal osteoporosis** (Ref: *KDT 6/e p305*)

151. Ans. (d) **Prednisone** (Ref: *KDT 6/e p286*)

- Steroids result in osteoporosis on long term use.

152. Ans. (c) **It increases risk of developing breast cancer** (Ref: *KDT 6/e p305*)

For details, see text.

153. Ans. (d) **Calcitriol** (Ref: *KDT 6/e p390*)

Most active vitamin D preparation is calcitriol.

154. Ans. (d) **Act as agonist in some tissues and antagonists in other tissues** (Ref: *KDT 6/e p303*)

SERMs are drugs with agonistic action on estrogen receptors in some tissues and antagonistic action in other tissues, e.g. tamoxifen, raloxifene.

155. Ans. (d) **Thyroxine** (Ref: *KDT 6/e p327*)

Thyroid hormones and glucocorticoids increase the risk of osteoporosis whereas other drugs mentioned in the options are used to treat osteoporosis.

156. Ans. (c) **Strong family history of breast cancer** (Ref: *KDT 6/e p305*)

157. Ans. (c) **Erosive esophagitis** (Ref: *KDT 6/e p334, 335*)

Bisphosphonates (alendronate, risedronate etc.) are used for the prophylaxis and treatment of osteoporosis. Esophageal toxicity is their distinct adverse effect.

158. Ans. (c) **PGE₂** (Ref: *Katzung 11/e p321-322*)

Major effect of prostaglandins especially PGE₂ is to increase bone turnover. PGs may contribute to the bone loss that occurs at menopause, it has been speculated that NSAIDs may be of therapeutic value in osteoporosis, however clinical evaluation is required.

159. Ans. (a) **Inhibiting bone resorption** (Ref: *KDT 6/e p330; Ganong 22/e p394*)

- Calcitonin inhibits bone resorption by *direct action* on osteoclasts. Calcitonin receptors are present on osteoclasts (inhibits osteoclastic activity → hypocalcemia)
- It also inhibits proximal tubular calcium and phosphate reabsorption by direct action on kidney. However, hypocalcemia which occurs overrides the direct action by decreasing the total Ca⁺⁺ filtered at the glomerulus → urinary Ca⁺⁺ actually decreased.

160. Ans. (a) IV (Ref: KDT 6/e p335)

161. Ans. (c) Decreasing the osteoclast mediated resorption of bone (Ref: KDT 6/e p334)

162. Ans. (a) Calcitonin (Ref: CMDT 2010/801)

Bisphosphonates are the treatment of choice for hypercalcemia of malignancy but require 48-72 hours before reaching full therapeutic effect. Calcitonin may be helpful to treat hypercalcemia before the onset of action of bisphosphonates.

163. Ans. (d) Multivitamins (Ref: Katzung. 11/e p765-766)

164. Ans. (d) Coronary heart disease (Ref: CMDT 2014/1140-1141)

Combined estrogen plus progesterone hormone replacement therapy increases the risk of coronary artery disease and breast cancer.

Estrogen alone has no effect or protective effect on CAD whereas combination with progesterone increases the risk.

Vaginal atrophy, hot flushes and osteoporosis are decreased by hormone replacement therapy

165. Ans. (c) Is slower and short acting and less safer than SERMs (Ref: Goodman and Gilman 11/e p1759-1760)

- Fulvestrant is selective estrogen-receptor downregulators (SERD), having an improved *safety profile, faster onset, and longer duration of action* than the SERMs due to its pure ER antagonist activity. Fulvestrant was approved in 2002 for postmenopausal women with hormone receptor-positive metastatic breast cancer that has progressed despite antiestrogen therapy.
- Fulvestrant is administered intramuscularly at monthly intervals and well tolerated with the most common adverse events being nausea, asthenia, pain, vasodilation (hot flushes), and headache.

166. Ans (a) Oral contraceptives (Ref: Katzung 11/e p715)

Oral contraceptives should be used with caution in

• Liver disease	• Asthma	• Eczema
• Migraine	• Diabetes mellitus	• Hypertension
• Optic neuritis	• Retrobulbar neuritis	• Convulsive disorder

167. Ans (a) Ectopic Pregnancy (Ref: Williams page 232, Katzung 11/e p717)

- Mifepristone is an antiprogesterin and anti-glucocorticoid agent. It increases uterine contractility by reversing the progesterone induced inhibition of contraction
- It can be used for terminating early pregnancy in first 7 weeks after conception.
- It is also indicated for medical management of ectopic pregnancy along with Methotrexate.
- It is also useful as an emergency contraceptive.

168. Ans. (c) Azoospermia (Ref: Goodman and Gilman, 11/e p1581)

- Continuous and prolonged use of GnRH agonists and gonadal hormones (testosterone, estrogen) leads to suppression of gonadal function.
- Increased androgens in blood suppress gonadotropin secretion resulting in decreased sperm production and testicular size
- Since this effect is usually reversible, it is investigated as a therapeutic approach for male contraception

169. Ans (d) Cancer in opposite breast (Ref: Goodman and Gilman 12/e p1179, CMDT 2010/1505)

Tamoxifen is a SERM that acts as antagonist at estrogen receptors in the breast. It decreases the risk of contralateral breast cancer and is approved for primary prevention of breast cancer in women at high risk.

Adverse effects of Tamoxifen include:

• Hot flashes	• Vaginal discharge or bleeding	• Menstrual irregularities
• Thromboembolic events (rare)	• Endometrial hyperplasia	• Cataract
• Hepatotoxicity	• Tumor flare	

170. Ans. (a) Aspirin (Ref: CMDT-2010/696)

Oral contraceptive failure can occur with:

- Enzyme inducers like phenytoin, phenobarbitone, rifampicin, carbamazepine etc
 - Drugs inhibiting the enterohepatic cycling e.g ampicillin, tetracycline etc.
- Aspirin does not interfere with oral contraceptives.

171. **Ans. (a) Levonorgestrel** (Ref: CMDT-2010/700, KDT 6/e p312)

For details see text.

172. **Ans. (a) Decreases HDL** (Ref: Katzung 10/e p658; KDT 6/e p301)

Metabolic effects of estrogens include a rise in HDL, rise of triglycerides, slight reduction of LDL and that of total cholesterol. Estrogens decrease hepatic oxidation of adipose tissue lipid to ketones and increase synthesis of triacylglycerol. Increase in triacylglycerol are prominent feature of estrogens. Fibrates are the drugs of choice for reducing triacylglycerol.

173. **Ans. (a) Raloxifene** (Ref: Katzung 10/e p672; KDT 6/e p305)

174. **Ans. (b) 5- α reductase enzyme** (Ref: KDT 6/e p294)

175. **Ans. (c) It blocks the conversion of dihydrotestosterone to testosterone** (Ref: KDT 7/e p302-303)

Finasteride is a 5- α -reductase inhibitor. It acts by blocking the conversion of testosterone to DHT. It can be used to relieve the static component of BHP (though its beneficial effect is delayed). Due to decrease in DHT, it can cause impotence. It can also be used in the treatment of male pattern baldness and prostate cancer.

176. **Ans. (d) Cimetidine** (Ref: KDT 6/e p317)

- Cimetidine is a microsomal enzyme inhibitor. It increases the plasma concentration of several drugs and can result in toxicity.
- Phenytoin and griseofulvin are microsomal enzyme inducers. These agents increase the metabolism and thus decrease the plasma concentration of oral contraceptives (estrogen and progesterone). Due to decreased plasma levels, contraceptive failure may occur.
- Ampicillin is an extended spectrum penicillin. It inhibits the intestinal bacteria responsible for enterohepatic circulation of oral contraceptives. Due to inhibition of enterohepatic circulation, the steroids are excreted in feces and become ineffective.

177. **Ans. (b) Rifampicin** (Ref: KDT 6/e p317)

Oral contraceptives are not given with rifampicin as it causes enhanced metabolism (due to enzyme induction) of these drugs which may lead to contraceptive failure.

178. **Ans. (c) Coronary heart disease** (Ref: KDT 6/e p301-302)

- Progesterone component of HRT decreases HDL-cholesterol and therefore predisposes to higher risk of MI particularly in obese and smokers.
- Estrogen component of HRT can reverse vaginal atrophy, hot flushes and osteoporosis.

179. **Ans. (b) Letrozole** (Ref: KDT 6/e p305)

- Aromatase is an enzyme required for the conversion of androgens (androstenedione) to estrogen. Drugs inhibiting this enzyme are useful in the treatment of breast carcinoma.
- Various aromatase inhibitors are:
*Aminoglutethimide
*Letrozole
*Anastrozole
*Exemestane

180. **Ans. (c) Carcinoma of the gall bladder** (Ref: KDT 6/e p302)

- Estrogen causes gall stones, which is a risk factor for gall bladder carcinoma but estrogen itself has no direct role in gall bladder cancer.
- Estrogen increases the risk of endometrial, breast and hepatocellular carcinoma.

181. **Ans. (b) Dihydrotestosterone** (Ref: KDT 6/e p290)

182. **Ans. (a) Levo-norgestrel; (b) Estrogen + progesterone; (c) Mifepristone** (Ref: KDT 6/e p310-313)

- Levonorgestrel alone or in combination with ethinylestradiol can act as emergency (post coital) contraceptive.
- Double of conventional OCPs (Estrogen + Progesterone) can also be used as post-coital contraceptive.
- Mifepristone single dose within 72 hours of intercourse can also be employed for this purpose.
- Norplant and DMPA are long acting contraceptive methods.

183. Ans. (c) Tamoxifen (d) LHRH analogue (Ref: KDT 6/e p204-306)

- Endocrine therapies for Breast cancer

*Castration	*Aromatase inhibitors e.g. –Aminoglutethimide, Letrozole etc.
– Surgical	
– LHRH	*High dose progestins e.g. Megestrol acetate
*Antiestrogens	
– Tamoxifen	*Estrogen e.g. Diethylstilbestrol
– Pure antiestrogens	

- Cyproterone acetate is a potent antiandrogen – competes with dihydrotestosterone for intracellular androgen receptor and inhibit its binding.
- Danazol is a drug having mild androgenic, anabolic and progestational activity.
- Methotrexate is used in breast carcinoma but it is not a hormonal therapy.

184. Ans. (a) Cyproterone; (b) Spironolactone; (e) Flutamide (Ref: KDT 6/e p293)

185. Ans. (b) Ethinyl estradiol (Ref: KDT 6/e p313)

186. Ans. (c) Infertility and development of vaginal cancer in female offspring (Ref: KDT 6/e p300)

187. Ans. (d) Reduce the production of DHT (Ref: KDT 6/e p294)

188. Ans. (d) Spermatogenesis (Ref: KDT 6/e p290)

Testosterone [not DHT] is required for

F – Feedback inhibition of LH secretion
I – Internal genitalia development
S – Spermatogenesis
H – Hematopoiesis

189. Ans. (b) Reduce adult stature (Ref: KDT 6/e p291)

Testosterone causes fusion of epiphyses and can result in reduction of adult stature.

190. Ans. (b) Finasteride (Ref: KDT 6/e p294, 295)

191. Ans. (b) Osteoporosis (Ref: KDT 6/e p301)

- Estrogen is used for the treatment of osteoporosis in post-menopausal female.

192. Ans. (c) Decreased FSH and LH secretion (Ref: KDT 6/e p303, 304)

- Clomiphene citrate is an antagonist of estrogen in the peripheral tissues. Due to this property, it can cause hot flushes.
- Due to decreased action of estrogen, feedback pituitary inhibition is blunted resulting in increased secretion of LH and FSH.
- It can cause polycystic ovaries and multiple pregnancy (hyperstimulation syndrome).

193. Ans. (b) Suppression of FSH and LH release (Ref: KDT 6/e p314)

- Oral contraceptive pills act by several mechanisms, most important of which is the inhibition of ovulation due to suppression of LH and FSH.
- Other mechanisms include disruption of proliferative and secretory phases of endometrium and increase in viscosity of cervical mucus.

194. Ans. (c) Ovarian cancer (Ref: KDT 6/e p317)

Oral contraceptives contain estrogens and these can lead to more chances of migraine and thromboembolism but because of progesterone component the chances of ovarian and endometrial carcinoma decrease.

195. Ans. (d) Has a history of migraine headache that is well controlled by sumatriptan (Ref: KDT 6/e p315)

Migraine attacks can be precipitated by oral contraceptives.

196. Ans. (c) Finasteride (Ref: KDT 6/e p294, 295)

- 5- α -reductase inhibitors are used to reduce the static component of urinary obstruction in BHP. It is delayed acting and takes more than 3 months to exert its beneficial effect.
- Selective α_1 blockers are used to relieve the dynamic obstruction in BHP. These provide rapid symptomatic relief.

197. **Ans. (b) Blocks the increased risk of endometrial carcinoma due to estrogen** (Ref: KDT 6/e p309)

Use of estrogen for the treatment or prevention of post-menopausal osteoporosis places a patient at the risk of breast and endometrial carcinoma. Progesterone is used to decrease the risk of endometrial carcinoma.

198. **Ans. (b) Mifepristone** (Ref: KDT 6/e p311)

- Single 600 mg dose of mifepristone taken within 72 hours of unprotected intercourse is an effective method to prevent pregnancy.
- Two tablets of OCP within 72 hours of unprotected intercourse followed by 2 tablets after 12 hours can also be used as a post-coital contraceptive method.
- Two tablets of levonorgestrel (0.75 mg each) taken 24 hours apart can also be used for emergency contraception.

199. **Ans. (b) Take 2 pills the next day and continue with the course** (Ref: KDT 6/e p315)

- If a woman misses one pill of OCP, she should take 2 pills next day and then continue one pill a day as usual.
- If the pills have been missed for 2-3 days, then the course should be stopped, mechanical barriers (like condom) should be used and the next course should start from the 5th day of menses as usual.

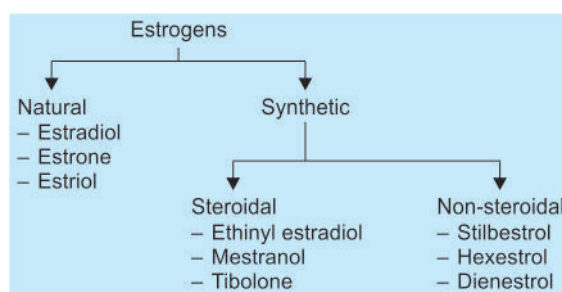
200. **Ans. (b) Dysmenorrhea** (Ref: Katzung 11/e p713, CMDT-2010/697)

- Oral contraceptive pills cause amenorrhea but not dysmenorrhea.
- Mastalgia, breakthrough bleeding and chloasma all can be seen due to OCP use.
- Breakthrough bleeding is more common with progesterone only pills.

201. **Ans. (d) Increased risk of ovarian cancer** (Ref: KDT 6/e p317)

- Ovarian carcinoma risk is decreased by oral contraceptives due to progestin component.

202. **Ans. (b) Ethinylestradiol** (Ref: KDT 6/e p297)



203. **Ans. (c) Has partial agonist and antagonistic action on estrogen receptors** (Ref: KDT 6/e p304)

- Tamoxifen is used for the treatment of breast carcinoma.
- It acts as estrogen receptor antagonist in the breast tissue and as partial agonist in uterus, bone, liver and pituitary.

204. **Ans. (c) Anti-implantation effect** (Ref: KDT 6/e p312-314)

205. **Ans. (d) Gossypol** (Ref: KDT 6/e p318)

Gossypol is a non-steroidal compound obtained from cotton seed. It causes suppression of spermatogenesis in 99.9% of men and reduces sperm motility. Most important adverse effect of this drug is hypokalemia and resultant muscles weakness.

Gelusil is an antacid containing aluminium-hydroxide

Gestodone is newer 19-testosterone derivative. It is a potent progestin with strong anti-ovulatory action.

206. **Ans. (c) Clomiphene** (Ref: KDT 6/e p303)

Clomiphene citrate is an estrogen antagonist with weak agonistic action.

- It increases gonadotropin secretion by blocking estrogenic feed back. Its chief use in ovulation induction.

207. **Ans. (c) Estrogen receptor positive breast carcinoma** (Ref: KDT 6/e p304)

Tamoxifen is used as a hormonal therapy by breast cancer in both pre and post menopausal women. Response is better in ER +ve breast cancers.

208. **Ans. (b) Estrogen** (Ref: KDT 6/e p301-302)

"Estrogen component of OCPs has been mainly responsible for venous thromboembolism, while both estrogen and progesterone have been blamed for the arterial phenomena.

- Estrogen tend to ↑ HDL/LDL ratio but progestin nullifies this benefits.

209. Ans. (d) Mifepristone (RU 486) (Ref: KDT 7/e p320)
210. Ans. (a) Oral mifepristone (Ref: KDT 6/e p310)
211. Ans. (b) Ovarian cancer (Ref: KDT 6/e p317)
212. Ans. (a) Progesterone antagonist (Ref: KDT 6/e p310)
213. Ans. (d) Dihydrotestosterone (Ref: KDT 6/e p294)
214. Ans. (a) Carcinoma breast (Ref: KDT 6/e p317)
215. Ans. (d) All (Ref: KDT 6/e p317)
216. Ans. (b) Induction of ovulation (Ref: KDT 6/e p304)
217. Ans. (d) All (Ref: KDT 6/e p307, 314)
218. Ans. (a) Bicalutamide (Ref: KDT 6/e p294)
219. Ans. (a) Flutamide (Ref: KDT 6/e p304-305)
220. Ans. (a) Finasteride (Ref: KDT 6/e p294)
221. Ans. (b) Anti-androgen (Ref: KDT 6/e p294, 828)
222. Ans. (c) Hot Flushes (Ref: KDT 6/e p300)

- Suppression of libido and gynaecomastia are well recognized adverse effects of estrogens.
- Fusion of epiphyses are not mentioned anywhere as the action of estrogens but definitely estrogen deficiency results in hot flushes and these are used for treatment of these vasomotor symptoms in post menopausal females. Therefore, according to us, the best answer should be 'hot flushes'

223. Ans. (d) Increased risk of ovarian cancer (Ref: KDT 6/e p316,317)

224. Ans. (d) Vasopressin (Ref: Katzung 11/e p301, Ganong 22/e p41-43)

Vasopressin acts via V_1 and V_2 receptors. V_1 receptors use IP_3 -DAG- Ca^{2+} pathway whereas V_2 use cAMP as second messenger. All other drugs mentioned in the question [corticotrophin, glucagon and dopamine] act by cAMP pathway only. Thus, all of these use cAMP as second messenger, but if we need to choose one option we can answer vasopressin as it is acting through IP_3 - DAG - Ca^{2+} pathway also.

225. Ans. (c) Clomiphene (Ref: Goodman Gilman 12/e p1846)

The drugs that have been associated with high incidence of hypospadias include:

- Valproic acid
- Phenytoin
- Progesterone (often given to mothers as part of IVF treatment)
- Diethylstilbestrol (prescribed up until the 1970s to prevent miscarriage)
- Clomiphene (used to induce ovulation during IVF treatment)

From the above information, in this question also there are two answers i.e. DES and clomiphene. As we have to choose one, we will go with clomiphene because it is being commonly used these days for fertility induction whereas diethylstilbestrol is rarely used now-a-days.

Further surgery books write that "Incidence of hypospadias is now increasing predominantly because of use of drugs to promote fertility."

Clomiphene is associated with increased risk of neural tube defects and hypospadias in the newborn babies.

226. Ans (a) Tamoxifen (Ref: CMDT 2014/757)

Treatment of vasomotor symptoms (hot flushes) in post-menopausal females:

- Estrogens alone or with progestin [Most effective]
- SSRI e.g. Paroxetine
- SNRI e.g. venlafaxine
- Gabapentin
- Clonidine [oral or transdermal]

227. Ans (b) Estrogen (Ref: Wikipedia)

A **spider angioma** (also known as a **nevus araneus**, **spider nevus**, **vascular spider**, and **spider telangiectasia**) is a type of telangiectasis found slightly beneath the skin surface, often containing a central red spot and reddish extensions which radiate outwards like a spider's web. Spider angiomas are due to failure of the sphincteric muscle surrounding a cutaneous arteriole. The central red dot is the dilated arteriole and the red "spider legs" are small veins carrying away the freely-flowing blood. The dilation is caused by increased estrogen levels in the blood. Many pregnant women, or women using hormonal contraception, have spider angiomas, due to high estrogen levels in their blood. People who have significant hepatic disease also show many spider angiomas, as their liver cannot detoxify estrogen from the blood, resulting in high levels of estrogen. About 33% of patients with cirrhosis have spider angiomas.

228. Ans. (b) **Corticosteroid** (Ref: KDT 6/e p232)

229. Ans. (d) **Epinephrine receptor** (Ref: KDT 6/e p232)

- Steroid receptor superfamily contain the receptors, which act by influencing nuclear changes. These receptors may be present in the cytoplasm or in the nucleus.

Steroid receptor superfamily	
	
Cytoplasmic receptors	Nuclear receptors
* Glucocorticoids	* Progesterone
* Mineralocorticoids	* Testosterone
* Vitamin D	* Estrogen
	* Vitamin A (retinoid)
	* Thyroid hormones
	* PPAR

- Epinephrine acts through α and β receptors, both of which are GPCRs (membrane receptors).

230. Ans. (c) **Spironolactone** (Ref: KDT 6/e p571)

231. Ans. (b) **Acts on myoepithelial cells of breast; (c) Causes contraction of uterus during labour; (d) May cause retention of water** (Ref: KDT 6/e p319, 321)

- Oxytocin is an octapeptide secreted by the **posterior pituitary** along with ADH. Both oxytocin and ADH are synthesized within the nerve cell bodies in **supraoptic** and **paraventricular nuclei** of hypothalamus; are transported down the axon and stored in the nerve endings within the neurohypophysis.
- Oxytocin **increases the force and frequency of uterine contractions**. Estrogen sensitizes the uterus to oxytocin; non pregnant uterus and during early pregnancy is rather resistant; sensitivity increases progressively in the third trimester; there is a sharp increase near term and quick fall during puerperium.
- Oxytocin contracts myoepithelium of mammary alveoli and forces milk into the bigger milk sinusoids- **milk ejection reflex** is initiated by suckling. Prolactin causes milk secretion.
- Oxytocin in high doses exerts an ADH like action-urine output is decreased; pulmonary edema can occur if large amounts of I.V. fluids and oxytocin are infused together.

232. Ans. (b) **Increases tone of uterine muscle** (Ref: KDT 6/e p322)

233. Ans. (a) **Ritodrine** (Ref: KDT 6/e p323)

Isoxsuprine and ritodrine are selective β_2 agonists useful as tocolytic agents for arresting labour. Pulmonary edema is an important adverse effect of these agents.

234. Ans. (b) **Diabetes mellitus** (Ref: Katzung 10/e p701)

Exenatide is a glucagon like peptide analogue which is proposed to be used in the treatment of post prandial hyperglycemia.

235. Ans. (a) **Osteoporosis** (Ref: KDT 6/e p329)

Teriparatide is a recombinant PTH having first 34 amino acids. It can be used for the treatment of osteoporosis.

236. Ans. (c) Prednisolone (Ref: KDT 6/e p232)

Prednisolone (corticosteroids) act through cytoplasmic receptors whereas thyroid hormones (T_3 , T_4), retinoids (vitamin A) and thiazolidinediones (like rosiglitazone) have nuclear receptors.

237. Ans. (b) Prednisolone (Ref: KK Sharma 2/e p573)

Osteoporosis is a common cause of pathological vertebral fractures. Chronic systemic use of corticosteroids like prednisolone promotes osteoporosis and therefore may cause such fractures.

238. Ans. (a) Lactogenesis (Ref: Katzung 11/e p657)

- Important actions of oxytocin are:
- Contraction of uterine smooth muscle (directly by acting on GPCR and indirectly by release of PG and LTs).
- Milk ejection by contraction of myoepithelial cells surrounding mammary alveoli.
- At high concentration; anti-diuretic and vasopressor action can be seen.

Note: Lactogenesis is the action of prolactin (not oxytocin)

239. Ans. (a) Metformin (Ref: CMDT 2014/744)

- PCOD is also known as Stein-Leventhal syndrome and is characterized by signs of androgen excess (hirsutism, acne etc.), anovulation and polycystic ovaries on gynaecological USG.
- Pathogenesis of PCOD involves excessive production of male hormones (particularly testosterone) by ovaries due to excessive LH release (by pituitary or by hyperinsulinemia).
- Hyperinsulinemia increases GnRH pulse frequency leading to excessive LH secretion.
- Weight loss by regular exercise, low glycemic index diet combined with insulin lowering drugs like metformin can restore fertility in 85% of females.
- For females who don't respond to weight loss, metformin therapy may be helpful.
- Clomiphene is even more effective to restore fertility.
- Cyproterone acetate, flutamide or spironolactone can be used for the treatment of hirsutism and acne.
- If fertility is not required, oral contraceptives can be used for the treatment of menstrual irregularity.

240. Ans. (b) Insulin (Ref: KDT 6/e p259)

Insulin is administered by s.c. route.

241. Ans. (a) Spontaneous premature labour (Ref: KDT 6/e p321-323)

Note: Spontaneous premature labour is an indication for use of tocolytics and not oxytocin.

242. Ans. (a) Methylidopa (Ref: KDT 6/e p286, 404, 548)**243. Ans. (a) Alcohol intoxication** (Ref: KDT 6/e p267)**244. Ans. (d) Orciprenaline** (Ref: KDT 6/e p319)**245. Ans. (b) 6** (Ref: KDT 6/e p314)**246. Ans. (b) Increase calcium absorption from intestine** (Ref: KDT 6/e p331)**247. Ans. (b) Induces uterine contractions** (Ref: KDT 6/e p321)**248. Ans. (a) Is an oxytocin receptor antagonist** (Ref: KDT 6/e p323)**249. Ans. (b) Terbutaline** (Ref: KDT 6/e p731)**250. Ans. (b) Dopamine** (Ref: KDT 6/e p323)**251. Ans. (d) Ketoconazole** (Ref: KDT 6/e p287)

ANSWERS OF RECENT QUESTIONS ASKED BY NATIONAL BOARD

1. Ans (b) Ulipristal (Ref: KDT 7th/320)**2. Ans (c) Helps in insulin secretion** (Ref: KDT 7th/270)**3. Ans (c) Leuprolide** (Ref: KDT 7th/242)

4. Ans (c) **Glaucoma** (Ref: KDT 7th/293)
Glaucoma occurs on long-term topical use, not due to ingestion.
5. Ans (b) **Bromocriptine** (Ref: KDT 7th/239)
6. Ans (b) **Inhibition of ovulation** (Ref: KDT 7th/324)
7. Ans (c) **Nandrolone** (Ref: KDT 7th/300)
8. Ans (c) **STEAR** (Ref: KDT 7th/311)
9. Ans (c) **Propylthiouracil** (Ref: KDT 7th/253)
10. Ans (b) **Cortisone** (Ref: KDT 7th/289)
11. Ans (c) **NPH insulin** (Ref: KDT 7th/263)
12. Ans (c) **Peripheral vascular disease** (Ref: KDT 7th/331)
13. Ans (b) **Prednisolone** (Ref: KDT 7th/289)
14. Ans (c) **Development of vaginal carcinoma in female offspring** (Ref: KDT 7th/309)
15. Ans (c) **Calcipotriol** (Ref: KDT 7th/343)
16. Ans (a) **Rosiglitazone** (Ref: KDT 7th/270)
17. Ans (d) **Diethylstilbestrol** (Ref: KDT 7th/306)
18. Ans. (a) **Biguanides** (Ref: KDT 6/e p269)
19. Ans. (d) **An absorbent** (Ref: KDT 6/e p235)
20. Ans. (b) **Insulin** (Ref: KDT 6/e p48)
21. Ans. (a) **Teriparatide** (Ref: KDT 7/e p339)
22. Ans. (c) **Cabergoline** (Ref: KDT 7/e p239-240)
23. Ans. (b) **Old man with decreased BP/decreased heart rate due to atenolol** (Ref: KDT 7/e p281)
24. Ans. (a) **Cabergoline** (Ref: KDT 7/e p239-240)
25. Ans. (c) **Dexamethasone** (Ref: KDT 7/e p289)
26. Ans. (b) **I¹³¹** (Ref: KDT 7/e p255)
27. Ans. (d) **Postmenopausal osteoporosis** (Ref: KDT 7/e p884)
28. Ans. (c) **Osteoporosis** (Ref: KDT 7/e p339)
29. Ans. (d) **Glargine** (Ref: KDT 7/e p265)
30. Ans. (b) **IV hydrocortisone** (Ref: KDT 7/e p290) (Ref: KDT 7/e p265)
31. Ans. (a) **Nateglinde** (Ref: KDT 7/e p273)
32. Ans. (d) **Repaglinide** (Ref: KDT 7/e p273)
33. Ans. (a) **Insulin glargine** (Ref: KDT 7/e p263)
34. Ans (b) **Used in treatment of gynaecomastia** (Ref: KDT 7/e p309)
 - Estrogens can result in suppression of libido, gynaecomastia and feminization as adverse effects when given to males.
35. Ans. (a) **Potassium iodide** (Ref: KDT 7/e p254)
36. Ans. (d) **Prednisolone** (Ref: KDT 7/e p895)
37. Ans. (d) **Vitamin D intoxication** (Ref: KDT 7/e p344-345)
38. Ans. (c) **Aldosterone** (Ref: KDT 7/e p289)

39. Ans. (a) 5%iodine & 10% KI (Ref: KDT 7/e p255)
40. Ans. (c) Actrapid (Ref: KDT 7/e p264-265)
- Actrapid (regular insulin) and monotard (Lente-insulin) are unmodified insulins with same amino acid sequence as natural insulin
 - Lispro, aspart, glulisine and glargine are insulin analogues in which slightly different amino acid sequence is present to modify pharmacokinetics.
41. Ans. (b) Ritodrine (Ref: KDT 7/e p136)
42. Ans. (b) Atosiban (Ref: KDT 7/e p333)
43. Ans. (c) Post partum hemorrhage (Ref: KDT 7/e p320)
44. Ans. (d) Etidronate (Ref: KDT 7/e p345)
45. Ans. (a) 5-alpha reductase (Ref: KDT 7/e p302)
46. Ans. (b) Hyperkalemia (Ref: KDT 7/e p293)
47. Ans. (a) Suppression of inflammation and improvement in functional capacity (Ref: KDT 7/e p291)
48. Ans. (c) Finasteride (Ref: KDT 7/e p302)
49. Ans. (d) Active liver disease (Ref: KDT 7/e p326)
50. Ans. (c) Cortical collecting duct (Ref: KDT 7/e p283-284)
51. Ans. (b) Prednisolone (Ref: KDT 7/e p293)
- Etidronate and phenytoin cause osteomalacia whereas calcitriol is used in treatment of osteoporosis.
52. Ans. (c) Level of thyroid stimulating hormone (Ref: KDT 7/e p248)
53. Ans. (c) Metformin (Ref: KDT 7/e p276)
54. Ans. (c) Oral I^{131} (Ref: CMDT 2014/ p1078)
55. Ans. (d) Irregular menstrual bleeding and prolonged anovulation (Ref: KDT 7/e p323)
56. Ans. (b) Ovarian cancer (Ref: KDT 7/e p326)
57. Ans. (b) Cortisone for Cushing's syndrome (Ref: KDT 7/e p291-293)
58. Ans. (a) Cerebral stroke (Ref: KDT 7/e p325)
59. Ans. (b) Propranolol (Ref: KDT 7/e p256)
60. Ans. (c) Anti-progestin (Ref: KDT 7/e p319)
61. Ans. (b) Stimulating the beta islet cells of pancreas to release insulin (Ref: KDT 7/e p270-271)
62. Ans. (d) Relaxin (Ref: KDT 7/e p306)
63. Ans. (b) Prolactin deficiency (Ref: KDT 7/e p239)
64. Ans. (c) To suspect adrenocortical insufficiency and start IV steroids (Ref: KDT 7/e p290)
65. Ans. (a) Metformin (Ref: KDT 7/e p276)
66. Ans. (a) Metformin (Ref: KDT 7/e p276)
67. Ans. (b) Intravenous fluids (saline) (Ref: CMDT 2014 p1190)
68. Ans. (a) Betamethasone valerate (Ref: KDT 7/e p895)
69. Ans. (c) Vitamin K (Ref: CMDT 2014 p712)

70. Ans. (c) Mifepristone (Ref: KDT 7/e p320, 331-332)
71. Ans. (c) Phenformin (Ref: KDT 7/e p275)
72. Ans. (b) Migraine (Ref: KDT 7/e p311)
73. Ans. (a) Inhibits prolactin release (Ref: KDT 7/e p239)
74. Ans. (a) Before surgery (Ref: KDT 7/e p255)
75. Ans. (b) Androgen (Ref: KDT 7/e p340-346)
76. Ans. (b) Delta cells (Ref: KDT 7/e p235)
77. Ans. (d) Regular insulin (Ref: KDT 7/e p263)
78. Ans. (d) Hypothyroidism (Ref: KDT 7/e p239)
79. Ans. (b) Thyroxine (Ref: KDT 7/e p250)
80. Ans. (d) Dexamethasone (Ref: KDT 7/e p289)
81. Ans. (a) Propylthiouracil (Ref: KDT 7/e p253)
82. Ans. (a) Combined pills 2 immediately and 2 after 12 hrs (Ref: KDT 7/e p322)
83. Ans. (b) Anti progesterone (Ref: KDT 7/e p320)
84. Ans. (c) Infective diarrhea (Ref: KDT 7/e p238)
85. Ans. (d) Papillary (Ref: KDT 7/e p252)
86. Ans. (b) Octreotide (Ref: KDT 7/e p238)
87. Ans. (a) Metformin (Ref: Goodman Gilman 12/e p1136)
 - Absorption of T_4 is reduced by:
 - Antacids
 - Bile acid binding agents
 - Calcium carbonate
 - Iron salts
 - Proton pump inhibitors
 - Raloxifene
 - Sucralfate
 - Metformin may decrease TSH without changing free T_4 in levothyroxine-treated patients.

This image shows a full page of blank, lined paper. It features approximately 20 evenly spaced horizontal grey lines across its entire width, providing a guide for handwriting or typing. The paper itself is a clean, off-white color.

NOTES

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NOTES

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SEDATIVE HYPNOTIC DRUGS

Sedative is a drug that calms a person whereas hypnotics induce sleep. CNS depressant drugs can produce sedation, hypnosis, anaesthesia and coma depending on the dose. Major group of drugs useful for the treatment of insomnia include barbiturates, benzodiazepines and newer drugs.

- **GABA_A-BZD-Cl⁻ channel complex** is an ion channel, which on opening increases the conductance of chloride ions resulting in CNS depression. Several compounds can modulate the effect of this channel.
- GABA increases the duration of channel opening by directly binding to GABA_A receptor site.
- **Barbiturates** bind to another site on this channel to exert **GABA mimetic** (direct activation of GABA_A receptors) **as well as GABA facilitatory** (increase the binding of GABA to GABA_A receptors) actions.
- **Benzodiazepines** bind to a different site (BZD receptor) and increase the binding of GABA to GABA_A receptor (**GABA facilitatory** action). These drugs increase the frequency of Cl⁻ channel opening.
- **Bicuculline** binds to GABA_A receptor and acts as a competitive inhibitor of GABA and **non competitive inhibitor of benzodiazepines**.
- **β-carboline** acts as an **inverse agonist** at benzodiazepine site and *thus produces convulsions* due to stimulation of the brain.
- **Flumazenil** acts as a **competitive antagonist at BZD site** and therefore **inhibits the action of benzodiazepines as well as β-carboline**.

GABA_C receptors are present in retina and are inotropic mediating influx of chloride (like GABA_A) whereas GABA_B receptors are G-protein coupled receptors.

1. Barbiturates

These are the derivatives of barbituric acid and act by increasing the Cl⁻ conductance across GABA_A-BZD-Cl⁻ channel complex. These drugs have GABA mimetic as well as GABA facilitatory action to increase the **duration of Cl⁻ channel opening** (no effect on frequency). Important indications of barbiturates in clinical practice are epilepsy (phenobarbitone) and anaesthesia (thiopentone as inducing agent). These are generally not used for other purposes because

- These have narrow therapeutic index due to **steep dose response curve** (with slight increase in dose, severe CNS depression leading to coma can occur).
- These are **powerful enzyme inducing agents** and are prone to several drug interactions.
- These have **high abuse liability** and may precipitate withdrawal symptoms.
- If poisoning occurs, **no specific antidote** is available.

Adverse effects and contraindications

- Due to the long duration of action, **hangover** is common. Barbiturates can cause distortion of sleep architecture by *decreasing the duration of REM and stage 3 and 4 sleep and increasing the duration of stage 2 sleep*.
- **Learning and memory impairment** can occur.
- **Idiosyncratic reaction** resulting in excitement can occur in some patients.
- These are **absolutely contraindicated in acute intermittent porphyria** (because porphyrin synthesis is increased due to induction of δ-ALA synthase; rate limiting enzyme in porphyrin synthesis, by barbiturates).

Barbiturates are absolutely contraindicated in acute inter-mittent porphyria

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Unsafe drugs in porphyria:

- S - Sulfonamides
- E - Erythromycin
- V - Valproate
- E - Ergot Alkaloids
- R - Rifampicin
- E - Estrogens
- P - Phenobarbitone (and other barbiturates like thiopentone)
- O] ORal contraceptives
- R]
- P - Phenytoin
- H] Hydralazine
- Y]
- R]
- I]
- A - Alcohol

- At high doses, acute poisoning may occur (manifests as coma, depressed respiration, hypotension, cardiovascular collapse and *barbiturate blisters*). It is treated by gastric lavage, symptomatic treatment and with **forced alkaline diuresis**. Hemodialysis can also be done.

2. Benzodiazepines

These drugs act by **GABA facilitatory** action. These also possess *anxiolytic, anticonvulsant and skeletal muscle relaxant properties*.

Benzodiazepines used for various indications are:

Hypnotic:	Diazepam, flurazepam, nitrazepam, flunitrazepam, temazepam, triazolam, quazepam and midazolam
Anti-convulsants:	Diazepam, clonazepam, clobazam, lorazepam
Anti-anxiety:	Diazepam, oxazepam, lorazepam, alprazolam, chlordiazepoxide
Muscle Relaxant:	Diazepam

Benzodiazepines are preferred over barbiturates as hypnotic drugs due to several reasons:

- BZDs have **flat dose response curves** (these have high therapeutic index and require high dose to produce coma).
- These cause **less hangover** and **less distortion of sleep architecture**. Duration of REM sleep is shortened but increase in the number of REM cycles compensate for that. **Nitrazepam** actually **increases REM sleep**.
- These are **less prone to drug interactions** (because they do not induce microsomal enzymes).
- Abuse liability is less.
- BZD poisoning can be treated with **specific antidote, flumazenil**.
- Diazepam can produce analgesia whereas *barbiturates may even cause hyperalgesia*.

Pharmacokinetics

All BZDs are almost completely absorbed except clorazepate (converted to nordiazepam by gastric juice which is absorbed). Most of the BZDs are metabolized in the liver to *produce active products* (thus long duration of action). *Active metabolites may result in cumulative effects*. After metabolism these are conjugated and are excreted via kidney. **Estazolam, lorazepam, oxazepam, temazepam and triazolam** are **directly conjugated without metabolism** to active products. These drugs are thus **short acting** and do not accumulate on repeated administration. Further these drugs can be **safely administered in liver failure and in elderly** because these are conjugated directly without undergoing metabolism in the liver. Compounds with *shorter half life* are favored in patients with *sleep onset insomnia* whereas *longer acting* BZDs are favored in patients with *day time anxiety*.

Adverse effects

Benzodiazepines are much safer than barbiturates (less chances of respiratory depression and coma) and also have less abuse potential. However, these drugs can also **impair learning and memory**. **Flunitrazepam** is a tasteless BZD and is implicated as a **date rape drug** due to its propensity to cause dose dependent amnesic effects. **Paranoia and other psychiatric disturbances can occur with triazolam**. **Midazolam** can cause *ataxia and blackouts in elderly*. **Flurazepam** results in *paradoxical stimulation and increase in nightmares* in some persons.

BENZODIAZEPINE ANTAGONIST

Flumazenil is the substance that acts as a competitive antagonist at BZD receptor. It *blocks the depressant action of benzodiazepines, zolpidem and zaleplon as well as the convulsant action of inverse agonists (like β carboline)*.

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Short acting Benzodiazepines are

Triazolam
Temazepam
Oxazepam
Lorazepam
Estazolam
STOLE

M

Benzodiazepine ends with pine which in hindi means drink. The antagonist will stop the enjoyment (in hindi maze). Thus, the name is Flu MAZE NIL [Maze of drinking have become nil]

It is administered i.v. for the treatment of **BZD poisoning** (specific antidote) and can also be used to reverse BZD anaesthesia. Its **duration of action** is *approximately 30-40 minutes* and **half life** is 1 hour.

3. Newer Hypnotic Drugs

A. Zopiclone

It stimulates $GABA_A$ receptors by binding to a site different than benzodiazepines. It prolongs stage 3 and 4 sleep and does not affect REM sleep. Chances of **rebound insomnia and hangover are less** than benzodiazepines and barbiturates. It is used for the treatment of insomnia. It is also **indicated in the patients taking benzodiazepines** regularly for induction of sleep. It helps in **weaning off** hypnotic medications in such patients. The active enantiomer, **eszopiclone** is also available now.

B. Zolpidem

It binds selectively to ω_1 **subtype of benzodiazepine receptors** and increases GABA mediated neuronal inhibition. It possesses pronounced hypnotic and amnesic effects but **lacks anti-anxiety, muscle relaxant and anticonvulsant actions**. It has **little effect on sleep architecture** and **does not produce hangover and rebound insomnia**. Abuse potential of zolpidem is very low. It is also **indicated for the short term treatment of insomnia**.

C. Zaleplon

It also acts by selectively binding to ω_1 **subtype of benzodiazepine receptors**. It **decreases sleep latency** without affecting total sleep time or sleep architecture (therefore useful in persons having difficulty to fall asleep). Other properties are similar to zolpidem.

D. Suvorexant

It is an orexin receptor antagonist. Orexin acts as a central promotor of wakefulness. Therefore, its antagonist (suvorexant) has been approved for insomnia.

4. Other Hypnotics

Chloral hydrate (active metabolite is trichloroethanol), **glutethimide** and **meprobamate** (a metabolite of carisoprodol, a skeletal muscle relaxant) have CNS depressant properties but are rarely used in clinical practice.

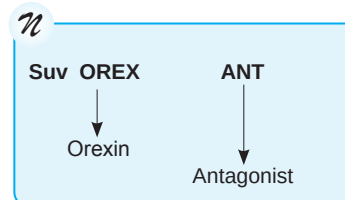
Trazodone is an antidepressant that can be used for insomnia at low doses. **Priapism** is a rare side effect of this agent.

MELATONIN is a hormone of pineal gland that synchronizes the circadian rhythm. It increases the sleep during night but has no effect on latency or duration of sleep. It is **used to reduce symptoms of jet lag**. It can also synchronize the sleep wakefulness cycle in **shift workers** and is also used in **elderly hypnotic dependent insomniacs**. **Lowering of seizure threshold** and **psychiatric changes** are the possible adverse effects.

Ramelteon is agonist of MT_1 and MT_2 receptors of melatonin in suprachiasmatic nucleus. It is approved for long term use in treatment of sleep onset insomnia. It **do not possess addictive property** but causes hyperprolactinemia, dizziness, somnolence and fatigue as adverse effects. It is metabolized by *microsomal enzymes* (CYP1A2) and should not be given with enzyme inducers (e.g. rifampicin) or inhibitors (e.g. ciprofloxacin)

Mnemonic: R A M E L T E O N

Receptor Agonist Melatonin



Ramelteon is agonist of MT_1 and MT_2 receptors of melatonin in suprachiasmatic nucleus. It is approved for long term use in treatment of sleep onset insomnia.

Tasimelteon is melatonin receptor agonist (like ramelteon) indicated for treatment of non-24 hour sleep-wake disorder in totally blind.

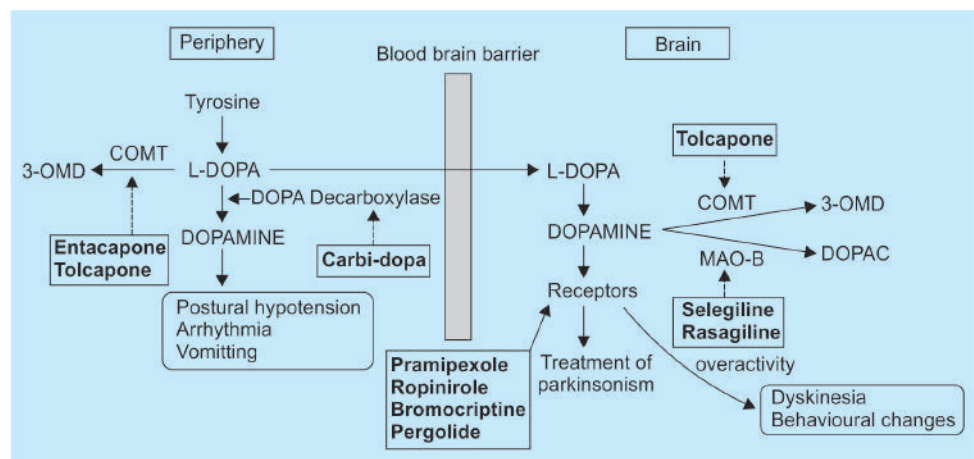
PARKINSONISM

It is a neurodegenerative disease characterized by rigidity, bradykinesia, dyskinesia, tremor, mask like facies and unstable gait. Idiopathic Parkinsonism is known as Parkinson's disease. In basal ganglia, the output neurons are controlled by dopamine and acetylcholine. Due to their opposite action, a balance is required between these two neurotransmitters for proper functioning of basal ganglia.

Major pathology in Parkinsonism is decrease in nigrostriatal dopaminergic neurons, (with appearance of **Lewy bodies**) consequently cholinergic activity becomes dominant. Thus, **two major strategies** for the treatment of Parkinsonism are to *increase brain dopaminergic activity* or to *decrease central cholinergic activity*.

Drugs Increasing Brain Dopaminergic Activity

Brain dopaminergic activity can be increased by precursors of dopamine, inhibitors of dopamine metabolism, dopamine receptor agonists and drugs increasing presynaptic release of dopamine.



A. DOPAMINE PRECURSORS

Dopamine itself cannot cross blood brain barrier (BBB) but its precursor levo-dopa can cross BBB. Levo-dopa is metabolized by **dopa decarboxylase** (contains pyridoxine as co-factor) to dopamine. This conversion occurs both in periphery as well as in the brain. Peripheral conversion is undesirable due to two reasons:

- It forms dopamine peripherally that cannot cross BBB, therefore only about 1-3% of l-dopa can reach its target site (brain).
- Peripherally formed dopamine will result in adverse effects like postural hypotension.

Therefore *levo-dopa is always given in combination with peripheral dopa decarboxylase inhibitors like carbidopa or benserazide*. This combination has beneficial effects on all symptoms of Parkinsonism, although **tremors respond less well than rigidity or bradykinesia**.

Adverse Effects

- Peripherally formed dopamine can lead to **postural hypotension** and **arrhythmias**. **Nausea and vomiting** occurs commonly due to CTZ stimulation by dopamine (*Domperidone but not metoclopramide can be used for the treatment of this vomiting*). On long term use "**wearing off**" effect and **on-off phenomenon** can result. 'On' means patient is having no symptoms of Parkinsonism (but abnormal movements are present) and 'off' means patient has full blown symptoms of Parkinsonism (like no treatment is given). This effect is **due to short half life (1-2hrs)** of l-dopa and is reduced by carbidopa. **Long acting dopamine agonists show little tendency to cause on-off phenomenon**.

Addition of carbi-dopa to l-dopa therapy

- Increase entry of L-dopa in brain.
- Decrease adverse effects due to peripherally formed dopamine

- **Abnormal choreiform movements** (dyskinesia) of limbs, trunk and tongue can occur with prolonged high dose treatment. **Carbidopa does not prevent** or decrease this adverse effect. This adverse effect **responds to amantadine and possibly levetiracetam**.
- L-dopa especially in elderly can result in **hallucinations, vivid dreams, sleep disturbances** and even **psychosis** (thus C/I in psychosis). These behavioural disturbances are not prevented by carbidopa. Clozapine and quetiapine can be used to treat levodopa induced psychosis.
- It may even cause **mydriasis** (C/I in angle closure glaucoma).
- Vitamin complexes containing **pyridoxine decrease the effectiveness** of levo-dopa (pyridoxine is a cofactor of dopa decarboxylase and increases the formation of dopamine in the periphery. This results in decrease in l-dopa's central penetration).
- *Abrupt withdrawal* of levodopa may precipitate *neurolept malignant syndrome*.
- Levo-dopa should be given **carefully** in patients with **active peptic ulcer** (increased risk of bleeding) and **malignant melanoma** (levo-dopa is a precursor of melanin).

Carbi-dopa decrease all adverse effects of l-dopa therapy except

- Abnormal movements
- Behavioural Changes

Adverse Effect of L-dopa

Adverse Effect	Mechanism	Remarks
1. Nausea, Vomiting	CTZ stimulation	Reduced by carbi-dopa
2. Postural hypotension	D ₁ stimulation	Reduced by carbi-dopa
3. Arrhythmias	β_1 stimulation	Reduced by carbi-dopa
4. Hypertension	α_1 stimulation	Reduced by carbi-dopa More likely when combined with MAO inhibitors
5. Mydriasis	α_1 stimulation	Contraindicated in acute angle closure glaucoma
6. Dyskinesia	↑ Activity of DA in Brain	Not reduced by carbi-dopa
7. Psychotic symptoms	↑ Activity of DA in Brain	Not reduced by carbi-dopa

B. DRUGS INHIBITING METABOLISM OF DOPAMINE

Dopamine is metabolized by MAO and COMT (catechol-o-methyl transferase).

(i) COMT Inhibitors

This enzyme metabolizes dopamine as well as l-dopa to form 3-O-methyldopa. **Tolcapone and entacapone** (act by inhibiting this enzyme) help in Parkinsonism because:

- Metabolism of l-dopa is inhibited, so more is able to cross BBB. These can be given in combination with l-dopa + carbidopa (*inhibition of dopa decarboxylase diverts the metabolism of l-dopa to methylation by COMT*)
- 3-O-methyl dopa formed by metabolism of l-dopa competes with it for entry in the brain. Tolcapone and entacapone decrease this interaction.
- By inhibiting dopamine metabolism in brain (tolcapone only), its duration of action is increased.

Tolcapone inhibits COMT in periphery as well as brain whereas entacapone acts only in the periphery.
Major beneficial effect of these drugs in Parkinsonism is due to **peripheral inhibition** of COMT. **Tolcapone** is more potent and longer acting than entacapone but is not preferred because of **hepatotoxic** effects.

(ii) MAO-B Inhibitors

Selegiline and rasagiline are irreversible and **selective inhibitors of MAO-B**. These drugs can be given in combination with levo-dopa + carbidopa to decrease the dose of levo-dopa

Tolcapone inhibits COMT in periphery as well as brain whereas entacapone acts only in the periphery.

Toxic to
Liver
Tolcapone

Ergot alkaloids are short acting and can cause digital **vasospasm** (leading to gangrene) and pleural, peritoneal and cardiac **fibrosis**.

Pramipexole and ropinirole are long acting and do not cause gangrene. These are now the **first choice drugs** for Parkinsonism.

Pramipexole and Ropinirole are used for treatment of restless leg syndrome

Subcutaneous apomorphine (D_4 agonist) has been approved as a rescue therapy of 'off' episodes when oral dopamine agonists or COMT inhibitors fail to control these episodes.

Rotigotine is a dopamine agonist that can be administered through a **transdermal patch** but was discontinued due to crystal formation on the patches.

Central anticholinergic drugs like trihexiphenidyl (benhexol), procyclidine, benzotropine, orphenadrine and biperiden are the drugs of choice for **drug induced Parkinsonism**.

(and thus decreased abnormal movements). At normal doses these inhibit only MAO-B and thus have no interaction with cheese or tricyclic antidepressants. However, at high doses, they also inhibit MAO-A and can lead to hypertensive crisis (**cheese reaction**) with tyramine containing foods and serotonin syndrome with TCAs. Rasagiline is more potent than selegiline. These drugs are thought to **reduce the disease progression**.

C. DOPAMINE AGONISTS

These drugs directly activate D_2 receptors and can be used as monotherapy in Parkinsonism. **Ergot derived** dopamine agonists include **bromocriptine and pergolide**. These drugs are **short acting** and can cause digital **vasospasm** (leading to gangrene) and erythromelalgia. These drugs can also result in *pleural, peritoneal and cardiac fibrosis*. Ergot alkaloids require slow upward titration of dose. Long term use of *pergolide* is associated with *cardiac valvular defects*. Newer **non-ergot dopamine agonists; pramipexole and ropinirole** do not have these limitations (these are **long acting** and **do not cause gangrene**). All four drugs can cause confusion and hallucinations. In developed countries, these are now the **first choice drugs for Parkinsonism** (preferred over levo-dopa). **Ropinirole** has also been approved for **restless leg syndrome**. Pramipexole is excreted mainly by kidney whereas ropinirole is metabolized by liver. Rare but important adverse effect of these drugs is **excessive day time sleepiness**. Recently, **dopamine agonists** have been associated with **impulse-control disorders** including *pathological gambling, hypersexuality, etc.*

Rotigotine is a dopamine agonist that can be administered through a **transdermal patch** but was discontinued due to crystal formation on the patches. **Apomorphine** can be given subcutaneously for *temporary relief of off-periods*. However, it cause *troublesome nausea*.

D. DRUGS INCREASING DOPAMINE LEVEL AT SYNAPSE

Amantadine is an **antiviral drug** that is also useful in Parkinsonism. It increases synaptic dopamine level by increasing presynaptic release and decreasing its reuptake. It also possesses anticholinergic and antiglutaminergic (NMDA blocking) activity. Adverse effects of this drug include nausea, insomnia, **ankle edema and livedo reticularis**. It ameliorates dyskinesia associated with chronic levo-dopa therapy.

Drugs Inhibiting Brain Cholinergic Transmission

Central anticholinergic drugs like trihexiphenidyl (benhexol), procyclidine, benzotropine, orphenadrine and biperiden are **the drugs of choice for drug induced Parkinsonism**. Drugs that act by blocking D_2 receptors in the brain (like antipsychotics, metoclopramide etc.) can cause Parkinsonism. In this condition, increasing dopamine level is not effective because the receptors on which it has to act (D_2) are already occupied, therefore anticholinergics are preferred.

First generation antihistaminics with high antimuscarinic activity like **promethazine** and **diphenhydramine** can also be used for this indication.

Adverse effects of antimuscarinic drugs include urinary retention, blurred vision, dry mouth and constipation.

OTHER NEURODEGENERATIVE DISEASES

Alzheimer's Disease (AD)

- It is a form of senile dementia that is due to the deposition of amyloid plaques in the hippocampus (Presence of neurofibrillary tangles). There is loss of cholinergic neurons in the brain. Anticholinesterases that can cross the blood brain barrier are the mainstay of treatment of this disease.
- **Tacrine** was used previously but its use has declined due to its **hepatotoxic** potential and the need of frequent (four times a day) dosing.
- **Donepezil, rivastigmine and galantamine** are newer cholinesterase inhibitors

useful in AD that are **less toxic** than tacrine. *Donepezil* can be administered *once daily*, offering an advantage over other anticholinesterases.

- **Acetyl-L-carnitine** (structural analogue of ACh) has **antioxidant property** apart from **increasing cholinergic transmission**. It shows promise in decreasing symptoms and slowing the progression of AD.
- **Memantine** is an **NMDA antagonist** approved by FDA for the treatment of advanced AD.

Rivastigmine is approved for treatment of dementia due to Alzheimer's disease as well as due to Parkinsonism.

Huntington's Chorea

It is due to loss of GABAergic neurons in the striatum that lead to dopaminergic overactivity (opposite to Parkinsonism). Thus **D₂ blockers** like chlorpromazine, haloperidol as well as olanzapine are useful in the treatment of this disease. **Tetrabenazine** (dopamine depletor) has been recently approved for this indication. **Reserpine** also act by depleting central monoamines.

Amyotrophic Lateral Sclerosis (ALS)

This disease is due to degeneration of neurons in spinal cord, medulla or cortex. Spasticity is the major presenting feature. **Riluzole** is an **NMDA antagonist** that is useful in ALS. Most useful agent for symptomatic treatment of spasticity in ALS is *baclofen*.

Multiple Sclerosis (MS)

It is an autoimmune disease resulting in demyelination of neurons. Frequency of relapses can be decreased by **beta-interferon** or **glatiramer** (resembles myelin basic protein) in relapsing remitting MS. Spasticity can be decreased by baclofen or tizanidine. Recently, a monoclonal antibody, **natalizumab** is being tried for multiple sclerosis. It has important adverse effect to cause progressive multifocal leuko-encephalopathy. **Fingolimod** is a sphingosine 1-phosphate receptor modulator recently approved for the treatment of patients with relapsing forms of multiple sclerosis. **Dalfampridine** is an oral K⁺ channel blocker indicated to improve walking in patients with multiple sclerosis. **Modafinil** is approved for improving fatigue in multiple sclerosis.

Mitoxantrone has broadest indication in multiple sclerosis (RRMS, SPMS and worsening RRMS) but not used as first-line drug because of cardiotoxicity

DRUGS USED FOR MULTIPLE SCLEROSIS

	Drug	Mechanism	Route	Frequency	Adverse Effects
1.	Interferon-β 1a	• Downregulates expression of MHC molecules on antigen presenting cells • ↓ Pro-inflammatory and ↑ regulatory cytokines • ↓ T-cell proliferation • ↓ Entry of inflammatory cells in CNS	i.m.	Once a week	• Flu-like symptoms • Altered LFT • Injection site reaction on s.c. route • Formation of neutralizing antibodies
	Interferon β 1b		S.C	Thrice a week	
2.	Glatiramer	• ↑ Suppressor T-Cells • Displace MBP by binding to MHC molecules • ↓ Pro-inflammatory and ↑ regulatory cytokines	S.C.	Thrice a week	• Injection site reactions • Flushing, Chest tightness, dyspnea, palpitations, anxiety • Lipoatrophy

M

Glatiramer consists of 4 amino acids

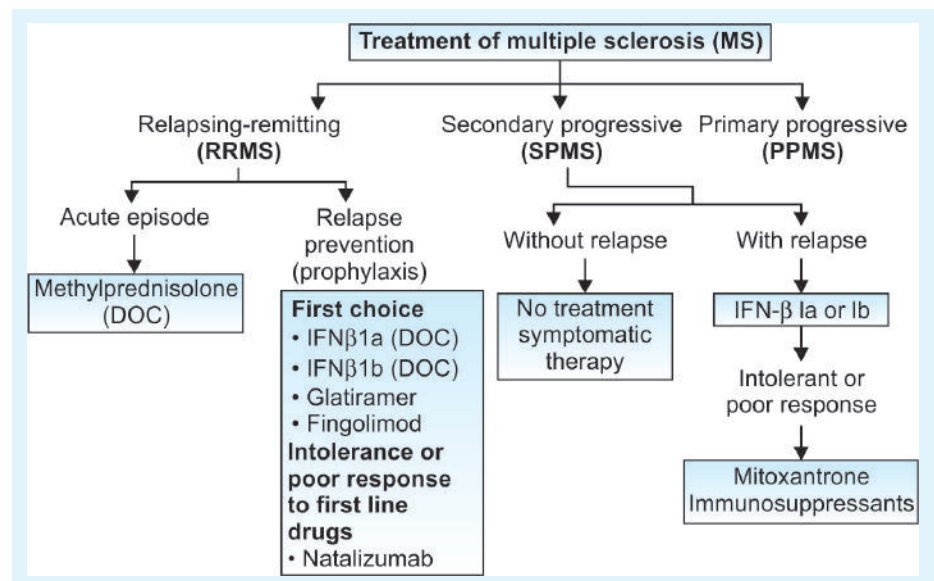
Glutamate
|
Lysine
|
Alanine
|
Tyrosine
|
GLATiramer

Drug of choice for acute attacks in MS is steroids whereas interferon-β is DOC for preventing the relapse in RRMS

Contd...

Contd...

3.	Natalizumab (Monoclonal antibody against $\alpha 4 \beta 1$ integrin on lymphocytes)	Prevents lymphocytes from binding to endothelial cells, thus inhibits transfer across BBB and entry in CNS	i.v. infusion	Once a month	Progressive multifocal leucoencephalopathy if used for >2years
4.	Fingolimod	- Traps lymphocytes in spleen and lymph nodes by preventing their egress - Thus, entry in CNS decreases	Oral	Once a day	- Altered LFT - First degree heart block - Bradycardia
5.	Mitoxantrone (Anthracycline anticancer drug)	Topoisomerase II inhibition	i.v.	Once in 3 months	- Cardiotoxicity - Acute leukemia
6.	Dimethyl fumarate (approved in UK, not in USA)	Promotes anti-inflammatory and inhibit pro-inflammatory cytokines	Oral	Twice a day	Progressive multifocal leucoencephalopathy
7.	Teriflunomide (Active metabolite of leflunomide)	Dihydroorotate dehydrogenase inhibitor	Oral	Once a day	Hepatotoxicity
8.	Cladribine (Purine analog anticancer drug)	Inhibit DNA synthesis and repair	Oral	Used for 2 weeks every year	- Immunosuppression - Secondary neoplasms - Herpes zoster
9.	Dalfampridine (4-Aminopyridine)	K⁺ Channel blocker to improve weakness in MS	Oral	Once a day	Seizures



Wilson's Disease

It is characterized by hepatolenticular degeneration due to excessive accumulation of copper. **d-Penicillamine** can be used as a copper chelating agent but it can cause lupus like syndrome, optic neuritis and blood dyscrasias. **Trientine** is another copper chelating agent with much less toxicity. *Zinc sulphate and potassium sulfide decrease intestinal absorption of copper and induce hepatic metallothionein synthesis, that sequester additional toxic copper. Zinc sulphate can be used for maintenance therapy and is much safer than other drugs.*

Penicillamine and trientine can worsen neurological symptoms in Wilson disease, therefore are not recommended for initial neurological therapy

Wilson disease	Drug of choice
1. Hepatitis or cirrhosis without decompensation	Zinc
2. Mild to moderate hepatic decompensation	Trientine + zinc
3. Neurological or psychiatric symptoms	Tetrathiomolybdate + zinc
4. For maintenance, children, pregnancy	Zinc

ANTIEPILEPTIC DRUGS

Epilepsy is the condition characterized by recurrent episodes of seizures. Seizures may be generalized, partial or unclassified. Generalized seizures include tonic clonic (grand mal), absence (petit mal), myoclonic, tonic, atonic and clonic seizures. Partial seizures may be simple partial (jacksonian) or complex partial (psychomotor or temporal lobe epilepsy). Febrile seizures and infantile spasms are unclassified forms of seizures. Lennox Gestaut syndrome is a form of epilepsy with impaired cognitive function.

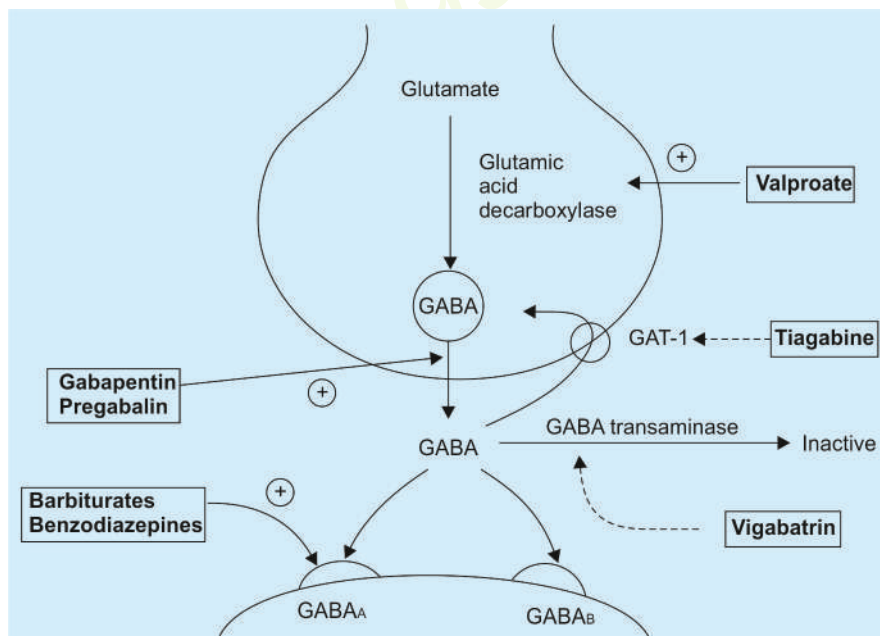
Adenosine is an endogenous antiepileptic substance.

Mechanism of Action

Drugs useful for epilepsy act by various mechanisms like:

(a) Inhibition of Use Dependent Na^+ Channels:

Phenytoin, carbamazepine, valproate, topiramate lamotrigine and lacosamide act by inhibiting the sodium channels when these are open. These drugs also *prolong the inactivated stage* of these channels (Na^+ channels are refractory to stimulation till these reach the closed/resting phase from inactivated phase).



(b) Increase in Inhibitory Neurotransmission:

GABA is a major inhibitory neurotransmitter in the brain. *Barbiturates* (phenobarbitone, primidone) and *benzodiazepines* (diazepam, clonazepam, clobazam) activate GABAA receptors by binding to GABA-BZD-Cl⁻ channel complex. *Ganaxolone* (a neurosteroid) also acts by activating this channel but the binding site is different. Drugs can also act by increasing the release (*Gabapentin*), decreasing the metabolism (*Vigabatrin*) or inhibiting the reuptake in neurons (*Tiagabine*).

(c) Decrease in Excitatory Neurotransmission:

Glutamate and aspartate are major excitatory amino acids in the brain. Glutamate can act by stimulating metabotropic (GPCRs) or ionotropic receptors (kainate, NMDA and AMPA). *Felbamate* acts by inhibiting NMDA receptors. Topiramate act by inhibiting kainate receptors.

(d) Inhibition of Ca²⁺ Channels:

T-type Ca²⁺ channels are **important in absence seizures**. Drugs inhibiting these channels (*ethosuximide*, *valproate*, *lamotrigine*) are useful in petit mal epilepsy.

Mechanism of Action of Anti Epileptic Drugs

DRUG	↑ GABA activity	↓ Glutamate Activity	Prolong inactivated Na ⁺ channels	Block T-Ca ²⁺ Channels	Other
1. Phenytoin			✓		
2. Carbamazepine			✓		
3. Valproate	✓ (a)		✓	✓	
4. Lamotrigine		✓ (b)	✓		
5. Ethosuximide				✓	
6. Gabapentin	✓ (c)				
7. Topiramate	✓ (d)	✓ (e)	✓		Activates K ⁺ Channel
8. Tiagabine	✓ (f)				
9. Phenobarbitone	✓ (g)				
10. Primidone	✓ (g)				
11. Benzodiazepines	✓ (g)				
12. Felbamate		✓ (h)			
13. Levetiracetam					Block SV ₂ A
14. Zonisamide			✓	✓	
15. Lacosamide			✓		CRMP-2 inhibitor
16. Rufinamide			✓		
17. Retigabine (Ezogabine)					K ⁺ channel opener

a - Increase GABA by activating Glutamic acid decarboxylase and inhibiting GABA transaminase

b - Inhibits release of glutamate

c - Inhibits release of GABA

d - Increases postsynaptic GABA activity

e - Blocks AMPA receptors of glutamate

f - Inhibits reuptake of GABA by inhibiting GAT-1

g - Act on GABA-BZD-Cl⁻ channel complex

h - Blocks NMDA receptors of glutamate

Important Drugs

1. BARBITURATES

Phenobarbitone and primidone act as anticonvulsant drugs due to GABA mimetic as well as GABA facilitatory properties. These drugs increase the duration of opening of chloride channels. These drugs are useful in generalized tonic clonic seizures (GTCS) and partial seizures. These drugs are *highly sedating* but tolerance develops to this effect. Barbiturates are *contraindicated in acute intermittent porphyria*. These drugs can cause *paradoxical* excitation in some patients. *Phenobarbitone is drug of choice for GTCS in infants but can cause hyperkinesia in older children.*

2. BENZODIAZEPINES

Diazepam, clonazepam, lorazepam and clobazam are benzodiazepines that act by GABA facilitatory activity. These drugs increase the frequency of Cl^- channel opening. Diazepam, lorazepam and clonazepam are useful for the management of acute seizures. These can also be used i.v. for **status epilepticus (Lorazepam is DOC)**. *Diazepam given by per rectal route is DOC for febrile seizures.* Benzodiazepines also have prominent **sedative** effects like barbiturates. Tolerance develops to the antiepileptic effect so these are not indicated for long term use.

3. PHENYTOIN

It is a **non sedating oral** antiepileptic drug. **Fosphenytoin** is a water soluble prodrug of phenytoin that can be administered **parenterally** (i.v. or i.m.) for acute attack of seizures (status epilepticus). These drugs act by blocking the use dependent Na^+ channels. Phenytoin is useful in GTCS and partial seizures.

- It can also be used as an **anti-arrhythmic drug (class Ib)** for the treatment of digitalis induced arrhythmia.
- **Recently** it has been found to **enhance wound healing**.
- This drug **follows saturation kinetics** (kinetics changes from first order to zero order within therapeutic concentrations).
- Phenytoin from different manufacturers (different brands) have different bioavailability and therefore **brand change can lead to toxicity** or suboptimal levels.
- **At toxic plasma levels oral dose of phenytoin** can result in **cerebellar symptoms** (ataxia, vertigo, nystagmus, diplopia).
- Fosphenytoin should be given by slow i.v. infusion because *fast* administration of high doses can lead to *arrhythmias, cardiovascular collapse and coma*.
- **Prolonged use** of phenytoin can result in **gingival hyperplasia** (gum hypertrophy). It results due to over-expression of platelet-derived growth factor (PDGF). It may regress after discontinuation of phenytoin. Other adverse effects on long-term use include **hirsutism, coarsening of facial features, megaloblastic anemia** (treated with folic acid), **vitamin D deficiency** (rickets and **osteomalacia**), vitamin K deficiency, **hyperglycemia** (due to inhibition of insulin release), **hypersensitivity** and **teratogenicity (fetal hydantoin syndrome; hypoplastic phalanges, cleft lip, cleft palate and microcephaly)**.
- **Osteomalacia** may not always be ameliorated by administration of vitamin D because some *vitamin K dependent proteins* also play a role in Ca^{2+} metabolism in bone.
- **Lymphadenopathy (pseudolymphoma) and malignant lymphoma** (associated with reduced IgA) and *inhibition of ADH release* (in SIADH patients) has also been reported.
- Phenytoin should be stopped gradually because sudden discontinuation may result in precipitation of seizures.
- It is also a **potent enzyme inducer** and can increase the metabolism of various drugs.

Benzodiazepines (preferably lorazepam) is drug of choice for status epilepticus

M

Adverse effect of phenytoin:

- H** – Hirsutism
- H** – Hypertrophy of gums
- O** – Osteomalacia
- T** – Teratogenicity
- M** – Megaloblastic anemia
- A** – Ataxia and nystagmus
- L** – Lymphadenopathy
- I** – Inhibits insulin release (hyperglycemia)
- K** – Vitamin K deficiency
- A** – Arrhythmias

M

Fetal Hydantoin syndrome:

- P** – Hypoplastic Phalanges
- C** – Cleft Lip and palate
- M** – Microcephaly

N

Eslicarbazepine is a Na^+ channel blocker (like carbamazepine) indicated for adjunctive treatment of focal seizures.

Carbamazepine is drug of choice for partial seizures and trigeminal neuralgia.

Phenytoin and carbamazepine can worsen generalized seizures including absence, myoclonic, tonic and atonic seizures.

Valproate is drug of choice for

- GTCS
- Myoclonic Seizures
- Atonic Seizures
- Absence Seizures
- Clonic Seizures
- Tonic Seizures

Drug of choice for infantile spasms is ACTH whereas infantile spasms associated with tuberous sclerosis is treated with vigabatrin.

Zonisamide and topiramate can cause renal stones.

4. CARBAMAZEPINE AND OXCARBAZEPINE

These drugs act by blocking the use dependent sodium channels. Oxcarbazepine has similar efficacy but less toxicity than carbamazepine (CBZ). These are the **drugs of choice for partial seizures** and can also be used in GTCS. *Carbamazepine is DOC for trigeminal neuralgia* and can also be used for glossopharyngeal and post herpetic neuralgia. Another use of carbamazepine is in the treatment of **bipolar disorder** (manic depressive psychosis) and as an **antidiuretic** in DI. It is a potent enzyme inducer and can **induce its own metabolism** (thus requiring more dose if used for long term). Major adverse effects of these drugs include dizziness, headache, ataxia, vertigo and diplopia. It can also cause leukopenia, aplastic anemia and hepatotoxicity. Congenital malformations are induced in children delivered to females taking this drug during pregnancy.

5. VALPROIC ACID

It is a broad spectrum antiepileptic drug effective in all types of seizures. It acts by several mechanisms including blockade of use dependent Na^+ channels, increased activity of GABA (by increasing synthesis due to stimulation of glutamic acid decarboxylase and decreasing metabolism by inhibiting GABA transaminase), inhibition of T type Ca^{2+} channels and decrease in release of glutamate in the brain. It is the **DOC in GTCS, myoclonic, atonic, atypical absence, clonic and tonic seizures**. It is also effective in Lennox Gestaut syndrome, absence seizures, infantile spasms and partial seizures.

It should be gradually stopped to avoid withdrawal seizures. **Other uses** of this drug include **bipolar disorder, prophylaxis of migraine** and as an alternative to carbamazepine in **trigeminal neuralgia**. Recently it has also been used in **tardive dyskinesia**. It is also the **drug of choice for bipolar disorder in patient having rapid cycles** (4 or more cycles per year).

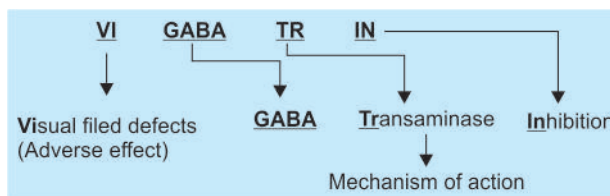
Valproic acid is a potent microsomal **enzyme inhibitor**. Adverse effect of this drug includes weight gain, alopecia, tremors, carnitine deficiency and **irreversible hepatic necrosis (more in children < 2 yrs old)**. It is **DOC for absence seizures** (petit mal epilepsy). However, it should be avoided in children <2 years due to risk of irreversible hepatic necrosis. As absence seizures rarely develop before 5 years of age, valproate may be considered as drug of choice for majority of absence seizures. In rare cases of absence seizure in young children (<2 years), ethosuximide should be used. **Acute pancreatitis and hyperammonemia** have been frequently associated with valproic acid. If used during pregnancy, it can result in **neural tube defects in the baby** (prevented by folic acid administration during pregnancy).

6. ETHOSUXIMIDE AND TRIMETHADIONE

These drugs act by inhibiting T type Ca^{2+} channels and are **useful only in absence seizures** (petit mal epilepsy). Ethosuximide is **DOC for this condition in children less than 2 years old**. Trimethadione is more toxic than ethosuximide and is therefore no longer used. **Characteristic adverse effect of trimethadione is hemarlopia** (photophobia and glare effect).

7. OTHER ANTIEPILEPTIC DRUGS

- **Vigabatrin** is an irreversible **inhibitor of GABA transaminase**, thus increases GABAergic activity. It is the **DOC for infantile spasms associated with tuberous sclerosis** (*ACTH is DOC for all other cases*). It can result in **irreversible visual field defects** due to retinal atrophy.



- **Lamotrigine** is a **broad spectrum** antiepileptic drug useful for various seizures including absence seizures and myoclonic epilepsy. It is **specifically indicated for depressive phase of manic depressive psychosis**. **Steven Johnson syndrome** and **toxic epidermal necrolysis** are important adverse effects of this drug.
- **Gabapentin** increases GABAergic transmission by increasing its synthesis and release. Its absorption from GIT is saturable, therefore it is safe even after overdosing. It is useful in GTCS and partial seizures. Non epileptic uses include **diabetic and post herpetic neuralgia** (DOC for both of these conditions) and pain associated with multiple sclerosis. Another drug similar to gabapentin is **pregabalin**.
- **Ganaxolone** is a **neurosteroid** (synthesized in the brain) and is effective for absence seizures, infantile spasms and catamenial epilepsy (seizures occurring during menstruation).
- **Topiramate** acts by blocking Na^+ channels, increasing GABA transmission and inhibiting kainate receptors. It is useful in GTCS, partial seizures and Lennox Gestaut syndrome. **It can cause weight loss**. **Zonisamide** (another antiepileptic drug) and **topiramate** can cause **renal stones** due to their carbonic anhydrase inhibitory activity.
- **Felbamate** is an NMDA blocker useful in drug resistant epilepsies but its use is limited due to hepatotoxicity and **aplastic anemia**.
- **Levetiracetam** is another antiepileptic drug useful for partial seizures. It modifies synaptic release of GABA and glutamate by *binding to synaptic vesicular protein SV2A*.
- **Magnesium sulphate** is **DOC for treating the convulsions during labour (eclampsia)**. Its toxicity is monitored by *patellar reflex* (knee jerk).
- **Tiagabine** is indicated for adjunctive treatment of partial seizures. It is a **rationally designed** drug as an inhibitor of GABA uptake (by inhibiting GAT-1).
- **Lacosamide** is a recently approved drug for the adjunctive therapy of partial-onset seizures. It acts by blocking Na^+ channels and CRMP-2 (Collapsin-Response Mediator Protein). Blockade of CRMP-2 result in stopping the effect of neurotrophic factors like BDNF and NT3 on axonal and dendritic growth.
- **Rufinamide** is another recently approved drug for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome. It is thought to act by inhibiting Na^+ channels.
- **Retigabine** (also called **ezogabine**) is approved as add-on drug for partial seizures in adults. **Urinary retention** is its major adverse effect.

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Perampanel is a new selective AMPA-type glutamate receptor antagonist. It is indicated for partial seizures

N

Retigabine (also called **ezogabine**) is approved as add-on drug for partial seizures in adults.



Magnesium sulphate is DOC for treating the convulsions during labour (eclampsia). Its toxicity is monitored by patellar reflex (knee jerk).

EPILEPSY IN PREGNANCY

- Most important step in management is to control the seizure.
- If a female is already on antiepileptic drugs, the **same drug should be continued** in pregnancy. *Folic acid should be added* to prevent neural tube defects (particularly with valproate). If phenytoin is being taken, vitamin K should be given during labour and to baby after delivery. Regular ultrasound and other assessments should be done to know the fetal malformations.
- If a female is planning to become pregnant, she should be *stabilized on minimum number of antiepileptic drugs*.
- *Newer antiepileptic drugs* are assumed to have *lesser teratogenicity* as compared to older ones (valproate being most teratogenic). However, the choice of drug depends primarily on type of seizure.
- Among the older drugs, *carbamazepine is assumed to be relatively safer*. However, *Lamotrigine has widest spectrum* (GTCS, typical Absence, atypical absence, myoclonic, atonic, focal seizures) and is *preferred drug in pregnancy*. Topiramate can also be used for all of these except typical absence seizures.

Drugs for Absence Seizures

- Ethosuximide
- Sodium valproate
- Lamotrigine
- Trimethadione
- Clonazepam

Drugs for Myoclonic Seizures

- Valproate
- Lamotrigine
- Topiramate
- Clonazepam
- Felbamate

DRUGS OF CHOICE FOR VARIOUS SEIZURES

Absence seizures	– Valproate
GTCS (Grand mal)	– Valproate
Partial seizures	– Carbamazepine
Myoclonic seizures	– Valproate
Atonic (Akinetic) seizures	– Valproate
Tonic seizures	– Valproate
Clonic seizures	– Valproate
Infantile spasms	– ACTH
Infantile spasms with tuberous sclerosis	– Vigabatrin
Febrile seizures	– Diazepam (per rectal)
Status epilepticus	– Lorazepam (i.v.)
Seizures in eclampsia	– Magnesium sulphate

Lennox Gastaut Syndrome

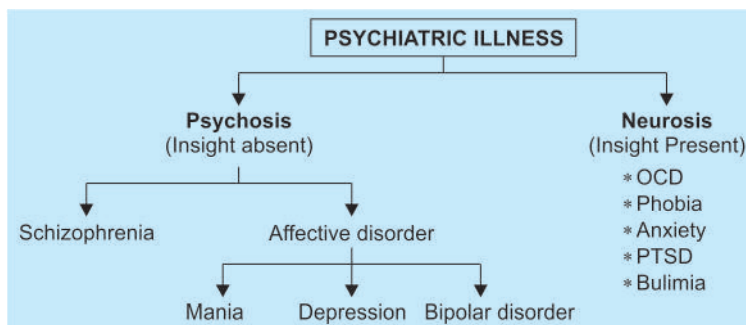
It is a difficult-to-treat form of childhood-onset epilepsy that most often appears between 2 to 6 years of age. It is characterized by frequent occurrence of different seizure types associated with developmental delay and psychological and behavioural problems. EEG shows characteristic slow spike-wave complexes. **First-line drugs** for treatment are **rufinamide, valproate and benzodiazepines** (clonazepam and clobazam). Second-line drugs are *felbamate* and *topiramate*.

DRUGS FOR PSYCHIATRIC ILLNESS

Two major types of psychiatric disorders are psychosis and neurosis.

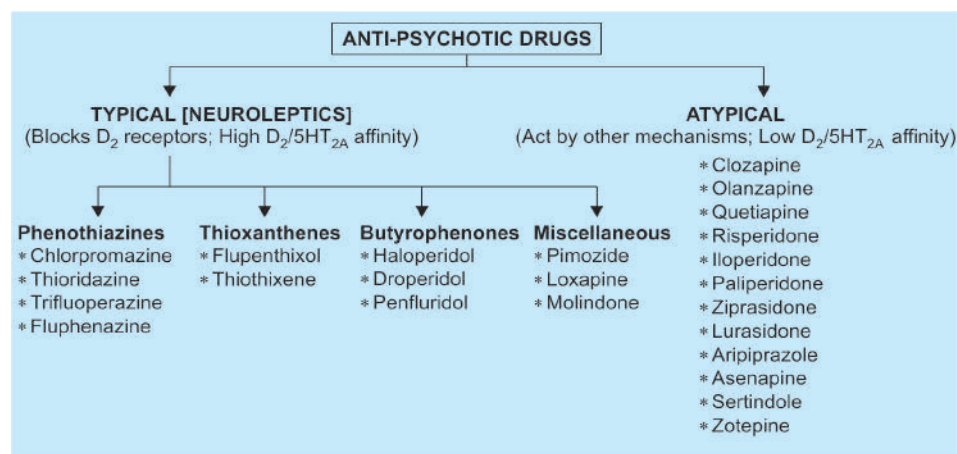
Psychosis: Patient is not aware of his illness (*insight is absent*) and refuses to take treatment. It includes major psychosis like schizophrenia as well as mood disorders (like mania, depression and bipolar disorder).

Neurosis: It is less serious and insight is present. It includes anxiety, obsessive compulsive disorder (OCD), phobias, eating disorders and post traumatic stress disorder (PTSD).

**Antipsychotic Drugs**

Schizophrenia is a severe psychiatric illness and is thought to be *due to dopaminergic overactivity in the limbic system* of brain. Other neurotransmitters like 5-HT and NA also probably

play a role in this disorder. All drugs for schizophrenia have equal efficacy, these *mainly differ in potency* and can be classified as typical (D_2 blockers) and atypical (acting via other mechanisms) antipsychotics.



ACTIONS OF TYPICAL ANTIPSYCHOTICS

- These drugs act by **blocking D_2 receptors** and differ significantly in potency. **Low potency drugs (like chlorpromazine)** are highly sedative whereas high potency drugs cause less sedation.
- High potency drugs are more likely to cause **extrapyramidal symptoms (maximum with haloperidol)** whereas it is **least common with thioridazine**.
- High potency drugs have low anticholinergic and autonomic side effects as compared to low potency drugs.
- These drugs **lower seizure threshold** and can precipitate convulsions in an epileptic patient.
- All of these agents are **potent antiemetic drugs except thioridazine**.
- **Low potency drugs** possess significant α **blocking** (maximum with chlorpromazine) and **anticholinergic** (maximum with thioridazine) properties. High potency compounds have less activity on these receptors.
- Due to blockade of D_2 receptors in hypothalamus and pituitary, these drugs can **increase prolactin release** resulting in *galactorrhoea and amenorrhoea*.

ACTIONS OF ATYPICAL ANTIPSYCHOTICS

These drugs act by *antagonistic actions at $5-HT_2$ and α receptors* and may or may not possess D_2 blocking activity. These drugs are *less likely to cause extrapyramidal symptoms*. However, most of these agents (*except ziprasidone and aripiprazole*) can result in **weight gain, hyperlipidemia and new-onset diabetes mellitus**.

INDIVIDUAL DRUGS

- **Thioridazine:** It has *least incidence of extrapyramidal symptoms among typical antipsychotic drugs* due to low potency D_2 blocking action and presence of central anticholinergic activity.
 - ❖ It interferes with male sexual function by *inhibiting ejaculation* (due to α blocking action)
 - ❖ It can cause cardiac arrhythmia (Prolongation of QT interval).
 - ❖ *Retinal damage* limits long term administration.

Long-acting Injectable antipsychotics for un-cooperative patients.

- Fluphenazine decanoate
- Haloperidol decanoate
- Risperidone microspheres
- Paliperidone palmitate

Clozapine induced convulsions are dose-dependent adverse effect whereas agranulocytosis is independent of dose.

Ziprasidone can cause QT prolongation and Quetiapine can cause cataract formation.

Asenapine is used sublingually.

- **Trifluperazine, fluphenazine and haloperidol**
 - ❖ These are high potency drugs and have *least* α blocking, anticholinergic, sedative and proconvulsant actions. However, extrapyramidal symptoms are marked.
- **Penfluridol** is the *longest acting* antipsychotic drug.
- **Pimozide** selectively blocks D_2 receptors without affecting α and muscarinic receptors. It also possesses long duration of action. It carries the risk of arrhythmias due to *QT prolongation*.
- **Clozapine** is an *atypical antipsychotic* drug having weak D_2 blocking action. It mainly acts by blocking $5-HT_2$, α adrenergic and D_4 receptors. It *suppresses both positive as well as negative symptoms* (First FDA approved drug for antisuicide indication) of schizophrenia. It is used only as a reserve drug due to the *risk of precipitation of seizures* (even in non-epileptics) and **agranulocytosis**. **Convulsions are dose-dependent adverse effect seen only in high doses whereas agranulocytosis is independent of dose**. Because of association with **myocarditis**, clozapine is *contra-indicated in patients with severe heart disease*. It has powerful anticholinergic effects (equivalent to chlorpromazine and thioridazine). Risk of *extrapyramidal symptoms* is *least* with the use of this drug. It specifically has two risks of intestinal dysfunction; *potentially severe ileus and sialorrhea*.
- **Risperidone**: It acts by blocking $5-HT_2$, α adrenergic and D_2 receptors. It is more potent D_2 blocker than clozapine and can cause extrapyramidal symptoms at high dose. Risk of precipitation of seizures is less than clozapine. **Hyperprolactinemia** has been reported more commonly with risperidone than other atypical antipsychotics. Its active metabolite (paliperidone) has lesser risk of causing metabolic adverse effects.
- **Olanzapine**: It has similar mode of action as risperidone. It is also a potent anticholinergic drug and can cause dry mouth and constipation. It can cause seizures and *weight gain*. Apart from its use in schizophrenia, it is also used in *acute mania and bipolar disorder*. It has been associated with significantly **higher risk of stroke and death** in elderly patients.
- **Ziprasidone**: It causes *QT prolongation* and carries risk of arrhythmias. Unlike other atypical antipsychotics, it is not associated with weight gain, hyperlipidemia or diabetes.
- **Quetiapine**: Can cause *cataract formation*. It has *shortest half life*.
- **Aripiprazole**: Acts as a partial agonist at $5-HT_{1A}$ and D_2 receptors and antagonist at $5-HT_{2A}$ receptors. It is also known as *dopamine-serotonin stabilizer*. It has quite long half life. It has also been approved for treatment of *irritability associated with autistic disorders in children*.
- **Asenapine** is used **sublingually** for schizophrenia and acute mania.
- **Iloperidone** has less risk of extrapyramidal adverse effects but cause orthostatic hypotension and can prolong QT interval.

ADVERSE EFFECTS

- Sedation (maximum with chlorpromazine; minimum with ziprasidone and aripiprazole), weight gain (with all, less with ziprasidone) and aggravation of seizures (more with clozapine, olanzapine and chlorpromazine; less chances with risperidone and quetiapine).
- Postural hypotension and inhibition of ejaculation (α blocking property).
- Weight gain (with all *except haloperidol*). All atypical anti-psychotics may result in **weight gain, hyperlipidemia and new-onset diabetes except ziprasidone**.

Acute muscular dystonia is the earliest appearing symptom whereas akathisia is the most common extrapyramidal symptom.

According to their potential to cause **adverse metabolic side effects**, anti-psychotics can be classified as:

High Potential:	Clozapine, Olanzapine
Intermediate potential:	Quetiapine
Low Potential:	Risperidone, Paliperidone
Least potential:	Ziprasidone, Aripiprazole, lloperidone, Asenapine

- Retinal degeneration with thioridazine.
- Agranulocytosis with clozapine.
- Cataract formation with quetiapine.
- Cholestatic jaundice with chlorpromazine.
- Dry mouth, blurred vision, constipation, urinary retention (due to anticholinergic effects; maximum with thioridazine).
- Hyperprolactinemia, amenorrhoea and galactorrhoea (due to D₂ blockade in pituitary).
- **Extrapyramidal symptoms** (due to D₂ blockade in limbic system) are closely **related to antipsychotic potency** of typical antipsychotic drugs

- ❖ **Acute muscular dystonia:** It is the *earliest appearing symptom* (within hours) and may manifest as torticollis, locked jaw, oculogyric crisis or spasm of other muscles. *Central anticholinergics* are useful in the treatment.
- ❖ **Parkinsonism:** It appears between 1-4 weeks of therapy. *Central anticholinergics* like benzhexol are drug of choice for drug induced Parkinsonism
- ❖ **Akathisia:** It is an irresistible desire to move about in the absence of anxiety. It is the **most common extrapyramidal symptom**. Cigarette smoking is associated with increased risk of akathisia. *Propanolol* is the preferred drug for this condition; however central anticholinergics are also useful in the treatment.
- ❖ **Malignant neuroleptic syndrome:** It presents as hyperthermia, extreme generalized rigidity, autonomic instability and altered mental status. It can be treated by *i.v. dantrolene (DOC)* or *bromocriptine*.
- ❖ **Tardive dyskinesia:** It occurs late in therapy and is characterized by purposeless involuntary movements like chewing or puffing of cheeks. There is no satisfactory treatment for this condition; however, *central anticholinergics* are contraindicated.

OTHER USES

- These agents can be used as an alternative to ECT in *severe depression with psychotic features*.
- Alcoholic hallucinosis.
- Gilles de la Tourette's syndrome and Huntington's disease (*Haloperidol* is drug of choice).

Note:

1. **Haloperidol and fluphenazine** are **most potent typical** antipsychotic drugs whereas **risperidone** is **most potent atypical antipsychotic agent**.
2. Risk of extrapyramidal adverse effects is negligible with clozapine, quetiapine and aripiprazole.
3. **Chlorpromazine, thioridazine and clozapine** possess **strongest anticholinergic** activity.
4. **Fluphenazine** (enanthate and decanoate) and **haloperidol** (decanoate) are long-acting **injectable** (s.c. or i.m) forms of typical antipsychotics. **Risperidone** is the **first atypical antipsychotic available** in long-acting **injectable** form.
5. Most commonly used antipsychotic by intravenous route is haloperidol

M

Use of antipsychotics

ANTI-emetics
 Psychosis
 CHorea
 TIC disorders
 (Gille de la
 Torrette
 syndrome)
 ANTI PSY CHO TIC

6. **Ziprasidone, aripiprazole, asenapine and iloperidone** has *negligible risk to cause metabolic adverse effects* (weight gain, hyperlipidemia and new onset diabetes mellitus)
7. **Asenapine, paliperidone and ziprasidone** has greatest potential to *prolong QT interval*.

ANTIDEPRESSANT DRUGS

Depression results due to decreased monoaminergic (5-HT and NA) activity in the brain, therefore drugs *increasing* their activity are called **typical anti-depressants**. Drugs acting by other mechanisms are called **atypical anti-depressants**.

A. Typical Antidepressants

Drugs may increase monoaminergic transmission by *inhibiting the reuptake or metabolism* of 5-HT or NA.

1. TRICYCLIC ANTIDEPRESSANTS (TCA)

These drugs act by inhibiting the reuptake of **both serotonin and noradrenaline**. This results in increased concentration of these transmitters in the synaptic cleft. *Bupropion also inhibits dopamine reuptake*. NA and serotonin *initially act on presynaptic* α_2 and 5HT_{1A} receptors respectively and decrease the firing of locus ceruleus (NA) and nucleus raphe magnus (5HT). On long term administration, desensitization of these receptors occurs and enhanced transmission is seen. This explains the *long latency (2-3 weeks)* for the anti-depressant action of TCA and SSRIs despite immediate inhibition of reuptake process.

Adverse Effects

- **Sedative** action of TCAs appears immediately and these drugs (particularly clomipramine, maprotiline and bupropion) **lower the seizure threshold**.
- **Weight gain** is another problem with the **use of TCAs**.
- Most TCAs possess **powerful anticholinergic and weak α blocking property**. Overdose manifestations are mainly anticholinergic (delirium, urinary retention, blurred vision and constipation) in nature. These also cause postural hypotension (due to α blockade) and cardiac arrhythmias at toxic levels.
- TCAs have **low safety margin**.
- **Amoxapine** acts by **blocking D₂ receptors** in addition to the inhibition of NA reuptake. It **possesses antipsychotic properties as well** (It is a metabolite of antipsychotic drug; loxapine). However, risk of extrapyramidal symptoms and convulsions is also present.
- *TCAs (imipramine) are also indicated for nocturnal enuresis in children (However, DOC is desmopressin).*

Mechanism of adverse effects of TCA

S.No.	Inhibition of	Adverse Effects
1	Presynaptic NT reuptake	Tremors, Insomnia
2	Cardiac fast Na ⁺ channels	Conduction defects, arrhythmias, hypotension
3	Muscarinic ACh receptors	Hyperthermia, flushing, mydriasis, Paralytic ileus, urinary retention, sinus tachycardia
4	α_1 Adrenergic receptors	Postural hypotension
5	H ₁ histamine receptors	Sedation

2. SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRI)

These drugs inhibit the reuptake of **5-HT only** (not NA) and lack anticholinergic and α blocking properties. SSRIs are now the **first choice drugs** for *depression, phobias, OCD, PTSD*,

Imipramine, amitriptyline, trimipramine and clomipramine inhibit the uptake of both 5-HT and NA whereas desipramine, nortriptyline and amoxapine are predominantly NA reuptake inhibitors.

bulimia, premenstrual tension syndrome and panic attacks because they offer several advantages over TCAs:

- No anticholinergic adverse effects
- No sedation or weight gain
- No propensity to cause seizures or arrhythmias

Adverse effects

Nausea is the **most frequent complaint** with the use of SSRIs. Anxiety is the next most common adverse effect followed by diarrhea. These can **also** cause **inhibition of ejaculation**. Coadministration of SSRIs with MAO inhibitors can result in *serotonin syndrome*. SSRIs can cause akathisia. Because SSRIs affect platelet serotonin levels, abnormal bleeding can occur. *Sertraline and citalopram appear to be safest SSRIs to be used with warfarin.*

Important compounds

- **Fluoxetine**: It is a prototype SSRI and is **longest acting** drug in this group. It is metabolized to nor-fluoxetine that retains the anti-depressant activity.
- **Fluvoxamine** is the **shortest acting** SSRI.
- **Paroxetine, sertraline and citalopram** are other SSRIs.
- **Escitalopram** is *most specific* SSRI.
- **Paroxetine** is **most teratogenic** among SSRIs.

Systematic desensitization by gradual exposure to feared situation is used for management of specific phobias. **Cycloserine** enhances extinction of fear responses with exposures

SSRIs are now the first choice drugs for

- Depression
- Obsessive-Compulsive Disorder
- Post-Traumatic Stress Disorder
- Bulimia
- Premenstrual Tension Syndrome
- Panic Disorder

3. MAO INHIBITORS

Two types of monoamine oxidase enzymes (MAO-A and MAO-B) are involved in the metabolism of monoamines.

- **MAO-A** predominantly metabolizes **NA, 5-HT and DA** and is present in the intestine, peripheral nerve endings and liver.
- **MAO-B** preferentially metabolizes **dopamine** and is present in the brain, platelets and liver.

Non selective MAO inhibitors

Tranylcypromine, isocarboxazid and phenelzine inhibits both isoforms of MAO irreversibly. Their anti-depressant effect takes 3-4 weeks to develop. These drugs exhibit a large number of drug and food interactions. The important ones are:

- **Cheese reaction**: *Cheese, beer and red wine contain tyramine* (indirectly acting sympathomimetic). Normally it is metabolized by MAO-A present in the intestine and is not absorbed. In persons taking non-selective MAO inhibitors, tyramine escapes degradation and can lead to **hypertensive crisis**. It is known as cheese reaction. So, cheese etc. should not be given to patients on long term non selective MAO inhibitor therapy. **Phentolamine** is the drug of choice for cheese reaction.
- Non-selective MAO inhibitors **increase the risk of seizures** if given along with pethidine due to enhanced generation of excitatory metabolite nor-meperidine.
- **Serotonin syndrome**: If given along with or just after discontinuation of MAO inhibitors, **SSRIs** can result in serotonin syndrome. To avoid this fatal condition, SSRIs should be started at least 14 days after discontinuation of MAO inhibitors. It allows sufficient time for regeneration of MAO.

Vortioxetine is a serotonin reuptake inhibitor with 5HT₃ antagonistic and 5HT_{1A} receptor agonistic action. It is indicated for major depressive disorder.

Prazosin decreases nightmares and improves quality of sleep in post-traumatic stress disorder

Reversible inhibitors of MAO-A (RIMA)

Moclobemide inhibits MAO-A selectively and reversibly. Because of its reversible and short action, it **does not exhibit cheese reaction** with foods. It can be used as an alternative to TCAs for the treatment of depression.

SSRIs should be started at least 14 days after discontinuation of MAO inhibitors to avoid the risk of serotonin syndrome.

Selective MAO-B inhibitors

Selegiline inhibits only MAO-B and is useful in **Parkinsonism**. It is available as a *transdermal patch* for treatment of depression.

B. Atypical Antidepressants

These drugs may or may not increase monoaminergic levels and possess different anti-depressant mechanisms.

Venlafaxine, milnacipran, levo-milnacipran and duloxetine inhibit reuptake of serotonin and NA but lack anticholinergic and α blocking properties. These are also referred to as serotonin and nor-adrenaline reuptake inhibitors (**SNRI**).

Mirtazapine is also known as nor-adrenergic and specific serotonergic anti-depressant (**NSSA**).

Bupropion is used for **smoking cessation**.

M**Uses of anti-depressants**

- D** - Depression
- E** - Enuresis (Imipramine)
- P** - Phobia
- R** - Recurrent panic attacks
- E** - Eating disorders (Bulimia)
- S** - Smoking cessation (Bupropion)
- S** - Stress disorder (Post traumatic)
- I** - Impulse disorder (Kleptomania)
- O** - Obsessive compulsive disorder
- N** - Neuropathic pain

- **Trazodone** is a prominent α blocker and weak 5-HT₂ antagonist. It produces *sedation, priapism* (prolonged and painful erection) and *postural hypotension* as adverse effects.
- **Mianserin** acts by **blocking presynaptic α_2 receptors** but *seizure* augmenting and *bone marrow depressant* actions restrict its use.
- **Tianeptin and amineptine** acts by **enhancing** the serotonin reuptake (*action opposite to SSRI*).
- **Venlafaxine, milnacipran, levo-milnacipran and duloxetine** inhibit reuptake of serotonin and NA but **lack anticholinergic and α blocking properties**. These are also referred to as serotonin and nor-adrenaline reuptake inhibitors (**SNRI**). Venlafaxine has **faster onset** of action. It has *minimum drug-drug interactions*.
- **Mirtazapine**: It inhibits presynaptic α_2 receptors and thus increases NA and 5-HT release due to inhibition of auto- and hetero-receptors respectively. Although it increases serotonin levels in synapse, there is selective activation of 5-HT₁ receptors due to antagonistic activity at 5-HT₂ and 5-HT₃ receptors. Therefore it is also known as **nor-adrenergic and specific serotonergic anti-depressant (NSSA)**. It has **minimal sexual side effects** compared with SSRIs. It commonly causes sedation, weight gain, lipid abnormalities and dizziness.
- **Bupropion**: It inhibits the uptake of NA and DA. It is metabolized to amphetamine like compound and possesses excitatory property. It is **used for smoking cessation** as sustained release formulation. It can precipitate **seizures** at high dose.
- **Nafazodone**: It blocks serotonin reuptake and antagonizes 5-HT₂ receptors. It lacks anticholinergic effects (of TCAs) and agitation (seen with SSRI). It has very short half life and is hepatotoxic.
- **Atomoxetine**: It is a selective inhibitor of NA reuptake and is useful for **Attention Deficit Hyperkinetic Disorder** (efficacy similar to methylphenidate).
- **Duloxetine** (a mixed NA and 5HT reuptake inhibitor) is also useful in treating **chronic neuropathic pain e.g. in diabetic neuropathy and fibromyalgia**.

Note:

• Most potent blocker of 5-HT reuptake	– Paroxetine
• Least potent blocker of 5-HT reuptake	– Bupropion
• Most potent blocker of NA reuptake	– Desipramine
• Least potent blocker of NA reuptake	– Mirtazapine
• Most selective inhibitor of 5-HT reuptake	– Escitalopram
• Most selective inhibitor of DA reuptake	– Bupropion
• Most selective inhibitor of NA reuptake	– Oxaprotiline
• Maximum antimuscarinic activity	– Amitriptyline
• Maximum antihistaminic activity	– Nefazodone
• Maximum α_1 blocking activity	– Doxepin
• Minimum antimuscarinic, α_1 blocking and antihistaminic activity	– Venlafaxine
• Doxepin contains high antimuscarinic, antihistaminic and α -blocking (maximum) activities.	
• Fluoxetine is longest acting and nefazodone is shortest acting antidepressant.	

ANTI MANIC DRUGS



Half-life of lithium is 24 hours

LITHIUM

It is a small monovalent cation that *does not produce any acute effect* but on prolonged use, acts as a mood stabilizer. It has no psychotropic effect in normal persons. It acts by *inhibiting the hydrolysis of inositol-1-phosphate* (required for the regeneration of IP_3 and DAG).

- It has **narrow margin of safety** (low therapeutic index) and therapeutic drug monitoring (TDM) is essential.
- It takes 1-2 weeks to exert its maximum effect. It is the **drug of choice for the prophylaxis of bipolar disorder**. Its $t_{1/2}$ is 24 hours.
- It can be used in **acute mania** but *benzodiazepines* like lorazepam must be added (due to slow action of Li). In patients not controlled by BZDs, antipsychotics like olanzapine may be added.
- Plasma concentration of lithium should be **0.5-0.8 mEq/L for maintenance** therapy of bipolar disorder and **0.8-1.2 mEq/L for acute mania**. Toxic symptoms are seen if plasma concentration exceeds 1.5mEq/L.
- **Diuretics** (particularly thiazides) decrease the renal excretion of lithium and thus **may result in toxicity**. This is due to increased reabsorption of Na^+ and lithium ions (as a compensatory response to excessive loss of Na^+)

Other effects of lithium are

- L** – **Leucocytes** are Useful in the treatment of cancer chemotherapy induced leucopenia
I – **Increased**
T – **Tremors** (Most common side effect)
H – **Hypothyroidism**
I – **Increased** } Nephrogenic diabetes insipidus, can be used for the treatment of SIADH.
U – **Urine** } *Amiloride is DOC for lithium induced DI.*
M should be avoided in expectant **Mothers** as it causes *Ebstein's anomaly*



L – Leucocytes
I – Increased
T – Tremors
H – Hypothyroidism
I – Increased } Polyuria
U – Urine }
M should be avoided in expectant mothers

- Acne and weight gain (due to Na^+ and water retention) are the other adverse effects.
- It can cause benign and reversible elevation of T waves in ECG.

Alternatives to Lithium

- **Carbamazepine and valproate** are useful in manic depressive psychosis (bipolar disorder). These can also be used for acute mania. **Valproic acid is the drug of choice for treatment of rapid cyclers** (> 4 cycles/year).
- **Benzodiazepines** like lorazepam are the **drugs of choice for acute mania** when combined with lithium. Olanzapine and other atypical antipsychotics show efficacy in bipolar disorder as well as acute mania.
- **Lamotrigine is specifically useful for depressive phase of bipolar disorder**. It is the first agent to be *approved* by FDA for bipolar disorder *without* an indication for acute mania.

Lithium Toxicity

- Acute intoxication is characterized by vomiting, diarrhea, coarse tremor (fine tremor in mild intoxication), ataxia, coma and convulsions.
- More serious effects involve mental confusion, hyperreflexia, dysarthria, seizures, and cranial and focal neurological signs progressing to coma and death.
- Other toxic effects are cardiac arrhythmias, hypotension and albuminuria.
- There is **no specific antidote** for lithium. **Dialysis** is most effective means of removing Li from body. It is indicated at serum Li levels of **> 4m Eq/L in acute overdose** or **> 1.5 mEq/L in chronic overdose**.

ANTI ANXIETY DRUGS

Reduction in the GABAergic activity or increase in serotonergic activity may result in anxiety. It is due to mild CNS stimulation. Drugs commonly used for anxiety are CNS depressants (like benzodiazepines) or those decreasing serotonin level (like buspirone).

BENZODIAZEPINES

- DOC for acute management of generalized anxiety is benzodiazepines
- SSRI are first line medications for sustained treatment of generalized anxiety disorders.

Chlordiazepoxide is used for **chronic** anxiety states whereas *oxazepam, lorazepam, alprazolam and diazepam* are indicated for *short lasting anxiety states*. *Oxazepam and lorazepam* are safe in *elderly and in patients with liver disease*. Benzodiazepines are most commonly used anxiolytic drugs; however sedation, cognitive impairment and abuse liability are potential limitations in their use.

AZAPIRONES

Buspirone, gepirone and ipsapirone act as *partial agonists* of presynaptic 5-HT_{1A} receptors and decrease the release of serotonin. These drugs *do not cause sedation* or cognitive impairment and are *devoid of abuse potential, muscle relaxant and anticonvulsant activity*. Therapeutic effect of these drugs takes up to 2 weeks and therefore these are **ineffective in acute anxiety states** like panic attacks. These are indicated for mild to moderate generalized anxiety states.

BETA BLOCKERS

Propanolol is indicated for **performance anxiety** where it decreases the sympathetic manifestations of anxiety.

OTHER DRUGS

- **Hydroxyzine** is H₁ antihistaminic having anti-anxiety activity but profound sedation limits its usefulness.
- **SSRIs** like fluoxetine are agents of choice for panic disorder whereas benzodiazepines are drug of choice for panic attacks and generalized anxiety disorder.

ALCOHOLS

ETHYL ALCOHOL (ETHANOL)

It is a CNS depressant drug that can result in psychological as well as physical dependence. It is an *imperfect food* because it lacks essential constituents and it *cannot be stored*. It follows **zero order kinetics** and plasma concentration >300 mg/dl may result in death. **Acute ingestion** of large quantities may result in **fall in blood pressure** whereas **chronic alcohol** consumption may contribute to **hypertension and dilated cardiomyopathy**. *Moderate consumption* of alcohol (18-20 g daily, roughly equivalent to 50-100 ml of whiskey) *decreases the risk of coronary artery disease* by increasing HDL and decreasing LDL cholesterol. Ethanol is **metabolized to acetaldehyde** (by alcohol dehydrogenase) and **finally to acetic acid** (by aldehyde dehydrogenase). **Disulfiram** (antabuse) and several drugs (*chlorpropamide, cefoperazone, moxalactam, cefamandole, metronidazole, griseofulvin* etc.) cause inhibition of aldehyde dehydrogenase resulting in accumulation of acetaldehyde. Acetaldehyde may lead to severe distressing symptoms known as *disulfiram like reaction*.

- **Chronic alcohol** consumption **induces microsomal enzymes**. More generation of toxic metabolite (NAPQI) of **acetaminophen** is responsible for increased risk of **hepatotoxicity** in alcoholics.
- Alcohol **increases** the chances of **hypoglycemia** in diabetic patients taking insulin and other oral hypoglycemic agents.

Treatment of Alcohol Dependence

Alcohol can produce physical and psychological dependence. In the treatment of alcohol

Disulfiram like reaction is caused by :

- *Chlorpropamide*
- *Cefoperazone*
- *Moxalactam*
- *Cefamandole*
- *Metronidazole*
- *Griseofulvin*

dependence, major aim is to prevent withdrawal symptoms first and to avoid relapse of addiction thereafter.

- **Benzodiazepines** (chlordiazepoxide and diazepam) are given to **prevent withdrawal**. These are long acting CNS depressants and can be withdrawn gradually.
- **Naltrexone** is an opioid antagonist that can be used to **reduce alcohol craving**.
- **Acamprosate** is an **NMDA antagonist** that can be used for **maintenance therapy of alcohol abstinence**.
- **Disulfiram** can be used in psychologically dependent persons who are motivated to quit alcohol. It is **contraindicated in physically dependent** individuals. Disulfiram produces severe distressing symptoms (like flushing, headache, vomiting, visual disturbances and mental confusion) after intake of alcohol. These symptoms are due to accumulation of acetaldehyde. Due to these symptoms, individual's resolution to quit alcohol is strengthened.
- **Topiramate and ondansetron** can also *decrease alcohol craving*.

Naltrexone is an opioid antagonist that can be used to reduce alcohol craving.

M

Drugs	decreasing	alcohol craving
None	–	Naltrexone
Of	–	Ondansetron
The	–	Topiramate
Above	–	Acamprosate

METHYL ALCOHOL (METHANOL)

It is metabolized to formaldehyde (by alcohol dehydrogenase) and finally to formic acid (by aldehyde dehydrogenase). Accumulation of **formic acid** may **result in lactic acidosis (high anion gap metabolic acidosis), blindness and death**. **Specific toxicity of formic acid is retinal damage** leading to blindness. Methanol poisoning can be treated by supportive measures, gastric lavage and sodium *bicarbonate* (to treat acidosis). **Ethanol** is useful because it **competitively inhibits the conversion of methanol to formic acid**. **Fomepizole** can also be used in methanol poisoning because it is a **specific inhibitor of alcohol dehydrogenase**. **Folic acid or folinic acid** can also be used because folate dependent systems are responsible for conversion of formic acid to CO₂.

ETHYLENE GLYCOL

It is used as a solvent and as an **anti-freeze** in industry. It is metabolized to glycolaldehyde and glycolic acid. At toxic levels, it can cause renal tubular acidosis with **excretion of oxalate crystals in the urine**. **Fomepizole is the drug of choice** for the treatment of ethylene glycol poisoning.

OPIOIDS

These are the substances obtained from the crude extract of *Papaver somniferum* (poppy plant). Morphine is the prototype opioid and acts by agonistic activity on μ , κ and δ receptors.

ACTIONS MEDIATED BY OPIOID RECEPTORS

μ	κ	δ
Sedation	Dysphoria (Psychomimetic effects)	Spinal Analgesia
Analgesia	Constipation	Modulation of hormone and
Constipation	Analgesia	NT release
Respiratory depression		
truncal Rigidity		
eUphoria		
Miosis		

Certain endogenous peptides (endorphins, dynorphins and enkephalins) act on these opioid receptors to produce analgesic effects. Recently a **new endogenous peptide, nociceptin** is isolated that acts on nociceptin/orphanin FQ (N/OFQ) or orphanin like receptors (ORL₁)

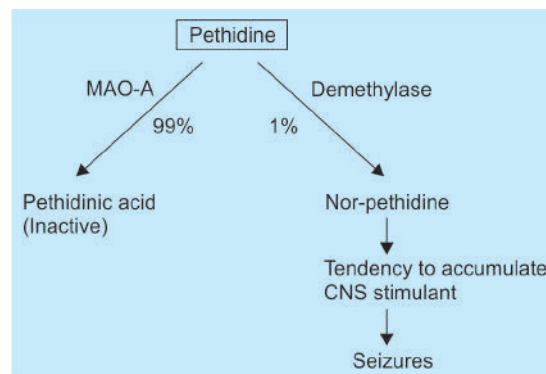
Endogenous peptide	Major action on receptors
Endorphin	μ
Dynorphin	κ
Enkephalin	δ
Nociceptin	N/OFQ

PHARMACOKINETICS



Pethidine can result in seizures if used for prolonged periods, in patients with renal failure or those taking MAO inhibitors (due to accumulation of norpethidine).

- **Sufentanil** is the **most potent** whereas meperidine (**pethidine**) and **propoxyphene** are the **least potent** opioids.
- Morphine is metabolized mainly to morphine-3-glucuronide (**M3G**) that has **neuroexcitatory** properties. Approximately 10% of morphine is metabolized to active product M6G. **Renal failure** can lead to **accumulation** of these metabolites and can result in **seizures** (due to M3G) or prolonged opioid action (due to M6G).
- **Pethidine** is metabolized mainly to meperidinic acid by MAO and very little is demethylated to **norpethidine**. Latter has **seizure inducing and cumulative properties**. Pethidine can result in **seizures** if used for prolonged periods, in patients with **renal failure** or those taking **MAO inhibitors** (due to accumulation of norpethidine).



ACTIONS OF PURE OPIOIDS

Pure agonists include *morphine, methadone, pethidine, levorphanol, codeine, hydrocodone, oxycodone and propoxyphene*. Actions of these drugs are:

1. CNS Actions

- Morphine produces spinal and supraspinal analgesia by acting on μ , κ and δ receptors.
- μ receptor opioids have **dependence** producing actions due to euphoric action. κ receptors mediate **psychomimetic** effects (dysphoria). Tolerance develops to all actions of opioids except 3C (Constipation, convulsions and constriction of pupil)
- Opioids produce **marked sedation** but chances of sedation are less with pethidine and fentanyl.
- Opioids can produce **respiratory depression and cough suppression**.
- Miosis can occur with morphine use and **pin point pupil** is a valuable sign in diagnosis of opioid poisoning.
- Highly lipid soluble drugs like **fentanyl, alfentanil and sufentanil** can result in **truncal rigidity** on rapid i.v. infusion.
- By stimulating CTZ, opioids can result in **nausea and vomiting**.

2. Peripheral Effects

- Opioids have no direct effect on heart except **pethidine and pentazocine** (that



Fentanyl is responsible for post operative muscle rigidity whereas succinylcholine causes post operative muscle pain and fasciculations.

increase heart rate). Blood pressure may decrease due to depression of vasomotor system and release of histamine.

- Constipation can result due to decreased motility and increased tone of GIT. Alvimopan is a peripheral opioid antagonist developed for **paralytic ileus**.
- Opioids **increase intrabiliary pressure** by constricting biliary smooth muscle. (C/I in biliary colic).
- These may **aggravate bronchoconstriction** in asthmatics by releasing histamine. (C/I in asthmatics).
- **Spinal or epidural** administration of opioids may result in **intense pruritus** over lips and torso (due to histamine release).

ACTIONS OF MIXED AGONISTS-ANTAGONISTS

- **Buprenorphine** is partial agonist at μ receptor with κ and δ antagonistic property. It is useful as an analgesic and as an **alternative to methadone** for the management of opioid withdrawal.
- **Nalbuphine, pentazocine and dezocine** are κ agonists and μ receptor antagonists. These drugs can produce **psychomimetic effects** with hallucinations, nightmares and anxiety.
- **Butorphanol** is a predominant κ agonist that produces **equivalent analgesia but more sedation than morphine**.

Nalbuphine, pentazocine and dezocine are κ agonists and μ receptor antagonists. These drugs can produce psychomimetic effects with hallucinations, nightmares and anxiety.

CLINICAL USES

- These are used as **analgesic** agents. Visceral, dull and constant pain is relieved more effectively than inflammatory pain. Opioids are however **contraindicated in biliary colic**.
- Morphine (i.v.) is useful in **myocardial infarction** as well as in **acute pulmonary edema**.
- **Codeine, pholcodeine, dextromethorphan and noscapine** are effective **cough suppressants**. *Dextromethorphan is devoid of constipating action* unlike other drugs in this group.
- **Loperamide and diphenoxylate** can be used for the treatment of non-infective diarrhea.
- Morphine is useful as a pre-anaesthetic medication whereas highly lipid soluble drugs (like **fentanyl, alfentanil, sufentanil** etc) are used as adjuncts to other anaesthetic agents.
- **Pethidine** is used to *reduce shivering* after anaesthesia [by its action on α_2 receptor]

Pethidine is used to reduce shivering after anaesthesia [by its action on α_2 receptor]

ROUTES OF ADMINISTRATION

- **Morphine** can be administered by **oral, rectal, i.v., i.m., intrathecal or epidural routes**.
- **Fentanyl** can be applied as **transdermal patch** or can be administered by **buccal transmucosal** route.
- **Butorphanol** is the only opioid available in **nasal** formulation.

ADVERSE EFFECTS AND TOXICITY

- **Respiratory depression, nausea, vomiting, constipation, urinary retention, itching and dysphoria** are important adverse effects of opioids.
- **Tolerance** develops to most of the actions of opioids **except miosis, constipation and convulsions**.
- Opioids are **highly addictive** substances and can lead to development of psychological as well as physical dependence. Sudden discontinuation of these drugs in a dependent subject may lead to **withdrawal syndrome** characterized

by **rhinorrhoea**, lacrimation, **yawning**, chills, mydriasis, vomiting, diarrhea and anxiety. Most of these symptoms are opposite to the normal actions of opioids.

CONTRAINDICATIONS AND PRECAUTIONS

- **Morphine** is absolutely contraindicated in **head injury** because it increases intracranial tension by causing retention of CO_2 (due to respiratory depression). It also interferes with the assessment of neurological function by masking the important pupillary signs (causes miosis).
- These drugs should be used cautiously in patients with pulmonary, hepatic or renal dysfunction.
- Use of opioids in infants and elderly also require caution.
- Patients of hypothyroidism may show exaggerated response to opioids.
- Prolonged use of opioids in pregnancy may lead to in-utero physical dependence of fetus and severe withdrawal symptoms may be precipitated after birth.

Morphine is absolutely contraindicated in head injury because it increases intracranial tension by causing retention of CO_2 (due to respiratory depression). It also interferes with the assessment of neurological function by masking the important pupillary signs (causes miosis).

IMPORTANT POINTS ABOUT SPECIFIC AGENTS

- Morphine, hydromorphone and oxycodone are strong opioid agonists useful as analgesics.
- Heroin (diacetylmorphine) is a potent and fast acting opioid but carries high risk of abuse potential.
- **Methadone** is a long acting opioid analgesic that can be administered by oral, i.v., s.c. and rectal routes. Apart from potent agonistic actions at μ receptors, it **also blocks NMDA** receptors and reuptake of monoamines. These properties explain its ability to **relieve neuropathic and cancer pain** that are not controlled with morphine. Due to its long $t_{1/2}$, development of dependence and tolerance is very slow, making it **useful for the treatment of opioid abuse**. It is also useful for opioid rotation therapy.
- **Pethidine and pentazocine** possess anticholinergic activity (can result in tachycardia). These drugs are therefore **C/I in MI**. Because of anticholinergic properties, these are **relatively safer in biliary colic** as compared to other agents. Accumulation of active metabolite of pethidine (**norpethidine**) can produce seizures.
- Levorphanol is similar to morphine in its actions.
- **Propoxyphene** is a *least potent and least efficacious* analgesic agent.
- **Diphenoxylate** and its active metabolite **difenoxin**, as well as **loperamide** are useful for diarrhea.
- **Nalbuphine** exhibits ceiling effect to its respiratory depressant action.
- **Buprenorphine** dissociates slowly from μ receptors and is thus **resistant to naloxone reversal**.
- **Butorphanol, pentazocine and dezocine** possess psychomimetic effects due to κ agonistic activity.
- **Ziconotide** is approved for intrathecal analgesia. It acts by blocking voltage-gated N type Ca^{2+} channels.
- **Tramadol** is a weak μ receptor agonist. It also inhibits reuptake of **NA and 5-HT**. These effects are responsible for its **analgesic action**, which can be **abolished by 5-HT₃ antagonists** like ondansetron. **At high doses**, it can lead to **seizures**.
- **Tapentadol** is a new analgesic drug with μ -receptor agonistic action and NA reuptake inhibiting action.

Nalbuphine exhibits ceiling effect to its respiratory depressant action.

Uses of opioid antagonists

Naloxone

- Acute opioid poisoning
- Neonatal resuscitation
- With opioids (oral)

Naltrexone

- Maintenance drug is opioid poisoning
- To prevent relapse in opioid de-addiction
- To decrease craving in alcoholics.

Opioid Antagonists

Naloxone, naltrexone and **nalmefene** are potent μ receptor antagonists with significant blocking action at κ and δ receptors also. **Alvimopan** and **methylnaltrexone** are peripheral opioid antagonists.

- **Naloxone** is given parenterally (**ineffective orally**) and is a **very short acting** drug.
- **Nalmefene** is also given **parenterally** but has a **longer half life**.
- **Naltrexone** is **long acting orally** effective opioid antagonist.

Actions

These have no action in the absence of agonists but promptly **reverses the opioid effects** when administered i.v. They **can precipitate withdrawal symptoms in opioid dependent** subjects

Uses

- **Naloxone** is the **drug of choice for acute opioid poisoning** but it has to be repeated frequently.
- **Naltrexone** is used as a **maintenance drug for opioid poisoning**. It is also used to **prevent relapse after opioid de-addiction**. It is also used to **decrease craving** in chronic alcoholics.
- **Naltrexone plus bupropion** has recently been approved for **treatment of obesity**
- **Naloxone** is also used in **neonatal resuscitation** to reverse the effects of opioids (if used during labour). However, it should **not be used** for this purpose **if mother is dependent** on opioids. (*Baby is also dependent in utero and naloxone can precipitate withdrawal*).
- Naloxone is being added to opioids meant for oral use to minimize their addictive potential. If the patient takes the combination orally, only opioid is absorbed not naloxone. Thus, it will produce the desired action. However, if the person takes it by i.v. route for addiction, naloxone also reaches the blood and stops euphoria.
- **Methylnaltrexone** and **alvimopan** are peripheral opioid antagonists indicated for **opioid-induced constipation**. **Naloxegol** is a new drug recently approved for same indication

Opioid De-addiction

Chronic intake of opioids can result in physical and psychological dependence. If suddenly stopped, the person may develop severe withdrawal symptoms, which may be life threatening. For de-addiction of opioids (or any addictive drug), first aim is to stop the further use of the drug by the patient followed by maintenance of de-addiction (i.e., to prevent relapse).

- If addiction is of short duration and with small doses of addictive drug, sudden stoppage of drug therapy can be attempted and the *mild withdrawal symptoms can be treated with β -blockers or clonidine (or lofexidine)*.
- If addiction is of long duration or with large dose of opioids, sudden withdrawal of the offending drug may be dangerous (due to severe withdrawal symptoms). In such patients, the addictive drug is replaced by equivalent dose of **methadone (known as methadone maintenance)**. It *prevents withdrawal symptoms* by stimulating opioid receptors but is much less addictive. The dose of methadone is then gradually decreased and finally stopped.
- To prevent relapse after de-addiction, naltrexone is used. Naltrexone prevents euphoric action by blocking μ receptors. If the person again takes opioids (after de-addiction), there will be no euphoria and the person's resolution to quit addiction will be strengthened.

Note:

- β -blockers and clonidine treat withdrawal symptoms.
- Methadone prevents withdrawal symptoms.
- Naltrexone is used to prevent relapse.
- Methadone is used as maintenance therapy in opioid dependence whereas naltrexone is used as maintenance therapy in opioid poisoning.

DRUG OF CHOICE	
Condition	Drug of choice
• Alcohol dependence	
– Withdrawal symptoms (including seizures)	Benzodiazepines like chlordiazepoxide or diazepam
– Maintenance therapy	Chlordiazepoxide
– To prevent craving	Naltrexone
• Methanol poisoning	Fomepizole
• Ethylene glycol poisoning	Fomepizole
• Anxiety disorders	
– Performance anxiety	Propanolol
– Generalized anxiety disorder (GAD)	
- Acute attacks	Benzodiazepines
- Sustained treatment	Antidepressants (venlafaxine/duloxetine)
– Panic disorder	
- Acute panic attacks	Benzodiazepines
- Sustained treatment	SSRI (Sertraline)
• Insomnia	Zolpidem
• Benzodiazepine poisoning	Flumazenil
• Epilepsy/seizure disorders	
– Grand mal (GTCS)	Valproate
– Petit mal (Absence)	Valproate
– Focal	Carbamazepine/Oxcarbazepine
– Myoclonic	Valproate
– Atonic	Valproate
– Infantile spasms	
- Without tuberous sclerosis (TS)	ACTH
- With TS	Vigabatrin
– Febrile seizures	Diazepam
– Status epilepticus	Lorazepam
– Eclamptic seizures	Magnesium sulphate
– Epilepsy in pregnancy	Lamotrigine/Topiramate/levetiracetam
– Lennox-Gastaut syndrome	Valproate/Rufinamide/Clonazepam
• Neuropathic pain	
– Trigeminal neuralgia	Carbamazepine
– Post-herpetic neuralgia	Pregabalin or gabapentin
– Diabetic neuropathic pain	Pregabalin or gabapentin
• Parkinsonism	
– Early	Pramipexole/Ropinirole
– Late	Pramipexole/Ropinirole
– Drug induced	Anticholinergics (Benzhexol)
• Levo-dopa induced	
– Vomiting	Domperidone
– Psychosis	Atypical antipsychotics (olanzapine)

Contd...

Contd...

• Schizophrenia	Olanzapine
– In non-compliant patients	Risperidone LAI (long acting injection)
– Refractory	Clozapine
• Manic disorder	
– Acute mania	Benzodiazepines/Antipsychotics (olanzapine) + lithium
– Prophylaxis of mania	Lithium
– Bipolar disorder	Lithium
– Rapid cyclers	Valproate
• Gille de la Tourette syndrome	• Haloperidol (FDA-approved) • Clonidine/Guanafacine (off label)
• Relapsing remitting multiple sclerosis	Beta-interferon
• Huntington's disease	Tetrabenazine
• Wilson disease	Zinc
• Depression	SSRI
– Mild to moderate	SSRI (Fluoxetine)
– Severe	SNRI (Venlafaxine)
• Neurotic disorders	
– Obsessive compulsive disorder	SSRI (Fluoxetine)
– Post-traumatic stress disorder	SSRI (Sertraline)
– Bulimia	SSRI (Fluoxetine)
– Phobia	SSRI (Sertraline)
– Impulse-control disorders	SSRI (Fluoxetine)
• Attention deficit hyperkinetic disorder	Methylphenidate
• Nocturnal enuresis	Desmopressin
• Severe (cancer) pain	Opioids (morphine)
• Neurolept analgesia	Droperidol + fentanyl
• Neurolept anaesthesia	Droperidol + Fentanyl + N ₂ O
• Opioid poisoning	Naloxone
– Acute	Naloxone
– Maintenance	Naltrexone
• Opioid de-addiction	
– Maintenance therapy	Methadone
– To prevent relapse	Naltrexone
– To treat withdrawal symptoms	Beta blockers/clonidine
• Alzheimer's dementia	Donepezil
• Amyotrophic lateral sclerosis	Riluzole
• Extrapyramidal symptoms	
– Acute muscular dystonias	Benzhexol
– Parkinsonism	Benzhexol
– Akathisia	Propanolol
– Neurolept malignant syndrome	Dantrolene
– Tardive dyskinesia	No treatment (benzodiazepines may help)
• Restless leg syndrome	Pramipexole

MULTIPLE CHOICE QUESTIONS

SEDATIVE HYPNOTICS

- Duration of action of flumazenil is:** (AIIMS Nov 2013)
 - 5 minute
 - 10 minute
 - 20 minute
 - 30 minute
- All are true about ramelteon except:**
 - Agonist at MT_1 and MT_2 receptors
 - Is a substrate of CYP1A2 (AIIMS Nov 2010)
 - Has high addiction liability
 - Approved for treatment of insomnia
- All of the following statements about flumazenil are true except:** (AIIMS Nov 2009)
 - It is a specific antagonist of benzodiazepines
 - It may be used to treat barbiturate poisoning
 - It is given intravenously
 - It acts on same site on GABA channel where benzodiazepines bind
- Which of the following compounds acts as a benzodiazepine antagonist?** (AIIMS May 2008)
 - Flumazenil (AI 2008)
 - Naloxone (AIIMS Nov 2006)
 - Furazolidone (RJ 2009, MP 2009)
 - Naltrexone (Karnataka 2008, 2006, 2003)
- The effect of thiopentone on the CNS is quickly terminated because of:** (DPG 2009)
 - Rapid metabolism in the CNS
 - Quick first-pass elimination
 - Redistribution
 - Rapid metabolism in systemic circulation
- All of the following benzodiazepines can be used in elderly and those with liver disease EXCEPT:** (AI 2006)
 - Lorazepam
 - Oxazepam
 - Triazolam
 - Diazepam
- Inverse agonist of benzodiazepine receptor is:** (AI 2005)
 - Phenobarbitone
 - Flumazenil
 - Beta carboline
 - Gabapentin
- Which of the following agents binds to GABA receptor chloride channel complex?** (AI 2004)
 - Ethanol
 - Alphaxolone
 - Zolpidem
 - Buspirone
- In which of the following disorders, administration of barbiturates is contraindicated?** (AI 2002)
 - Anxiety disorders
 - Acute intermittent porphyria
 - Kernicterus
 - Refractory status epilepticus
- Which of the following agents do not act via $GABA_A$ - Cl^- channel complex receptors?** (AIIMS Nov., 2007)
 - Zopiclone
 - Benzodiazepines
 - Thiopentone
 - Promethazine
- Drugs that can be used safely in porphyria are:** (PGI Dec. 2002)
 - Phenobarbitone
 - Ketamine
 - Sodium valproate
 - Midazolam
 - Pethidine
- Which of the following statements are true regarding benzodiazepines?** (PGI Dec. 2001)
 - It acts as GABA agonist
 - Diazepam is a short acting benzodiazepine
 - Diazepam causes lesser respiratory depression than midazolam
 - Nitrazepam is metabolized in liver
 - Diazepam has higher abuse potential than midazolam
- Which of the following drugs is an antagonist to diazepam?** (PGI June, 2001)
 - Phenargan
 - Flumazenil
 - Domperidone
 - Bromocriptine
 - Naloxone
- In strychnine poisoning, convulsions occur because of the antagonist effects at receptors for:**
 - Aspartate
 - Glycine
 - GABA
 - Glutamate
- Which of the following statements regarding barbiturates is accurate?**
 - Benzodiazepines exhibit a steeper dose response relationship as compared to barbiturates
 - Barbiturates may increase the half lives of drugs metabolized by the liver

- (c) Alkalization of the urine will accelerate the elimination of phenobarbital
- (d) Respiratory depression caused by barbiturate over-dosage can be reversed by flumazenil
- 16. Which of the following statements best describes the mechanism of action of benzodiazepines?**
- (a) Benzodiazepines activate GABA_B receptors in the spinal cord
- (b) Benzodiazepines block glutamate receptors in neuronal pathways in the brain
- (c) They increase the frequency of opening of chloride ion channels that are coupled to GABA_A receptors
- (d) They are direct acting GABA receptor agonists in the CNS
- 17. Flumazenil can reverse the respiratory depression caused by which of the following?**
- (a) Fentanyl
- (b) Ketamine
- (c) Midazolam
- (d) Propofol
- 18. Increased tendency to fall asleep at night without causing central nervous system depression is a property exhibited by:**
- (a) Pyridoxine
- (b) Diphenhydramine
- (c) Melatonin
- (d) Ethanol
- 19. Which of the following hypnotic drugs facilitates the inhibitory actions of GABA but lacks anticonvulsant or muscle relaxing properties and has minimal effect on sleep architecture?**
- (a) Buspirone
- (b) Diazepam
- (c) Phenobarbital
- (d) Zaleplon
- 20. A very potent and short acting benzodiazepine was given to a patient Kallu for the purpose of causing hypnosis but the drug caused psychiatric disturbances in him. Which of the following can be the hypnotic used?**
- (a) Flurazepam
- (b) Nitrazepam
- (c) Temazepam
- (d) Triazolam
- 21. A 40 years old patient with liver dysfunction is scheduled for a surgical procedure. Lorazepam can be used for pre-anaesthetic medication in this patient without concern for excessive CNS depression because the drug is:**
- (a) Selective anxiolytic like buspirone
- (b) Conjugated directly
- (c) Reversible by administration of naloxone
- (d) Forming several active metabolites
- 22. Which of the following drugs is contra-indicated in acute intermittent porphyria?** (DELHI-PG-2007)
(MPPG-2001)
- (a) Thiopentone
- (b) Midazolam
- (c) Propofol
- (d) Etomidate
- 23. Action of flumazenil on benzodiazepine receptor is:** (DPG 2003)
- (a) Agonist
- (b) Partial agonist
- (c) Inverse agonist
- (d) Antagonist
- 24. Both barbiturates and salicylates are maximally absorbed in stomach because:** (DPG 2002)
- (a) They are weakly basic and so highly ionised in stomach
- (b) They are highly basic and so less ionized in stomach
- (c) They are weakly acidic and do not ionise in stomach
- (d) They are highly acidic and are highly ionised in stomach
- 25. Which of the following drug is not metabolized by liver:** (MPPG 2003)
- (a) Flunitrazepam
- (b) Diazepam
- (c) Oxazepam
- (d) Nitrazepam
- 26. Shortest acting benzodiazepine is:** (AP 2008)
- (a) Midazolam
- (b) Alprazolam
- (c) Lorazepam
- (d) Diazepam

NEURODEGENERATIVE DISORDERS

- 27. Drug of choice for relapsing remitting multiple sclerosis is:** (AIIMS Nov-2011)
- (a) α IFN
- (b) β IFN
- (c) γ IFN
- (d) Natalizumab
- 28. Which is the only drug effective in improving EDSS in multiple sclerosis?** (AIIMS Nov-2011)
- (a) Methotrexate
- (b) Fingolimod
- (c) Glatiramer acetate
- (d) Natalizumab
- 29. Which of the following drug is not used in multiple sclerosis?** (AIIMS Nov-2011)
- (a) Interferon β 1b
- (b) Interferon β 1a
- (c) Glatiramer acetate
- (d) Mycophenolate mofetil
- 30. Which of the following drug is used as Transcranial patch for Parkinson's disease?** (AIIMS Nov-2011)
- (a) Levodopa
- (b) Rotigotine
- (c) Selegiline
- (d) Carbidopa

31. Which of the following if combined with rivastagmine, decreases its efficacy? (AI 2010)
- Selective serotonin reuptake inhibitors
 - Reversible inhibitor of MAO-A
 - Tricyclic antidepressants
 - Atypical antidepressants
32. All of the following statements about trientine use in Wilson's disease are true except:
- It is more potent than penicillamine.
 - It is used as an alternative to penicillamine in non-tolerant patients (AI 2010)
 - It should not be administered within 2 hours of iron supplementation.
 - It can cause iron deficiency anemia which is reversible by oral iron supplements
33. Which of the following agents enhances the bioavailability of levodopa in patients with Parkinson's disease: (DPG 2009)
- Amantadine
 - Ropinirole
 - Entacapone
 - Selegiline
34. All the following statements regarding levodopa are correct EXCEPT: (AI 2004)
- In Parkinsonism, phenothiazines reduce its efficacy
 - It is a prodrug
 - Pyridoxine reduces effect of levodopa in Parkinsonism
 - Domperidone blocks levodopa induced emesis and its therapeutic potential.
35. A patient of Parkinsonism is managed with levodopa. If Vitamin B complex is administered concurrently to the patient: (AI 2000)
- The action of levodopa in brain will be potentiated
 - Decarboxylation of l-dopa in brain will be decreased
 - Side effects will be ameliorated
 - Decreased efficacy will result
36. Ropinirole is most useful for the treatment of: (AIIMS Nov, 2004)
- Parkinson's disease
 - Wilson's disease
 - Hoffmann syndrome
 - Carpal tunnel syndrome
37. Which of the following statements is FALSE regarding drugs used in the treatment of Parkinsonism?
- Amantadine causes ankle edema (AIIMS Nov, 2002)
 - Levodopa is effective in reducing tremors
 - Amantadine is more effective than levodopa
 - Anti-muscarinic agents are effective in drug induced Parkinsonism
38. Drugs used for treatment of Parkinson's disease include: (PGI June, 2003)
- Levodopa
 - Mazindol
 - Bromocriptine
 - Acyclovir
 - Benserazide
39. Drugs causing Parkinsonism include: (PGI Dec. 2001)
- Bromocriptine
 - Phenothiazine
 - Haloperidol
 - Amantadine
 - Carbidopa
40. Entacapone may be useful in patients being treated with levodopa-carbidopa combination because it:
- Activates COMT
 - Decreases formation of 3-OMD
 - Inhibits monoamine oxidase type B
 - Inhibits dopamine uptake
41. Which of the following adverse effects of levodopa is not minimized even after combining it with carbidopa?
- Involuntary movements
 - Nausea and vomiting
 - Cardiac arrhythmia
 - 'On-off' effect
42. Which of the following antiparkinsonian drugs directly activates dopaminergic D₂ receptors in the striatum?
- Pramipexole
 - Entacapone
 - Benserazide
 - Selegiline
43. Which of the following statements about donepezil is CORRECT?
- It is a topical carbonic anhydrase inhibitor used in glaucoma
 - It is a catechol-o-methyl transferase inhibitor used as an adjuvant in Parkinson's disease
 - It is a cerebroselective anticholinesterase that affords symptomatic improvement in Alzheimer's disease
 - It is a synthetic cannabinoid with antiemetic property
44. Which statement is CORRECT about pramipexole?
- Activates brain dopamine receptors
 - Commonly a first line therapy for Parkinson's disease
 - Not an ergot derivative
 - All of the above
45. Entacapone is an anti-Parkinsonism drug. It acts by:
- Agonism at dopamine receptors
 - Antagonism at dopamine receptors
 - Monoamine oxidase inhibition
 - Catechol-o-methyl transferase inhibition.
46. A compound X decreases the functional activities of several CNS neurotransmitters including dopamine, adrenaline and serotonin. At high doses it may cause Parkinsonism like extrapyramidal system dysfunction. Which of the following can be X?
- Baclofen
 - Diazepam

- (c) Ketamine
(d) Reserpine
47. A patient of Parkinsonism, Mr. Ghai noticed that the therapeutic effect of levodopa decreased when he was given another drug by his physician but no interaction was seen when he switched over to levodopa-carbidopa combination. The possible drug prescribed by his physician can be:
(a) Metoclopramide
(b) Vitamin B complex
(c) Chlorpromazine
(d) Isoniazid
48. Which of the following drug should not be given along with levodopa: (DELHI-PG-2008)
(a) Carbidopa
(b) MAO inhibitors
(c) Vitamin B complex
(d) Benserazide
49. Drug of choice in drug induced parkinsonism is: (UP 2008, Kolkata 2005, DPG 2005, RJ 2003)
(a) Levodopa
(b) Benhexol
(c) Amantidine
(d) Carbidopa
50. Which of the following abolishes the therapeutic effect of levodopa: (MPPG 2003)
(a) Thiamine
(b) Carbidopa
(c) Pyridoxine
(d) Benzerazide
51. Which one of the following drug is used in Alzheimer's disease: (TN 2004, MH 2003)
(a) Tacrine
(b) Pemoline
(c) Doxapram
(d) Methylphenidate
52. Which drug is not used in Alzheimer Disease?
(a) Memantine (RJ 2009)
(b) Galantamine (MP 2009)
(c) Ropinirole
(d) Donepezil
53. In treatment of Parkinsonism, L-Dopa is combined with carbidopa mainly: (MH 2000)
(a) To decrease the treatment duration
(b) To decrease central side effects of L-Dopa
(c) To decrease effectiveness of L-Dopa
(d) To increase crossing of L-Dopa through BBB
54. Which of the following is a 'nootropic' drug? (MH 2005)
(a) Rivastigmine
(b) Tacrine
(c) Amantidine
(d) Piracetam
55. Mechanism of action of donepezil is: (MH 2006)
(a) Centrally acting reversible anticholinesterase
(b) Centrally acting irreversible anticholinesterase
(c) Irreversible cholinergic action
(d) Reversible anticholinesterase
56. Anti-Parkinsonism drug that is a selective COMT inhibitor: (MH 2008, MH 2007)
(a) Entacapone
(b) Ropinirole
(c) Pergolide
(d) Pramipexole
57. True statement about drugs used in Parkinsonism is: (Bihar 2005)
(a) Amantidine is a cholinergic drug
(b) Vitamin B₆ enhances the L-Dopa action
(c) COMT inhibitors prolong the action of L-dopa
(d) None
58. A 72-year-old patient with Parkinsonism presents with swollen feet. They are red, tender and very painful. You could clear up these symptoms within a few days if you tell the patient to stop taking: (Karnataka 2008)
(a) Amantidine
(b) Benztropine
(c) Bromocriptine
(d) Levodopa
59. The drug found to be beneficial in amyotrophic lateral sclerosis is: (Karnataka 2004)
(a) Riluzole
(b) Methylprednisolone
(c) Hydroxyurea
(d) None of the above

■ ANTIEPILEPTIC DRUGS

60. All of the following adverse effects are associated with carbamazepine except: (AIIMS Nov 2013)
(a) Teratogenicity
(b) Neurotoxicity
(c) Decrease in antidiuretic hormone
(d) Hypersensitivity
61. Which is a treatment of juvenile myoclonic epilepsy in pregnancy? (AIIMS Nov 2013)
(a) Levetiracetam
(b) Carbamazepine
(c) Vigabatrin
(d) Phenytoin
62. Which of the following statements about anti-epileptics is false? (AIIMS Nov 2013)
(a) Phenytoin and carbamazepine act by prolonging the inactivated state of Na⁺ channels

- (b) Carbamazepine can be used in trigeminal neuralgias
- (c) Diazepam is an anticonvulsant drug
- (d) Lamotrigine mainly acts by causing GABA mediated Cl^- channel opening

63. A 65 years old male presented to a hospital with focal seizures. His renal function was normal. Which of the following is the drug of choice for this patient?

- (a) Valproate (AIIMS Nov-2011)
- (b) Pregbalin
- (c) Levetiracetam
- (d) Oxcarbazepine

64. Which among the following is an early sign of magnesium toxicity? (AI 2011)

- (a) Depression of deep tendon reflexes
- (b) Respiratory depression
- (c) Cardiac arrest
- (d) Decreased urine output

65. A pregnant woman with primary generalized tonic-clonic seizures, well controlled on Phenobarbital, stops taking her antiepileptic medication 4 months into her pregnancy. Which of the following best describes her decision? (DPG 2011)

- (a) Her decision is wrong, as the risk of teratogenicity was the highest in the first trimester
- (b) Her decision is wrong because antiepileptic drugs do not increase the risk of fetal malformations
- (c) Her decision is correct as the risk of seizures is reduced in pregnancy
- (d) Her decision is wrong but her medication needs to be changed and a newer antiepileptic drug added

66. All of the following are used for myoclonic seizures except: (AI 2010)

- (a) Sodium valproate
- (b) Zonisamide
- (c) Carbamazepine
- (d) Topiramate

67. Fetal hydantoin syndrome is seen if following drug is used in pregnancy? (AI 2010)

- (a) Phenytoin
- (b) Alcohol
- (c) Ethosuximide
- (d) Phenobarbitone

68. All of the following statements about phenytoin are true except: (AI 2010)

- (a) It follows saturation kinetics
- (b) Anti-seizure activity closely resembles plasma concentration
- (c) Does not depress CNS
- (d) Cerebellar degeneration occurs on long-term administration

69. Ethosuximide can be used for the treatment of:

- (a) Generalized tonic clonic seizures
- (b) Absence seizures (AI 2010)
- (c) Complex seizures
- (d) Myoclonic seizures

70. Which of the following statement about phenytoin is true? (AIIMS Nov 2009)

- (a) It follows zero order kinetics
- (b) It is not teratogenic
- (c) It is excreted unchanged in urine
- (d) It does not induce microsomal enzymes

71. The drug of choice for prevention of seizures in a patient with severe preeclampsia is: (DPG 2009)

- (a) Phenytoin
- (b) Magnesium sulphate
- (c) Diazepam
- (d) Nifedipine

72. All of the following are adverse effects of sodium valproate EXCEPT: (AI 2009)

- (a) Weight gain
- (b) Alopecia
- (c) Liver damage
- (d) Osteomalacia

73. Which statement is TRUE about carbamazepine?

- (a) Used in trigeminal neuralgia (AIIMS May 2008)
- (b) Carbamazepine is an enzyme inhibitor
- (c) Can cause megaloblastic anemia
- (d) It is the drug of choice for status epilepticus

74. First drug to be used in absence seizures is:

- (a) Phenytoin (AIIMS May 2008)
- (b) Benzodiazepines
- (c) Valproate
- (d) Carbamazepine

75. Which of the following drugs is not an anticonvulsant?

- (a) Phenytoin (AI 2007)
- (b) Flunarizine
- (c) Topiramate
- (d) Phenobarbitone

76. Which antiepileptic drug does not act via inhibition of sodium channels? (AI 2007)

- (a) Vigabatrin
- (b) Carbamazepine
- (c) Lamotrigine
- (d) Phenytoin

77. Granulocytopenia, gingival hyperplasia and facial hirsutism are all possible side effects of one of the following anticonvulsant drugs? (AI 2003)

- (a) Phenytoin
- (b) Valproate
- (c) Carbamazepine
- (d) Phenobarbitone

78. A patient on phenytoin therapy develops depression, for which he was prescribed tricyclic anti-depressants. He now complains of lassitude and his Hb reading is 8 gm/dl, the next step in the management of this patient is: (AI 2001)

- (a) Chest X ray
- (b) MCV should be estimated
- (c) GGT should be estimated
- (d) None of the above

79. Drug of choice for myoclonic epilepsy in pregnancy is: (AI 2000)
- Carbamazepine
 - Sodium valproate
 - Phenobarbitone
 - Phenytoin
80. Regarding Phenytoin, false is: (AIIMS Nov., 2007)
- Induces microsomal enzymes
 - At very low doses, zero order kinetics occurs
 - Higher the dose, higher is the half life
 - Highly protein bound
81. Prolonged use of one of the following anticonvulsant drugs can produce weight loss: (AIIMS May, 2006)
- Gabapentin
 - Oxcarbazepine
 - Topiramate
 - Valproic acid
82. Which of the following antiepileptic agents acts on the GABAergic system to decrease the uptake of GABA into neurons and glial cells? (AIIMS Nov, 2005) (RJ 2007)
- Vigabatrin
 - Progabide
 - Gabapentin
 - Tiagabine
83. A 30-year old epileptic female, Kamla on phenytoin therapy, developed weakness and fatigue. Blood examination revealed Hb = 4.6 gm. MCV = 102 fl and MCH = 40 pg/dl. What is the most probable diagnosis? (AIIMS Nov, 2003)
- Heart failure
 - Iron deficiency anemia
 - Phenytoin induced agranulocytosis
 - Megaloblastic anemia
84. A patient with recent-onset primary generalized epilepsy develops drug reaction and skin rash due to phenytoin sodium. The most appropriate course of action is: (AIIMS May, 2003)
- Shift to clonazepam
 - Restart phenytoin sodium after 2 weeks
 - Shift to sodium valproate
 - Shift to ethosuximide
85. Adverse effect of phenytoin include all of the following EXCEPT: (AIIMS Nov, 2002)
- Lymphadenopathy
 - Ataxia
 - Hypercalcemia
 - Hirsutism
86. On chronic treatment with a drug, a patient presents with gingival hyperplasia and facial hirsutism. The drug most likely to cause these side effects is: (AIIMS May, 2002)
- Phenytoin
 - Carbamazepine
 - Valproic acid
 - Phenobarbitone
87. Which of the following is correctly matched:
- Gabapentin – GABA transaminase inhibitor
 - Zonisamide – Ca^{2+} channel blocker
 - Carbamazepine – Na^{+} channel blocker
 - Lamotrigine – NMDA blocker (PGI Dec. 2007)
 - Tiagabine – Increases release of GABA
88. Which of the following are the features of phenytoin toxicity: (PGI June, 2007)
- Gum hypertrophy
 - Acne rosacea
 - Exacerbation of acne vulgaris
 - Loss of hair
 - Nystagmus
89. Mg^{++} can be administered in: (PGI June, 2006)
- Eclampsia
 - Cardiac arrhythmia
 - Seizure
 - Tetany
 - Asthma
90. Therapeutic level of phenytoin is: (PGI Dec. 2005)
- 0-9 mg/ml
 - 10-19 mg/ml
 - 20-29 mg/ml
 - 30-39 mg/ml
 - 40+ mg/ml
91. Drugs used in GTCS is/are: (PGI Dec 2005)
- Ethosuximide
 - Sodium-valproate
 - Lamotrigine
 - Propofol
92. Side effects of phenytoin are: (PGI Dec. 2004)
- Gum hypertrophy
 - Alopecia
 - Subungual exostosis
 - Onycholysis
 - Acne rosacea
93. Which of the following statements about vigabatrin is TRUE?
- Blocks neuronal reuptake of GABA
 - Drug of choice in absence seizures
 - Life threatening skin disorders may occur
 - Visual disturbances can occur
94. Phenytoin pharmacokinetics is highlighted by which of the following characteristics?
- High first pass metabolism
 - Nonsaturation kinetics of metabolism
 - Capacity limited metabolism saturating at higher therapeutic concentration range
 - Extrahepatic metabolism
95. High plasma drug concentration of phenytoin can cause which of the following adverse effects?
- Ataxia
 - Hirsutism

- (c) Gum hyperplasia
- (d) All of the above

96. The drug used in absence seizures and having a narrow spectrum of antiepileptic activity is:
- (a) Lamotrigine
 - (b) Ethosuximide
 - (c) Sodium valproate
 - (d) Primidone
97. The most common adverse effect particularly seen in young children because of the use of sodium valproate is:
- (a) Hepatitis
 - (b) Loss of hair
 - (c) Anorexia
 - (d) Tremor
98. A patient, Rama was diagnosed to be having febrile convulsions in the paediatric emergency. Which of the following can be used for the treatment of this patient?
- (a) Intramuscular phenobarbitone
 - (b) Intravenous phenytoin
 - (c) Rectal diazepam
 - (d) Oral sodium valproate
99. Regarding lamotrigine, which of the following is a TRUE statement?
- (a) It is a dopaminergic agonist used in Parkinsonism
 - (b) It acts by blocking NMDA type of glutamate receptors
 - (c) It is a broad spectrum antiepileptic drug
 - (d) It suppresses tonic-clonic seizures but worsens absence seizures
100. Status epilepticus is managed best with the use of which of the following drugs?
- (a) Intravenous diazepam
 - (b) Intravenous phenytoin sodium
 - (c) Intramuscular phenobarbitone
 - (d) Rectal diazepam
101. Antiepileptic drug implicated in causing toxic epidermal necrolysis is:
- (a) Felbamate
 - (b) Gabapentin
 - (c) Lamotrigine
 - (d) Vigabatrin
102. Raju, a 10 yr old boy is having difficulty in learning at school. He has short lapses of awareness with eyelid fluttering that occur every 5-10 minutes. EEG studies reveal brief 3 Hz spike and wave discharges appearing synchronously in all the leads. Which of the following drugs would be effective but has the disadvantage that it causes sedation and tolerance?
- (a) Diazepam
 - (b) Ethosuximide
 - (c) Clonazepam
 - (d) Valproic acid
103. A young male, Farhan suffers from a seizure disorder which is characterized by tonic rigidity of limbs followed in 20-30 sec by tremors progressing to massive jerking of the body. This clonic phase lasts for 1-3 min. The anti-seizure drug of choice for this patient is:
- (a) Clonazepam
 - (b) Ethosuximide
 - (c) Fosphenytoin
 - (d) Valproic acid
104. An antiepileptic drug 'A' can also be used for the treatment of post-herpetic neuralgia and pain due to diabetic neuropathy. Which of the following can be the agent 'A'?
- (a) Carbamazepine
 - (b) Gabapentin
 - (c) Lamotrigine
 - (d) Primidone
105. Which of the following will you like to give to a pregnant patient to decrease the risk of neural tube defects in the offspring, if your patient is receiving antiepileptic drugs?
- (a) Folic acid
 - (b) Vitamin A
 - (c) Vitamin E
 - (d) Pyridoxine
106. Carbamazepine in elderly causes: (DPG 2010)
- (a) Hypernatremia
 - (b) Hyponatremia
 - (c) Hyperkalemia
 - (d) Hypokalemia
107. Pseudolymphoma can result from long-term use of: (DPG 2010)
- (a) Phenytoin
 - (b) Carbamazepine
 - (c) Sodium valproate
 - (d) Phenobarbital
108. Management of typical febrile seizures include all the following except: (DPG 2010)
- (a) Tepid sponging
 - (b) Paracetamol and ibuprofen
 - (c) Intermittent diazepam
 - (d) Prophylactic phenobarbitone.
109. The drug of choice in treatment of infantile spasms is: (Karnataka 2009)
- (a) ACTH
 - (b) Phenobarbitone
 - (c) Carbamazepine
 - (d) Phenytoin
110. Which of the following is not a side effect of phenytoin? (DPG 2006)
- (a) Hypoglycemia
 - (b) Osteomalacia
 - (c) Gum hypertrophy
 - (d) Lymphadenopathy
111. Drug of choice for Trigeminal neuralgia is: (DPG 2005)
- (a) Carbamazepine
 - (b) Phenobarbitone

- (c) Phenytoin
(d) Valproic acid
112. Myoclonus in children is best treated by: (DPG 2005)
(a) Clonazepam
(b) Sodium Valproate
(c) Phenobarbitone
(d) Ethosuccimide
113. DOC for myoclonic seizure is: (DPG 2004 Jharkhand 2004)
(a) Phenobarbitone
(b) Ethosuximide
(c) Lamotrigine
(d) Valproic acid
114. All are the side effects of prolonged phenytoin therapy EXCEPT: (DPG 2002)
(a) Osteomalacia
(b) Gynaecomastia
(c) Megaloblastic anemia
(d) Gum hyperplasia
115. Antiepileptic drug that can cause folate deficiency anemia is: (DPG 1999)
(a) Valproate
(b) Phenytoin
(c) Phenobarbitone
(d) Carbamazepine
116. Which of the following antiepileptic drugs acts by affecting the levels of GABA? (DPG 1997)
(a) Sodium valproate
(b) Ethosuximide
(c) Phenytoin sodium
(d) Carbamazepine
117. Which one of the following drugs is used to treat status epilepticus? (MPPG 2007)
(a) Primidone
(b) Carbamazepine
(c) Diazepam
(d) Sodium valproate
118. The antiepileptic drug which does not produce enzyme induction is: (MPPG 2005)
(a) Phenobarbitone
(b) Sodium valproate
(c) Phenytoin sodium
(d) Carbamazepine
119. Osteomalacia is adverse effect of: (UP 2006)
(a) Primidone
(b) Phenytoin
(c) Carbamazepine
(d) Valproic acid
120. Among the following structures which one is not used in the treatment of epilepsy? (AP 1998) (TN 2000)
(a) Barbiturates
(b) Hydantoins
(c) Acetylurea
(d) Atropine
121. Gum hypertrophy is an adverse effect of the following drug when used at therapeutic levels: (TN 2003)
(a) Phenobarbitone
(b) Phenytoin
(c) Carbamazepine
(d) Sodium evaporate
122. Drug of choice in complex partial seizure is: (MH 2005, RJ 2004)
(a) Phenytoin
(b) Valproate
(c) Carbamazepine
(d) Phenobarbitone
123. Which drug should be avoided in pregnancy? (RJ 2004)
(a) Phenytoin
(b) Insulin
(c) Heparin
(d) All
124. Which of the following antiepileptic agent does not act via Na^+ channel modulation? (RJ 2008)
(a) Vigabatrin
(b) Phenytoin
(c) Valproate
(d) Lamotrigine
125. Side effects of phenytoin are all except: (MH 2002)
(a) Osteomalacia
(b) Maculopapular rash
(c) Sedation
(d) Megaloblastic anaemia
126. Antiepileptics used as analgesics are: (MH 2002)
(a) Carbamazepine and valproate
(b) Phenytoin and valproate
(c) Carbamazepine and phenytoin
(d) Diazepam and Chlorpromazine
127. A patient on anticonvulsant therapy took 20 tablets at a time following which he developed hyponatremia and BP of 160/100 mm of Hg. Which of the following anticonvulsant toxicity is most likely responsible for this? (MH 2007)
(a) Carbamazepine
(b) Phenytoin sodium
(c) Phenobarbital
(d) Sodium valproate
128. The side effect of phenytoin when its plasma concentration is above therapeutic level is: (Bihar 2003)
(a) Ataxia
(b) Gum hypertrophy
(c) Osteomalacia
(d) Hirsutism
129. Neural tube defect is an adverse effect of: (Bihar 2004)
(a) Valproate
(b) Phenytoin
(c) Diazoxide
(d) None

- 130. False about mechanism of action of anticonvulsants is:** (Bihar 2005)
 (a) Ethosuximide – K^+ channel opener
 (b) Phenytoin – Na^+ channel blocker
 (c) Diazepam – Facilitates GABA action
 (d) Gabapentin - Increase GABA release
- 131. Folate deficiency occurs due to:** (Jharkhand 2005)
 (a) Phenytoin
 (b) Phenobarbitone
 (c) Primidone
 (d) All
- 132. Drug of choice for absence seizures is:** (Karnataka 2006, Jharkhand 2006)
 (a) Valproate
 (b) Phenytoin
 (c) Diazepam
 (d) Ethosuximide
- 133. Sodium valproate is an:** (AP 2002)
 (a) Antiepileptic drug
 (b) Antihypertensive drug
 (c) Antituberculous drug
 (d) Antipsychotic drug
- 134. Weight gain is not seen with:** (AP 2003)
 (a) Chlorpromazine
 (b) Sodium valproate
 (c) Carbamazepine
 (d) Phentermine
- 135. Renal stones are seen as a complication by using the following drug:** (AP 2008)
 (a) Tiagabine
 (b) Oxcarbazepine
 (c) Zonisamide
 (d) Phenytoin
- 136. Lamotrigine has common side effects of:** (Karnataka 2005)
 (a) Rash
 (b) Irritability
 (c) Nephrotoxicity
 (d) Behavioral disturbances
- 137. With chronic use in seizure state, the adverse effects of this drug include coarsening of facial features, hirsutism, gingival hyperplasia and osteomalacia:** (Karnataka 2005)
 (a) Carbamazepine
 (b) Ethosuximide
 (c) Gabapentin
 (d) Phenytoin
- 138. Which one of the following statements about phenytoin is accurate?** (Karnataka 2005)
 (a) Displaces sulfonamides from plasma proteins
 (b) Drug of choice in myoclonic seizures
 (c) Half-life is increased if used with phenobarbital
 (d) Toxicity may occur with only small increments in dose
- 139. The drug of choice for a patient with a combination of primary generalized tonic clonic seizure and absence seizures is:** (Karnataka 2004)
 (a) Ethosuximide
 (b) Carbamazepine
 (c) Valproic acid
 (d) Phenytoin sodium
- 140. Side effects of diphenyl hydantoin may include all except:** (Karnataka 2002)
 (a) Gingival hyperplasia
 (b) Acute cerebellar syndrome
 (c) Inter-nuclear ophthalmoplegia
 (d) Megaloblastic anaemia
- 141. Carbamazepine has drug interaction with all of the following except:** (Karnataka 2000)
 (a) Erythromycin
 (b) Phenytoin
 (c) Doxycycline
 (d) Barbiturates
- 142. The drug of choice to control convulsions in eclampsia is:** (Delhi PG 2008)
 (a) Pethidine
 (b) Diazepam
 (c) Magnesium sulphate
 (d) Phenytoin

DRUGS FOR PSYCHIATRIC ILLNESS

- 143. A person taking tricyclic antidepressants presents with blurred vision and dry mouth. These adverse effects result due to blockade of:** (AIIMS Nov 2013)
 (a) M_3 muscarinic receptors
 (b) $GABA_A$ receptors
 (c) H_1 histamine receptors
 (d) $5HT_2$ receptors
- 144. A patient of depression is stabilized on selective serotonin reuptake inhibitor (SSRI). This group of drugs produced withdrawal symptoms when stopped. Which of the following drugs has minimum risk of causing drug discontinuation symptoms?** (AIIMS Nov 2013)
 (a) Paroxetine
 (b) Fluoxetine
 (c) Sertraline
 (d) Fluvoxamine
- 145. Best agent for premenstrual syndrome management is?** (AIIMS May 2013)
 (a) Progesterone
 (b) Anxiolytic
 (c) SSRI
 (d) Vitamin E

146. Which of the following antipsychotic drugs is available as a depot injection? (AIIMS May 2013)
- Fluphenazine
 - Ziprasidone
 - Trifluoperazine
 - Aripiprazone
147. A female treatment for depression took a massive dose of amitriptyline for suicide. Which of the following statement regarding her management is WRONG? (AIIMS Nov 2010)
- Gastric lavage should be done
 - Sodium bicarbonate should be administered to treat acidosis
 - Atropine sulphate should be administered as an antidote
 - Diazepam should be injected to control seizures.
148. All are true about Clozapine except: (AI-2012)
- More potently blocks D_2 as compared to D_1 receptors
 - Blood level below 350 ng/ml should be maintained to avoid agranulocytosis
 - Should not be used along with Carbamazepine
 - Should be discontinued if the WBC count is below 3,000/mm³ cells
149. Which of the following agent is not a serotonin and dopaminergic blocker? (AI-2012)
- Doxepin
 - Amisulpiride
 - Sertindole
 - Zotepine
150. Antidepressant drug that can be used in nocturnal enuresis is? (AI 2011)
- Imipramine
 - Fluvoxamine
 - Phenelzine
 - Bupropion
151. A female patient presented with depressed mood, loss of appetite and no interest in surroundings. There is associated insomnia. The onset of depression was preceded by a history of business loss and soon after it she developed the following symptoms for the past one year. True statement regarding management of this patient is? (AI 2011)
- No treatment is necessary as it is due to business loss
 - SSRI is the most efficacious of the available drugs
 - Start SSRI treatment based on side effect profile
 - Combination therapy of 2 anti-depressant drugs
152. A patient on lithium therapy was found to be hypertensive also. Which of the following antihypertensive drugs is contraindicated in a patient on lithium therapy in order to prevent toxicity? (AI 2011)
- Clonidine
 - Beta blockers
 - Calcium channel blockers
 - Diuretics
153. A schizophrenic patient started on haloperidol 2 days back, comes with complaints of torticollis and orofaciolingual movements. What is the diagnosis? (AI 2011)
- Acute dystonia
 - Tardive dyskinesia
 - Parkinsonism
 - Akathisia
154. A woman treated with lithium during pregnancy, the fetus should be tested for: (AIIMS Nov 2010)
- Neural tube defects
 - Cardiac malformations
 - Urogenital abnormalities
 - Scalp defects
155. What is the drug of choice for Obsessive Compulsive Disorder? (AIIMS May 2007, 2010)
- Imipramine
 - Fluoxetine
 - Benzodiazepines
 - Alprazolam
156. Which of the following has highest potential to cause metabolic syndrome? (DPG 2011)
- Clozapine
 - Risperidone
 - Quetiapine
 - Aripiprazole
157. Which of the following is not a serotonin-norepinephrine reuptake inhibitor? (DPG 2011)
- Venlafaxine
 - Duloxetine
 - Milnacipran
 - Tianeptin
158. Which of the following is not a side effect of paroxetine? (DPG 2011)
- Premature ejaculation
 - Erectile dysfunction
 - Decreased libido
 - Diarrhea
159. Which of the following is not a mood stabilizer? (DPG 2011)
- Lithium
 - Valproate
 - Carbamazepine
 - Fluoxetine
160. All of the following can result in serotonin syndrome when combined with MAO inhibitors except (AI 2010)
- Tricyclic antidepressants
 - Selective serotonin reuptake inhibitors
 - Carbamazepine
 - Tyramine containing foods
161. Compared to the other antidepressant drugs mirtazapine has the distinct ability to act as an antagonist of:
- Beta receptors
 - D_2 receptors
 - Alpha 2 receptors
 - 5-HT receptors

162. Buspirone is used as a/an: (AIIMS Nov 2009)
 (a) Anxiolytic
 (b) Sedative
 (c) Muscle relaxant
 (d) Anticonvulsant
163. All are indications of lithium except: (AI 2009)
 (a) Neutropenia
 (b) Major Depression
 (c) Vasculogenic Headache
 (d) Generalized anxiety disorder
164. All of the following drugs are atypical antipsychotics EXCEPT? (AIIMS May 2008)
 (a) Olanzapine
 (b) Clozapine
 (c) Risperidone
 (d) Thioridazine
165. Increased suicidal tendency is associated with alteration in the brain levels of: (AIIMS May 2008)
 (a) Noradrenaline
 (b) Serotonin
 (c) Dopamine
 (d) GABA
166. All of the following drugs can cause neuroleptic malignant syndrome except: (AIIMS Nov 2008)
 (a) Amantadine
 (b) Domperidone
 (c) Haloperidol
 (d) Metoclopramide
167. Correct about the use of lithium as an important component of management of manic-depressive psychosis is: (DPG 2009)
 (a) Is associated with delayed (>2 weeks) electrolyte disturbances
 (b) Can be given alone for acute episodes
 (c) Monitoring of serum concentration is seldom useful for guiding dose adjustment
 (d) Cause benign and reversible depression of T wave on ECG
168. In depression, there is deficiency of: (DPG 2009)
 (a) 5-HT
 (b) Acetylcholine
 (c) Dopamine
 (d) GABA
169. Nocturnal enuresis is commonly treated with: (DPG 2009)
 (a) Imipramine
 (b) Chlordiazepoxide
 (c) Haloperidol
 (d) Chlorpromazine
170. Lithium is used in the prophylactic treatment of: (DPG 2009)
 (a) Schizophrenia
 (b) MDP
 (c) Acute depression
 (d) Conversion reaction
171. Risperidone is most commonly used to treat which of the following disorders? (DPG 2009)
 (a) Dementia
 (b) Depression
 (c) Schizophrenia
 (d) Obsessive-compulsive disorder
172. As a side effect the metabolic syndrome is most commonly associated with which of the following group of medications? (DPG 2009)
 (a) Anti-anxiety drugs
 (b) Anti-depressant drugs
 (c) Anti-psychotic drugs
 (d) Anti-cholinergic drugs
173. Which of the following is the most common side effect seen with fluoxetine therapy? (AI 2006)
 (a) Seizure
 (b) Anxiety
 (c) Hypotension
 (d) Loose stools
174. All are side effects of clozapine EXCEPT: (AI 2006)
 (a) Granulocytopenia
 (b) Seizures
 (c) Sedation
 (d) Extrapyrimal side effects
175. Antipsychotic drug induced Parkinsonism is treated by: (AI 2005)
 (a) Anticholinergics
 (b) Levodopa
 (c) Selegiline
 (d) Amantadine
176. Oculogyric crisis is known to be produced by all of the following drugs EXCEPT: (AI 2005)
 (a) Trifluoperazine
 (b) Atropine
 (c) Prochlorperazine
 (d) Perphenazine
177. Mechanism of action of tianeptin in the brain is: (AI 2002)
 (a) Selective serotonin reuptake inhibition
 (b) Selective serotonin reuptake enhancement
 (c) Selective dopamine reuptake inhibition
 (d) Selective norepinephrine reuptake inhibition
178. False statement about selegiline is: (AI 2001)
 (a) It is a MAO-A inhibitor
 (b) Does not cause cheese reaction
 (c) It decreases wearing off effect of levo-dopa
 (d) It is used in Parkinsonism
179. The following statements are true for the therapy with lithium EXCEPT: (AIIMS May, 2004)
 (a) It is used in bipolar disorder
 (b) Amiloride is useful in treating lithium induced diabetes insipidus

- (c) Regular measurements of blood concentration of lithium is necessary
(d) Sodium ion is a specific antidote for lithium clearance
180. **Prolactin secretion is inhibited by:** (AIIMS Nov, 2002), (AIIMS Nov, 2003)
(a) Dopamine antagonist
(b) GABA
(c) Neurophysin
(d) Bromocriptine
181. **A 30 year old manic patient was prescribed haloperidol 3 months back. For last two days, he has become restless and kept pacing in the room for a day. On examination he was found to have tremors of hand. He is most likely to be suffering from:** (AIIMS Nov, 2003)
(a) Anhedonia
(b) Dystonia
(c) Restless leg syndrome
(d) Akathisia
182. **A patient ingested some unknown substance and presented with myoclonic jerks, seizures, tachycardia and hypotension. ECG shows a heart rate of 120/min. The arterial blood revealed a pH of 7.25, pCO₂ of 30 mm Hg and bicarbonate ions are 15 mmol/L. The most likely poisonous agent is:** (AIIMS Nov, 2002)
(a) Amanita phylloids
(b) Ethylene glycol
(c) Imipramine
(d) Phencyclidine
183. **Which of the following diuretics decreases the renal lithium clearance?** (AIIMS Nov, 2002)
(a) Acetazolamide
(b) Mannitol
(c) Furosemide
(d) Spironolactone
184. **Lithium is used in a pregnant woman. Which of the following congenital anomaly occurs in the fetus?** (AIIMS Nov, 2001)
(a) Tetralogy of Fallot
(b) Bicuspid atresia
(c) Ebstein's anomaly
(d) Pulmonary stenosis
185. **A psychotic female on phenothiazine therapy complains of sudden onset of high grade fever, muscle rigidity and altered sensorium. The diagnosis is:** (AIIMS May, 2001)
(a) Malignant hyperthermia
(b) Neuroleptic malignant syndrome
(c) Tardive dyskinesia
(d) Akathisia
186. **Drugs used in generalized anxiety disorder are:** (PGI Dec, 2007)
(a) Alprazolam
(b) Paroxetine
(c) Venlafaxine
(d) Buspirone
(e) Gabapentin
187. **Risperidone increases the risk of:** (PGI Dec, 2006)
(a) Cerebrovascular accidents
(b) Extrapyramidal symptoms
(c) Agranulocytosis
(d) Diabetes insipidus
(e) Gout
188. **A patient on anti-psychotic drugs develops temperature of 104°C, BP about 150/100 and abnormal behavior. What is the likely diagnosis?** (PGI Dec, 2005)
(a) Aggravation of psychosis
(b) Parkinsonism
(c) Dystonia
(d) Neuroleptic malignant syndrome
(e) Akathisia
189. **Which of the following drugs are SSRI?** (PGI June, 2001, 2003)
(a) Citalopram
(b) Fluoxetine
(c) Mirtazapine
(d) Imipramine
(e) Sertraline
190. **Which of the following drugs is both effective and safe to use in a pregnant patient suffering from bipolar disorder?**
(a) Carbamazepine
(b) Lithium
(c) Olanzapine
(d) Valproic acid
191. **Which of the following drugs has a high affinity for 5-HT₂ receptors in the brain, does not cause extrapyramidal dysfunction or hematotoxicity, and is reported to increase the risk of significant QT prolongation?**
(a) Chlorpromazine
(b) Clozapine
(c) Olanzapine
(d) Ziprasidone
192. **Which of the following effects is unlikely to occur during treatment with imipramine?**
(a) Elevation of seizure threshold
(b) Mydriasis
(c) Sedation
(d) Urinary retention
193. **An adverse effect of neuroleptic drugs is directly correlated positively to the antipsychotic potency of the different compounds. Which of the following is it?**
(a) Sedation
(b) Extrapyramidal motor disturbances
(c) Postural hypotension
(d) Lowering of seizure threshold
194. **All actions of chlorpromazine are based on its antidopaminergic property EXCEPT:**
(a) Antipsychotic
(b) Hyperprolactinemic
(c) Antiemetic
(d) Hypotensive

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195. The secretion of which of the following hormones increases with chlorpromazine therapy?
- Prolactin
 - Gonadotropin
 - Corticotropin
 - Antidiuretic hormone
196. A patient, Hari has been diagnosed to have schizophrenia. Which of the following acts as a limiting factor in the use of clozapine as an antipsychotic drug in this patient?
- Its potential to cause agranulocytosis
 - Its inability to benefit negative symptoms of schizophrenia
 - High incidence of extrapyramidal side effects
 - Production of hyperprolactinemia
197. Propanolol is useful in the management of which of the following side effects of a typical neuroleptic?
- Parkinsonism
 - Acute muscle dystonia
 - Tardive dyskinesia
 - Akathisia
198. Which of the following adverse effect can occur even after the offending drug has been withdrawn a long time back?
- Paradoxical tachycardia
 - Tardive dyskinesia
 - Malignant hyperthermia
 - Gynaecomastia
199. All of the following statements about buspirone are incorrect EXCEPT?
- It interacts with benzodiazepine receptor as an inverse agonist
 - It is a rapidly acting anxiolytic: good for panic states
 - It produces physical dependence and suppresses barbiturate withdrawal syndrome
 - It has anxiolytic but no anticonvulsant or muscle relaxant property
200. Which of the following drugs is preferred for long term treatment of severe anxiety disorder with intermittent panic attacks?
- Phenothiazine
 - Azapirone
 - β blocker
 - Selective serotonin reuptake inhibitor
201. The selective MAO-B inhibitor out of the following is:
- Selegiline
 - Clorgyline
 - Moclobemide
 - Tranlycypromine
202. An antidepressant drug which is known to have both high sedative and anticholinergic activity is:
- Phenelzine
 - Amitriptyline
 - Fluoxetine
 - Trazodone
203. All of the following are limitations of typical tricyclic antidepressants EXCEPT:
- Narrow safety margin
 - Low oral bioavailability
 - Frequent side effects
 - Long latent period for response
204. One of the following limitations of typical tricyclic antidepressants has been overcome by selective serotonin reuptake inhibitors. Which is it?
- Frequent anticholinergic, sedative and hypotensive side effects
 - High risk of cardiac arrhythmias and seizures in overdose
 - Delayed response
 - Both (a) and (b) are correct
205. Now-a-days, the selective serotonin reuptake inhibitors are the preferred drugs for which of the following psychiatric disorder apart from their role in the treatment of depression:
- Phobias
 - Obsessive compulsive disorder
 - Post-traumatic stress disorder
 - All of the above
206. A patient has been diagnosed to be having mania and bipolar illness. Which of the following drugs can be used in this patient apart from lithium?
- Carbamazepine
 - Carisoprodol
 - Clomipramine
 - Diethylcarbamazine
207. Which of following statements about extrapyramidal effects of antipsychotic drugs is FALSE?
- Caused by blockade of dopamine receptors
 - Less likely to be produced by clozapine than by chlorpromazine
 - Can be countered to some degree by antimuscarinic drugs
 - Haloperidol does not cause extrapyramidal syndrome
208. A psychiatric patient taking medication develops a tremor, thyroid enlargement and leucocytosis. Drug implicated is:
- Clomipramine
 - Haloperidol
 - Lithium
 - Olanzapine
209. MAO inhibitors are contra-indicated in all the following conditions EXCEPT:
- With tricyclic antidepressants
 - With indirectly acting sympathomimetics
 - Cheese
 - Aspirin

210. A patient Rajnish having depressive disorder has taken 25 times the normal dose of amitriptyline. Which of the following is not likely to be observed in this patient?
- Coma and shock
 - Hot dry skin
 - Hypotension
 - Pinpoint pupil
211. A patient Manoj with severe pain thought to be of gastrointestinal origin received 60 mg of meperidine subsequent to which he developed reaction characterized by tachycardia, hypertension, hyperpyrexia and seizures. He gave the history that he is also taking some medicine for his psychiatric condition. Which of the following drug can be held responsible for this sort of reaction?
- Alprazolam
 - Imipramine
 - Lithium
 - Phenelzine
212. A patient presents in your psychiatry OPD with complaints of diminished vision. Ophthalmological examination revealed corneal and lenticular opacities. He had been prescribed some antipsychotic drug during his last visit. Which of the following it can be?
- Thioridazine
 - Haloperidol
 - Flupenthixol
 - Pimozide
213. A patient Ashwani has been brought to the hospital with non-stop talking, singing, uncontrollable behavior and apparent loss of contact with reality. You diagnose it to be a case of acute mania. Which of the following is the most suitable drug for rapid control of his symptoms?
- Lithium carbonate
 - Phenobarbitone
 - Haloperidol
 - Valproic acid
214. A hypertensive patient Sattu already receiving a drug 'X' to control his BP was prescribed a tricyclic antidepressant. This resulted in the abolition of the antihypertensive action of 'X'. Which of the following drug can be 'X'?
- Enalapril
 - Clonidine
 - Atenolol
 - Diltiazem
215. A patient of endogenous depression was prescribed imipramine. After what duration of time interval is the therapeutic effect of imipramine likely to manifest?
- Three days
 - One week
 - Three weeks
 - Three months
216. After starting your patient on imipramine, his heart rate rises to 120/min and he has blurred vision. These effects can be explained by the fact imipramine:
- Is a muscarinic antagonist
 - Potentiates epinephrine
 - Is a ganglionic blocker
 - Is a potent α -adrenergic blocker
217. A 46-year-old male, Prabash being treated for depression was admitted to the emergency with severe confusion and hallucinations. His mouth was dry and his face was flushed. On examination, his blood pressure was found to be 84/62 mmHg and his heart rate is 108 beats per minute. ECG of the patient reveals sinus tachycardia, prolongation of PR and QT interval and widened QRS complex. Which of the following agents would best correct this patient's cardiac abnormalities?
- Propanolol
 - Flumazenil
 - Atropine
 - Sodium bicarbonate
218. A 45-year-old male, Sanjeev was brought to the emergency with severe agitation and aggressive behavior. He was started on haloperidol and the patient became responsive and cooperative. After 8 days of treatment, he developed high grade fever, diarrhea, confusion and muscle rigidity. Which of the following should be used for the treatment of this condition?
- Diazepam
 - Benzhexol
 - Dantrolene
 - High dose of haloperidol
219. Drug of choice in intractable hiccups is: (DPG 2010)
- Metoclopramide
 - Fluoxetine
 - Selegiline
 - Chlorpromazine
220. All of the following drugs cause hyperprolactinemia EXCEPT: (Karnataka 2009)
- Haloperidol
 - Chlorpromazine
 - Bromocriptine
 - Metoclopramide
221. Dryness of mouth caused by antipsychotic drug is caused by blockade of: (DELHI-PG-2008)
- Muscarinic ACh receptors
 - GABA receptors
 - Serotonergic receptors
 - Dopaminergic receptors
222. Selective serotonin reuptake inhibitors are drug of choice for all of the following conditions EXCEPT: (DELHI-PG-2008)
- Acute panic attack
 - Social phobia
 - Post traumatic stress disorder
 - Generalized anxiety disorder

223. Prophylactic plasma concentration range of lithium in mEq does not include: (DELHI-PG-2008)
 (a) 0.5
 (b) 0.8
 (c) 0.6
 (d) 1.0
224. Drug having proven efficacy in bipolar depression is: (DELHI-PG-2007)
 (a) Carbamazepine
 (b) Valproate
 (c) Tiagabine
 (d) Lamotrigine
225. Drug of choice for rapid cyclers in manic-depressive psychosis is: (DELHI-PG-2007)
 (a) Carbamazepine
 (b) Valproate
 (c) Phenytoin
 (d) Lithium
226. Akathisia is treated by all EXCEPT: (DPG 2005)
 (a) Trihexyphenidyl
 (b) Propanolol
 (c) Haloperidol
 (d) Promethazine
227. Which of the following drug causes sedation but no extra pyramidal side effect: (DPG 2004)
 (a) Clozapine
 (b) Pimozide
 (c) Fluphenazine
 (d) Haloperidol
228. Akathisia is seen with the use of: (DPG 2004)
 (a) Clozapine
 (b) Propanolol
 (c) Benztropine
 (d) Haloperidol
229. Which of the following is not a side effect of clozapine: (DPG 2004)
 (a) Agranulocytosis
 (b) Seizure
 (c) Sialosis
 (d) Weight loss
230. With MAO inhibitors, food not given is: (DPG 2003)
 (a) Cheese
 (b) Beer
 (c) Fish
 (d) All of the above
231. Which of the following has least extrapyramidal side effect: (DPG 2002) (MPPG 2003)
 (a) Haloperidol
 (b) Fluphenazine
 (c) Clozapine
 (d) Flupenthixol
232. Buspirone as compared to benzodiazepines: (DPG 2002)
 (a) Is more potent anticonvulsant
 (b) Does not interfere with GABAergic transmission
 (c) More effective in severe anxiety with panic attacks
 (d) Produces significantly more sedation
233. Depression is not a side effect of: (MPPG 2007)
 (a) Propanolol
 (b) Oral contraceptives
 (c) Reserpine
 (d) Flupenthixol
234. Schizophrenia can be treated with all the following EXCEPT: (MPPG 2007)
 (a) Pemoline
 (b) Olanzapine
 (c) Sulpiride
 (d) Chlorpromazine
235. Which of the following is not a side effect of amitriptyline: (MPPG 2003)
 (a) Constipation
 (b) Fine tremors
 (c) Weight loss
 (d) Dry mouth
236. Which of the following drug may cause hypertensive crisis in a patient on MAO inhibitor therapy? (MPPG 2002)
 (a) Tyramine
 (b) Guanethidine
 (c) Phenobarbitone
 (d) Nor-epinephrine
237. Antipsychotic drug with least extra pyramidal side effect is: (UP 2007)
 (a) Triflupromazine
 (b) Thioridazine
 (c) Pimozide
 (d) Trifluoperazine
238. Which of the following drug treatment increases thirst and causes dilute diuresis? (UP 2008)
 (a) Phenobarbitone
 (b) Lithium
 (c) Chlorpromazine
 (d) Clozapine
239. False statement regarding Lithium is: (UP 2005)
 (a) Maximum plasma concentration is avoided due to low therapeutic index
 (b) Contraindicated in pregnancy
 (c) No individual variation in the rate of excretion
 (d) 80% reabsorbed in the proximal convoluted tubule
240. Extrapyramidal symptoms are a complication of treatment with following drugs: (TN 2006)
 (a) Antipsychotics
 (b) Anti anxiety drugs
 (c) Anti depressants
 (d) Anti malarial drugs
241. Which of the following is an atypical antipsychotic? (TN 2006)
 (a) Clozapine
 (b) Chlorpromazine
 (c) Thiothixene
 (d) Haloperidol

242. Drug useful in malignant hyperthermia is: (RJ 2000)
(a) Halothane (Karnataka 2002)
(b) Succinyl choline
(c) Dantrolene
(d) Haloperidol
243. Antipsychotic drug is: (RJ 2005)
(a) Doxepin
(b) Fluoxetine
(c) Clozapine
(d) All
244. Antidepressant drug is: (RJ 2005)
(a) Pimozide
(b) Haloperidol
(c) Thioridazine
(d) Citalopram
245. Risperidone acts on which receptor: (RJ 2005)
(a) D₂
(b) 5 HT₂
(c) Both
(d) NA
246. Neuroleptic malignant syndrome is caused by: (MH 2002)
(a) Carbamazepine
(b) Clonazepam
(c) Haloperidol
(d) Fluoxetine
247. Non-selective serotonin and nor-adrenaline reuptake inhibitor is: (MH 2002)
(a) Sertraline
(b) Citalopram
(c) Venlafaxine
(d) Paroxetine
248. Half-life of lithium is: (MH 2002)
(a) 8 hours
(b) 16 hours
(c) 24 hours
(d) 36 hours
249. Therapeutic levels of lithium (in meq/l) in a patient of acute mania is: (MH 2002)
(a) 0.4-0.8 (DPG 2009)
(b) 0.8-1.2
(c) 1.2-1.6
(d) 1.6-2.0
250. Which of the following drugs should not be given with tyramine as it may result in dangerous reaction? (MH 2002)
(a) Selegiline
(b) Meperidine
(c) Tranylcypromine
(d) Dextromethorphan
251. Drug used to treat extrapyramidal syndrome due to phenothiazines: (MH 2002)
(a) Diphenhydramine
(b) Benzhexol
(c) Clonidine
(d) Promethazine
252. True statement regarding lithium toxicity is: (MH 2002)
(a) Increased by increased serum sodium levels
(b) Increased by decreased serum sodium levels
(c) Increased in acute tubular necrosis
(d) Appears when the serum levels become triple the dose of therapeutic levels
253. Which of the following antidepressants causes urine retention? (MH 2003)
(a) Imipramine
(b) Fluoxetine
(c) Dothiepin
(d) Risperidone
254. Anti-depressant drug that can be safely used in children is: (MH 2003)
(a) Imipramine
(b) Fluoxetine
(c) Dothiepin
(d) Risperidone
255. Coarse tremors, dysarthria and ataxia are side effects of (MH 2003)
(a) Lithium
(b) Haloperidol
(c) Imipramine
(d) None
256. Tranylcypromine (MAO Inhibitor) should be avoided with as it causes dangerous drug interaction: (MH 2007)
(a) Morphine
(b) Amitriptyline
(c) Alprazolam
(d) Any of the above
257. Which among the following is not an antipsychotic? (Bihar 2006)
(a) Risperidone
(b) Haloperidol
(c) Fluoxetine
(d) Clozapine
258. Galactorrhoea is caused by: (Jharkhand 2003)
(a) Phenothiazines
(b) Bromocriptine
(c) Pyridoxine
(d) None
259. Common side effects of chlorpromazine are all except: (Jharkhand 2004)
(a) Osteoporosis
(b) Parkinson's disease
(c) Skin rash
(d) Amenorrhoea
260. All are selective serotonin reuptake inhibitor except: (Jharkhand 2006, Jharkhand 2005)
(a) Fluoxetine
(b) Fluvoxamine
(c) Paroxetine
(d) Amoxapine
261. All are atypical antipsychotic drugs except: (Jharkhand 2006)
(a) Clozapine
(b) Risperidone

- (c) Olanzapine
(d) Loxapine
262. Treatment of malignant neuroleptic syndrome include all except: (AP 2002)
(a) Chlorpromazine
(b) Dantrolene
(c) Peripheral cooling
(d) Diazepam
263. Long-term antipsychotic use may cause: (AP 1997) (AP 2003)
(a) Depression
(b) Mania
(c) Schizophrenia
(d) Tardive dyskinesia
264. Moclobemide is: (AP 2006)
(a) SSRI
(b) Antipsychotic drug
(c) MAO inhibitor
(d) Tricyclic antidepressant
265. Which of the following is not associated with increase in prolactin? (AP 2007)
(a) Haloperidol
(b) Chlorpromazine
(c) Hydroxysulpiride
(d) Quetiapine
266. Pimozide belongs to class of: (AP 2008)
(a) Thiothixene
(b) Phenothiazine
(c) Butyrophenone
(d) Diphenyl butyl piperidine
267. Antipsychotic drug with the longest elimination half life is: (MP 2009)
(a) Aripiprazole
(b) Loxapine
(c) Quetiapine
(d) Ziprasidone
268. Dopamine and noradrenaline reuptake inhibitor is: (Kolkata 2008)
(a) Clozapine
(b) Bupropion
(c) Zolpidem
(d) Mirtazapine
269. Which of the following is NOT a MAO inhibitor? (Kolkata 2009)
(a) Tranylcypromine
(b) Isocarboxazide
(c) Phenelzine
(d) Maprotiline
270. The clinical indications for tricyclic anti-depressants include all the following EXCEPT: (Karnataka 2008)
(a) Enuresis in elderly subjects
(b) Neuropathic pain
(c) Panic disorder
(d) Uncontrolled seizure
271. Which of the following statements is NOT correct of Tardive dyskinesia: (Karnataka 2007)
(a) It is an unwanted effect of antipsychotics
(b) Levodopa exacerbates the symptoms
(c) Antimuscarinic drug reduces its severity
(d) Often diazepam is used to bring improvement
272. Which of the following medication is associated with an increased risk of agranulocytosis? (Karnataka 2005)
(a) Clozapine
(b) Imipramine
(c) Lithium
(d) Haloperidol
273. The side effects of lithium used in psychiatry practice include all except: (Karnataka 2003)
(a) Nausea, vomiting
(b) Tremors
(c) Hypothyroidism
(d) Hypercalcemia
274. Drug of choice for the treatment of negative symptoms of schizophrenia is: (Karnataka 2002)
(a) Chlorpromazine
(b) Haloperidol
(c) Clozapine
(d) Doxepin
275. Which among the following medications has been found to be effective in smoking cessation? (DPG 2007)
(a) Bupropion
(b) Buspirone
(c) Paroxetine
(d) Venlafaxine
276. Drug of choice in nocturnal enuresis is: (UP 2008)
(a) Imipramine
(b) Diazepam
(c) Amoxapine
(d) Reboxetine
277. A patient presents with malignant hyperthermia and metabolic acidosis. Immediate treatment should be started with
(a) Intravenous Dantrolene
(b) Sodium bicarbonate
(c) Intravenous fluids
(d) Paracetamol

■ OPIOIDS AND DRUG ADDICTION

278. Dysphoria caused by opiates is mediated by which receptor? (AIIMS May 2013)
(a) mu
(b) kappa
(c) delta
(d) sigma

279. Preferred drug for alcohol withdrawal seizures is: (AIIMS May 2013)
 (a) Diazepam
 (b) valproate
 (c) Phenobarbitone
 (d) Carbamazepine
280. All are true regarding METHANOL poisoning except: (AIIMS May 2013)
 (a) Hemodialysis should be done when serum methanol concentration is above 50 mg/dl
 (b) Fomepizole acts by inhibiting aldehyde dehydrogenase
 (c) High anion gap metabolic acidosis is seen in severe cases
 (d) Visual disturbances are commonly seen
281. A young man is with known heroin addiction is brought in the emergency in unconscious state. On examination, the patient has decreased bowel sounds, depressed respiration and pin point pupil. The treatment of choice for this patient is (AIIMS Nov 2012)
 (a) Oral naltrexone
 (b) IV naloxone
 (c) Oral diazepam
 (d) Oral Buprenorphine
282. Which among the following drug is contra-indicated in renal failure? (AI-12)
 (a) Pethidine
 (b) Morphine
 (c) Fentanyl
 (d) Atracurium
283. All of these are the adverse effects of naloxone in the treatment of opioid poisoning except: (AIIMS May 2011)
 (a) Hypertension
 (b) Pulmonary edema
 (c) Seizures
 (d) Ventricular dysrhythmia
284. All of the following can be used to treat alcohol dependence except: (AI 2011)
 (a) Naltrexone
 (b) Acamprosate
 (c) Flumazenil
 (d) Disulfiram
285. Rave drug is? (AI 2011)
 (a) Cannabis
 (b) Cocaine
 (c) Heroin
 (d) Amphetamine
286. Which of the following drugs is used worldwide for the maintenance therapy of opioid dependence? (AI 2011)
 (a) Naltrexone
 (b) Methadone
 (c) Pethidine
 (d) L-NAME
287. True about epidural opioids are all except?
 (a) Act on dorsal horn substantia gelatinosa
 (b) Can cause Itching (AI 2011)
 (c) Function of the intestine is not affected
 (d) Can cause respiratory depression
288. Buprenorphine is? (AI 2011), (RJ 2007) & (AIIMS May 2008)
 (a) Partial agonist at μ Receptor
 (b) Partial agonist at κ Receptor
 (c) Full Agonist at μ Receptor
 (d) Full Agonist at κ receptor
289. Tolerance develops to all of the following actions of opioids except? (AI 2011)
 (a) Miosis
 (b) Analgesia
 (c) Euphoria
 (d) Nausea and vomiting
290. An addict presents with increased sweating, lacrimation, diarrhea, yawning and rhinorrhea. These symptoms may occur due to withdrawal of? (AIIMS Nov 2010)
 (a) Heroin
 (b) Cocaine
 (c) Cannabis
 (d) Alcohol
291. A newborn developed respiratory depression in a postoperative ward. It can result from the use of? (AIIMS Nov 2010)
 (a) Opioid
 (b) Propofol
 (c) Furosemide
 (d) Heparin
292. Respiratory centre depression can be caused by all except: (AIIMS Nov 2010)
 (a) Opium
 (b) Strychnine
 (c) Barbiturates
 (d) Gelsemium
293. Naltrexone is used for which of the following function in opioid addiction? (AIIMS May 2007, 2010) (AI 2007)
 (a) Prevention of relapse
 (b) Treatment of withdrawal
 (c) Treatment of overdose
 (d) Prevention of withdrawal
294. All of the following can be used to treat heroin dependence except: (AIIMS May 2010)
 (a) Disulfiram
 (b) Buprenorphine
 (c) Clonidine
 (d) Lofexidine
295. Which of the following drug is not an opioid agonist? (AIIMS May 2010)
 (a) Heroin
 (b) Ketamine
 (c) Methadone
 (d) Codiene

296. Naltrexone is used to maintain abstinence following opioid withdrawal in addicts. It blocks all of the following features of opioid use, except: (DPG 2011)
 (a) Euphoriant effects of opioids
 (b) Craving for opioids
 (c) Miosis
 (d) Respiratory depression
297. All of the following are true about opioids except? (AI 2010)
 (a) Naloxone is short acting
 (b) Naltrexone is used to lower craving in alcoholics
 (c) Nalmefene can be used for opioid poisoning
 (d) Nalmefene is shorter acting than naloxone
298. Which of the following is not a feature of fetal alcohol syndrome? (AIIMS Nov 2009)
 (a) Microcephaly
 (b) Low intelligence
 (c) Large proportionate body
 (d) Intrauterine growth retardation
299. Which of the following is least narcotic opioid? (AIIMS Nov 2009)
 (a) Morphine
 (b) Codeine
 (c) Heroin
 (d) Papaverine
300. Anti-craving agents for alcohol dependence are all except: (AIIMS May 2009)
 (a) Lorazepam
 (b) Acamprosate
 (c) Topiramate
 (d) Naltrexone
301. Drug used to prevent alcohol withdrawal in de addiction is? (AIIMS May 2008)
 (a) Diazepam
 (b) Clonidine
 (c) Propanolol
 (d) Methadone
302. The following symptoms may be seen in opium withdrawal: (DPG 2009)
 (a) Constipation
 (b) Lacrimation
 (c) Dry nose and mouth
 (d) Constipation
303. In alcohol withdrawal, drug of choice is: (DPG 2009)
 (a) TFP
 (b) Chlormethazole
 (c) Chlordiazepoxide
 (d) Buspirone
304. Which of the following is used to maintain abstinence in alcohol dependence? (DPG 2009)
 (a) Naltrexone
 (b) Clonidine
 (c) Disulfiram
 (d) Naloxone
305. Which of the following actions is ascribed to delta type of opioid receptors? (AI 2004)
 (a) Supraspinal analgesia
 (b) Respiratory depression
 (c) Euphoria
 (d) Reduced intestinal motility
306. Morphine can be used in all the following conditions EXCEPT: (AI 2004)
 (a) Head injury
 (b) Asthma
 (c) Hypothyroidism
 (d) Diabetes
307. Naloxone is contraindicated in neonatal resuscitation if the mother is on: (AIIMS May, 2007)
 (a) Cocaine
 (b) Amphetamine
 (c) Methadone
 (d) Phencyclidine
308. Which of the following opioids has maximum plasma protein binding capacity? (AIIMS Nov, 2004)
 (a) Morphine
 (b) Sufentanil
 (c) Fentanyl
 (d) Pethidine
309. The μ opioid receptor is responsible for the following effects: (AIIMS Nov, 2002)
 (a) Miosis
 (b) Tachycardia
 (c) Hyperthermia
 (d) Bronchodilation
310. The drug not used for analgesia in a patient of head injury is: (AIIMS May, 2002)
 (a) Morphine
 (b) NSAIDs
 (c) Rofecoxib
 (d) Acetaminophen
311. Antidote for ethylene glycol poisoning is/are: (PGI Dec 2005)
 (a) Methyl violet
 (b) Fluconazole
 (c) Fomepizole
 (d) Ethyl alcohol
312. True about methyl alcohol poisoning is: (PGI Dec. 2004)
 (a) Ethyl alcohol is used
 (b) Formation of formic acid produces blindness
 (c) Activated charcoal is given in all cases
 (d) Gastric lavage done
 (e) Fomepizole inhibits the formation of formic acid
313. True statement about dezocine is: (PGI June, 2003)
 (a) It is slower acting than morphine
 (b) It is less potent than morphine
 (c) It acts via GABA receptors
 (d) It doesn't increase histamine release
 (e) It increases plasma catecholamines

314. Morphine can administered by all of the following routes EXCEPT: (PGI Dec. 2002)
- Intramuscular
 - Transdermal
 - Epidural
 - Subarachnoid
 - Oral
315. Established routes of administration of morphine include: (PGI June, 2002)
- Inhalation
 - Rectal
 - SC
 - IV
 - IM
316. Which of the following statements regarding naltrexone are true? (PGI Dec. 2001)
- It is an opioid antagonist
 - It is an opioid agonist
 - It is used in alcohol dependence
 - It is used to treat opioid dependence
 - It is used as a respiratory stimulant
317. The combination of alcohol and disulfiram results in nausea and hypotension as a result of accumulation of:
- Acetaldehyde
 - Acetate
 - Methanol
 - NADH
318. The intense craving experienced by the people recovering from chronic alcoholism can be treated by a drug which acts by being an:
- Agonist of serotonin receptors
 - Agonist of alpha adrenoceptors
 - Agonist of beta adrenoceptors
 - Antagonist of opioid receptors
319. Which of the following opioid should not be used with MAO inhibitors? (AI 2010)
- Morphine
 - Pentazocine
 - Buprenorphine
 - Pethidine
320. Disulfiram (antabuse) is used for the treatment of:
- Acute alcoholic intoxication
 - Both physically and psychologically dependent alcoholics
 - Alcoholics psychologically but not physically dependent on alcohol
 - Both (a) and (b) are correct
321. The rationale for using ethanol in methanol poisoning is that it:
- Antagonises the actions of methanol
 - Stimulates the metabolism of methanol and reduces its blood level
 - Inhibits the metabolism of methanol and generation of toxic metabolite
 - Replenishes the folate stores depleted by methanol
322. The drug which is a specific inhibitor of the enzyme alcohol dehydrogenase and is useful in the treatment of methanol and ethylene glycol poisoning is:
- Disulfiram
 - Ethylene glycol
 - Calcium leucovorin
 - Fomepizole
323. Use of morphine should be avoided in all of the following patients EXCEPT?
- Ischemic heart disease patients
 - Bronchial asthma patients
 - Elderly male patients
 - Biliary colic patients
324. An analgesic 'X' acts through opioid as well as additional spinal monoaminergic mechanisms. Which of the following can be 'X'?
- Tramadol
 - Etioheptazine
 - Dextropropoxyphene
 - Alfentanil
325. Which of the following opioid analgesic acts primarily through κ opioid receptors?
- Pentazocine
 - Methadone
 - Buprenorphine
 - Pethidine
326. Long term use of pethidine is avoided because a metabolite of pethidine is associated with:
- Constipation
 - Dependence
 - Seizures
 - Respiratory depression
327. Patients should be cautioned not to consume alcohol when given a prescription for any of the following EXCEPT:
- Cefixime
 - Cefoperazone
 - Chlorpropamide
 - Metronidazole
328. Which of the following drugs does not activate opioid receptors, has been proposed as a drug in the management of opioid addiction and with just a single dose blocks the action of injected heroin for up to 48 hours?
- Amphetamine
 - Buspirone
 - Methadone
 - Naltrexone
329. Which of the following drugs is a full agonist at opioid receptors, has excellent oral bioavailability, analgesic equipotency to morphine and a longer duration of action with milder withdrawal symptoms on abrupt discontinuation?
- Fentanyl
 - Hydromorphone

- (c) Methadone
- (d) Nalbuphine

330. Which of the following drugs reduces alcohol craving and chances of resumed heavy drinking by alcoholics after they have undergone a detoxification programme with this drug?
- (a) Chlordiazepoxide
 - (b) Chlorpromazine
 - (c) Methadone
 - (d) Naltrexone
331. A drug 'X' is more selective for the $\omega 1$ subtype of BZD receptors. It has hypnotic action but absent or little antianxiety, muscle relaxant and anticonvulsant actions. Which of the following can be 'X':
- (a) Zopiclone
 - (b) Zolpidem
 - (c) Flumazenil
 - (d) Melatonin
332. A patient is having a malignancy and has been suffering from severe pain. Which of the following opioid analgesics can be used as transdermal patch for alleviation of pain in him?
- (a) Morphine
 - (b) Pentazocine
 - (c) Fentanyl
 - (d) Tramadol
333. In methyl alcohol poisoning there is CNS depression, cardiac depression and optic nerve atrophy. These effects are produced due to:
- (a) Formaldehyde and formic acid (DPG 2010)
 - (b) Acetaldehyde
 - (c) Pyridine
 - (d) Acetic acid
334. Drugs used in alcohol withdrawal are all, except:
- (a) Naltrexone (DPG 2007, 2010)
 - (b) Naloxone
 - (c) Acamprosate
 - (d) Disulfiram
335. Characteristic features of opioid withdrawal is:
- (a) Rhinorrhea and lacrimation
 - (b) Seizures (DELHI-PG-2007)
 - (c) Delirium Tremors
 - (d) Transient visual, tactile or auditory hallucinations
336. Drug of choice for controlling severe pain in cancer patients is:
- (a) Morphine (DELHI-PG-2007)
 - (b) Diclofenac
 - (c) Ibuprofen
 - (d) Codeine
337. Which of the following statement is FALSE about Naltrexone?
- (a) Parenterally administered
 - (b) Used to prevent relapse of heavy drinking
 - (c) Long acting
 - (d) Cause hepatotoxicity
338. Dysphoria is mediated by which opioid receptor:
- (a) Mu (DPG 2004, Bihar 2003)
 - (b) Kappa
 - (c) Delta
 - (d) None
339. In acute morphine poisoning, the drug of choice is:
- (a) Atropine (DPG 2003, RJ 2004)
 - (b) Methadone (DPG 1999, 2001)
 - (c) Naloxone
 - (d) Alcohol
340. Naltrexone is used for which of the following poisoning?
- (a) Heroin (DPG 1999)
 - (b) Atropine
 - (c) Cannabis
 - (d) Diazepam
341. Disulfiram like reaction is not seen with:
- (a) Amoxicillin (DPG 1999)
 - (b) Metronidazole
 - (c) Cefoperazone
 - (d) Disulfiram
342. Regarding opioid induced seizures:
- (a) They usually occur at therapeutic doses (MPPG 2006)
 - (b) Children are more susceptible
 - (c) Seizures occur only with μ -opioid agonists
 - (d) Diazepam is the drug of choice in treatment
343. Antabuse:
- (a) Inhibits glucuronide conjugation (MPPG 2004)
 - (b) Inhibits oxidation of alcohol
 - (c) Inhibits excretion of alcohol through kidney
 - (d) None of the above
344. The drug acamprosate is therapeutically used for:
- (a) Cough (TN 2002)
 - (b) Rickets
 - (c) Thrombolysis
 - (d) Maintenance therapy of alcohol abstinence
345. Which one of the following drug is contraindicated in acute myocardial infarction:
- (a) Morphine (TN 2003)
 - (b) Pentazocine
 - (c) Nitroglycerin
 - (d) Beta blockers
346. The most important feature of the following opioid analgesic is high oral parenteral activity ratio (1:2):
- (a) Morphine (TN 2003)
 - (b) Oxymorphone
 - (c) Methadone
 - (d) Diacetylmorphine
347. Actions of opiates in man include all except:
- (a) Constipation (TN 2005)
 - (b) Vomiting

- (c) Analgesia
(d) Mydriasis
348. **Disulfiram and acamprosate are used for:** (TN 2008)
(a) Alcohol abstinence
(b) Cocaine abuse
(c) Opium poisoning
(d) Atropine over dose
349. **Which drug has more analgesic effects than morphine?** (TN 2006)
(a) Heroin
(b) Apomorphine
(c) Codeine
(d) Pethidine
350. **Ethanol is given in methyl alcohol poisoning because:** (RJ 2006)
(a) It inhibit alcohol dehydrogenase
(b) It inhibit aldehyde synthetase
(c) It binds 100 times stronger than methanol
(d) None
351. **Which of the following is not an opioid peptide?** (RJ 2007)
(a) β -Endorphin
(b) Epinephrine
(c) Leu5-enkephalin
(d) Met5-enkephalin
352. **In liver, which of the following is responsible for metabolism of alcohol?** (RJ 2008)
(a) Alcohol dehydrogenase (ADH)
(b) Aldehyde dehydrogenase (ALDH)
(c) Microsomal ethanol-oxidizing system (MEOS)
(d) All of the above
353. **Pure opiate antagonists are all of the following except:** (RJ 2009, RJ 2008)
(a) Naloxone
(b) Nalorphine
(c) Nalmefene
(d) Naltrexone
354. **Endogenous opioid peptide includes:** (RJ 2008)
(a) Enkephalin
(b) Endorphins
(c) Dynorphins
(d) All of the above
355. **Antidote of methyl alcohol poisoning is:** (RJ 2008)
(a) Barbiturate
(b) Fomepizole
(c) Phenytoin
(d) Lamotrigine
356. **Which of the following opioid analgesic is suitable for haemodynamically unstable patients?** (MH 2002)
(a) Morphine
(b) Meperidine
(c) Fentanyl
(d) Pentazocine
357. **Tramadol is:** (MH 2002)
(a) Antiflatulent
(b) Antireflux drug
(c) Beta-blocker
(d) Opioid analgesic
358. **Opioid analgesic used in treatment of cough is?** (MH 2002)
(a) Loperamide
(b) Diphenoxylate
(c) Codeine
(d) Meperidine
359. **True about naltrexone is all except:** (MH 2003)
(a) Acts on opioid receptors
(b) Is used in treatment of alcohol dependence
(c) Is used to reduce craving in dependence
(d) Is an opioid agonist
360. **Dextromethorphan differs from codeine in:** (MH 2006)
(a) Its antitussive action can be blocked by naloxone
(b) Depresses mucociliary function of the airway mucosa
(c) Addiction common
(d) Causes no constipation
361. **Which of the following is 100 times more potent than morphine?** (Karnataka 2001), (MH 2007)
(a) Pethidine
(b) Fentanyl
(c) Pentazocine
(d) Meperidine
362. **Drugs that can be used in opioid de-addiction are?** (MH 2007)
(a) Clonidine
(b) Diazepam
(c) Methadone
(d) All of the above
363. **Site of action of opioid receptor is:** (Bihar 2006)
(a) Area postrema
(b) Dorsal horn
(c) Injury site
(d) Brain
364. **Opium is a derivative of:** (AP 2003)
(a) Solanum tuberosum
(b) Datura stramonium
(c) Papaver somniferum
(d) Nicotiana glauca
365. **The most potent analgesic agent is:** (MP 2009)
(a) Fentanyl
(b) Sufentanil
(c) Remifentanyl
(d) Alfentanil
366. **Non- synthetic alkaloid compound acting similar to amphetamine is:** (Kolkata 2006)
(a) Caffeine
(b) Cocaine
(c) Nicotine
(d) All of the above

367. Morphine can be given by all the following routes except: *(Kolkata 2007)*

- (a) Intravenous
- (b) Intramuscular
- (c) Subcutaneous
- (d) Sublingual

368. "Opioids" differ from "opiates" in that they are:

- (a) More powerful in action *(Karnataka 2008)*
- (b) More long acting
- (c) Synthetic derivatives
- (d) Derived directly from opium

369. Which of the following is a naturally occurring opioid?

- (a) Pentazocine *(Karnataka 2008)*
- (b) Heroin
- (c) Fentanyl
- (d) Morphine

RECENT QUESTIONS ASKED BY NATIONAL BOARD

1. Which is a late side effect of typical anti-psychotics ?

- (a) Parkinsonism
- (b) Tardive dyskinesia
- (c) Acute muscular dystonia
- (d) Akathisia

2. 'Vigabatrin' a new antiepileptic agent acts by:

- (a) GABA - antagonism
- (b) GABA - agonism
- (c) NMDA antagonism
- (d) Carbonic anhydrase inhibition

3. Use of Buspirone is:

- (a) Anxiolytic
- (b) Sedative
- (c) Acute panic attacks
- (d) Muscle relaxant

4. Shortest acting benzodiazepine among these is:

- (a) Flurazepam
- (b) Alprazolam
- (c) Triazolam
- (d) Diazepam

5. Off label use of topiramate is

- (a) Alcohol de-addiction
- (b) Extrapyramidal symptoms on anti-psychotic use
- (c) Opioid withdrawal
- (d) Sedative agent

6. Fosphenytoin is different from phenytoin in which of the following aspect?

- (a) Can be used in absence seizures
- (b) Can be mixed with dextrose
- (c) Can be given orally
- (d) It is the drug of choice for myoclonic seizures

7. Which of the following is a serotonin and nor epinephrine reuptake inhibitor?

- (a) Fluoxetine

(b) Venlafaxine

(c) Sertraline

(d) Amoxapine

8. Which of the following antipsychotics have least risk of causing extrapyramidal side-effects?

- (a) Clozapine
- (b) Haloperidol
- (b) Thioridazine
- (d) Fluphenazine

9. Extrapyramidal adverse effect is commonly caused by:

- (a) Anti-depressants
- (b) Anti-psychotics
- (c) Anti-manics
- (d) Anti-epileptics

10. Toxic dose of lithium is:

- (a) 0.6 mEq/L
- (b) 1.2 mEq/L
- (c) 2.0 mEq/L
- (d) <0.6 mEq/L

11. Most effective non habit forming sedative is:

- (a) Lorazepam
- (b) Zolpidem
- (c) Flurazepam
- (d) Trazadone

12. Which drug is used for pain control in cancer patients?

- (a) Pethidine
- (b) Fentanyl
- (c) Methadone
- (d) Remifentanyl

13. Drug of choice for infantile spasms in a patient with tuberous sclerosis is:

- (a) Vigabatrin
- (b) Tiagabine
- (c) Lamotrigine
- (d) Levetiracetam

14. Weight gain caused by antipsychotics is due to antagonism of:

- (a) 5 HT₃
- (b) 5 HT_{2A}
- (c) 5 HT_{2B}
- (d) 5 HT_{2C}

15. Drug of choice for absence seizure is:

- (a) Clonazepam
- (b) Diazepam
- (c) Phenytoin
- (d) Valproate

16. All of the following are side effect of ropinirole except:

- (a) Sedation
- (b) Nausea
- (c) Retroperitoneal Fibrosis
- (d) Hallucination

17. Antiparkinson drug known to cause cardiac valvular fibrosis is:
 - (a) Levo-dopa
 - (b) Ropinirole
 - (c) Pramipexole
 - (d) Pergolide
18. The effect of morphine which has least tolerance is?
 - (a) Analgesis
 - (b) Respiratory depression
 - (c) Constipation
 - (d) Bradycardia
19. Valproic acid causes all except:
 - (a) It is an enzyme inducer
 - (b) It causes obesity
 - (c) It causes hepatotoxicity
 - (d) It causes neural tube defects
20. Regarding phenytoin, all of the following are correct except:
 - (a) It acts on voltage sensitive neuronal Na⁺ channels
 - (b) Used by slow IV injection in status epilepticus
 - (c) Kinetics change from 1st order to zero order over therapeutic range
 - (d) It inhibits microsomal enzymes
21. Drug of choice in lithium induced polyuria is:
 - (a) Amiloride
 - (b) Demeclocycline
 - (c) Thiazide diuretics
 - (d) Indomethacin
22. Not true about fosphenytoin is:
 - (a) Used for GTCS
 - (b) Prodrug of phenytoin
 - (c) Lipid soluble
 - (d) Highly protein bound
23. Which of the following is not a SSRI?
 - (a) Escitalopram
 - (b) Sertraline
 - (c) Paroxetine
 - (d) Amitriptyline
24. Opioid that activates monoamine action is:
 - (a) Tramadol
 - (b) Pentazocine
 - (c) Pethidine
 - (d) Meperidine
25. Antagonist of benzodiazepine is:
 - (a) Naltrexone
 - (b) Flumazenil
 - (c) Naloxone
 - (d) N-Acetyl-cysteine
26. All are dopaminergic agonists used for Parkinsonism except:
 - (a) Bromocriptine
 - (b) Ropinirole
 - (c) Pramipexole
 - (d) Selegiline
27. Drug with both antidepressant and antipsychotic properties is:
 - (a) Buspirone
 - (b) Amoxapine
 - (c) Trazodone
 - (d) Mianserin
28. Which of the following drug does not affect GABA_A gated chloride channel?
 - (a) Muscimol
 - (b) Alcohol
 - (c) Picrotoxin
 - (d) Buspirone
29. Emergence delirium is characteristic of:
 - (a) Midazolam
 - (b) Ketamine
 - (c) Thiopentone
 - (d) Opioids
30. Which of the following drugs does not possess even slightest agonist action?
 - (a) Buprenorphine
 - (b) Butorphanol
 - (c) Nalbuphine
 - (d) Nalmefene
31. All of the following are side effects of valproic acid, except:
 - (a) Alopecia
 - (b) Hepatitis
 - (c) Nephrotoxicity
 - (d) Skin rashes
32. Methadone is used in the management of opioid addiction because:
 - (a) Its analgesic activity is less than that of morphine
 - (b) It is an opioid receptor antagonist
 - (c) It is not addictive
 - (d) It is longer acting and causes milder withdrawal symptoms
33. The specific antidote for benzodiazepine poisoning is:
 - (a) Naloxone
 - (b) Flumazenil
 - (c) Fomepizole
 - (d) Pralidoxime
34. Fomepizole is a selective antidote for poisoning with:
 - (a) MAO inhibitors
 - (b) Ethyl alcohol
 - (c) Methyl alcohol
 - (d) Tricyclic antidepressants
35. Which one of the following drug is effective in painful tingling sensation due to diabetic neuropathy:
 - (a) Aspirin
 - (b) Ibuprofen
 - (c) Gabapentin
 - (d) Tramadol

36. Morphine is used in the treatment of which one of the following:
- Asthma
 - Kyphoscoliosis
 - Chronic cor pulmonale
 - Left ventricular failure
37. The drug of choice in obsessive compulsive disorder is which one of the following:
- Sertraline
 - Amoxapine
 - Hydroxyzine
 - Alprazolam
38. Drug of choice for tonic-clonic seizures is:
- Sodium valproate
 - Carbamazepine
 - Phenobarbitone
 - Felbamate
39. All of the following may be used for detoxification therapy of chronic alcoholism except:
- Naltrexone
 - Disulfiram
 - Flumazenil
 - Acamprostate
40. Which of the following anti-Parkinson drugs has the potential to cause retro peritoneal fibrosis:
- Pramipexole
 - Entacapone
 - Bromocriptine
 - Ropinirole
41. Which of the following is the treatment of choice for patients with schizophrenia, who refuse to take treatment:
- Clozapine
 - Thioridazine
 - Olanzapine
 - Fluphenazine
42. Hallucinations, psychosis, hypertension and tachycardia are adverse effects typically associated with which of the following narcotics:
- Morphine
 - Meperidine
 - Pentazocine
 - Buprenorphine
43. The drug of choice for status epilepticus is:
- Propofol
 - Lorazepam
 - Thiopentone
 - Haloperidol
44. Drug of choice for treatment of absence seizures is:
- Phenytoin
 - Valproate
 - Ethosuximide
 - Carbamazepine
45. Gabapentin has which mechanism of action for its antiepileptic effect?
- Inhibits monoamine oxidase
 - Blocks the re-uptake of neurotransmitters
 - Increase the release of neurotransmitters
 - Block Na⁺ channels
46. A 20 years old female with generalized tonic clonic epilepsy is well controlled of Tab. phenytoin 300 mg/day, becomes pregnant. Pick the correct advise you would give her:
- Stop Phenytoin + start Phenobarbitone and Folic acid
 - Stop Phenytoin + start Lamotrigine and Folic acid
 - Stop Phenytoin + start Magnesium infusion
 - Continue with Phenytoin and add Tab. Folic acid and during the last 2 weeks of pregnancy give oral Vitamin K too
47. Which is the drug of choice for maintenance therapy in uncomplicated bipolar disorder?
- Sodium valproate
 - Carbamazepine
 - Lithium
 - Lamotrigine
48. A 25 years old male started taking antipsychotic (haloperidol) since last three days. He presented to the emergency department with protruded tongue, breathing difficulty along with spasm of neck and jaw muscles. What could be the most likely diagnosis:
- Drug hypersensitivity reaction
 - Acute dystonia
 - Neuroleptic malignant
 - Tardive dystonia
49. Neuroleptic malignant syndrome is characterized by:
- Hypothermia
 - Labile blood pressure
 - Bradycardia
 - Flaccidity
50. Features of opioid intake are all of the following except:
- Feeling of relaxation
 - Euphoria
 - Analgesia
 - Dilated pupils
51. Administration of which antiepileptic drug is associated with development of hyperkinesia in children:
- Phenytoin sodium
 - Sodium valproate
 - Carbamazepine
 - Phenobarbitone
52. One of the following is not true about melatonin:
- Induces sleep
 - Used in treatment of jet lag syndrome
 - Is secreted by pituitary
 - Is a pineal hormone

53. Which drug is the most useful in treating an episode of antipsychotic induced acute dystonia:
- Lorazepam
 - Haloperidol
 - Promethazine
 - Phenobarbitone
54. All of the following are CNS stimulants except:
- Amphetamines
 - Benzodiazepines
 - Cocaine
 - Methylphenidate
55. The disulfiram alcohol reaction occurs due to inhibition of which enzyme:
- Alcohol reductase
 - Alcohol dehydrogenase
 - Aldehyde reductase
 - Aldehyde dehydrogenase
56. Schizophrenia is treated by:
- Anti depressants
 - Anti psychotics
 - Anti epileptics
 - Mood stabilizers
57. Antidote of choice in acute benzodiazepine toxicity is:
- Flunitrazepam
 - Naloxone
 - Forced alkaline diuresis
 - Flumazenil
58. Drug of choice for MDP is:
- Lithium
 - Diazepam
 - Olanzapine
 - Carbamazepine
59. The toxicity of methyl alcohol is due to:
- Formic acid
 - Ethanol
 - Methanol itself
 - All of the above
60. Extrapyramidal symptoms are seen with the use of:
- Metoclopramide
 - Domperidone
 - Prolactin
 - All of the above
61. Drug of choice in drug induced Parkinsonism is:
- Levodopa
 - Carbidopa
 - Amantadine
 - Benzhexol
62. Which of the following analgesics should not be given in acute MI?
- Methadone
 - Morphine
 - Buprenorphine
 - Pentazocine
63. Which of the following is not an antidepressant?
- Amitriptyline
 - Fluoxetine
 - Imipramine
 - Chlorpromazine
64. Drug of choice for obsessive compulsive disorder is:
- Clozapine
 - Alprazolam
 - Amoxapine
 - Fluoxetine
65. Drug of choice for prophylaxis of mania is:
- Lithium
 - Haloperidol
 - Clozapine
 - Carbamazepine
66. GABA transmission is facilitated by:
- Vigabatrin
 - Carbamazepine
 - Phenytoin
 - Buspirone
67. Which of the following drugs is not used for anxiety?
- Propanolol
 - Alprazolam
 - Buspirone
 - Haloperidol
68. Derivative of morphine used for diarrhea is:
- Oxymorphone
 - Diphenoxylate
 - Pethidine
 - Codeine
69. Which of the following is a short acting benzodiazepine?
- Diazepam
 - Flurazepam
 - Lorazepam
 - Chlordiazepoxide
70. Drug of choice for myoclonic seizures is:
- Valproic acid
 - Phenytoin
 - Ethosuximide
 - Carbamazepine
71. Drug of choice for schizophrenia is:
- Olanzapine
 - Haloperidol
 - Lithium
 - Chlorpromazine
72. Drugs which can be used to treat mania in ICU are all except:
- Carbamazepine
 - Lithium
 - Diazepam
 - Lorazepam
73. Fomepizole is antidote of:
- Mushroom poisoning
 - Benzodiazepine poisoning
 - Ethylene glycol poisoning
 - Organophosphorus poisoning

EXPLANATIONS

1. **Ans. (d) 30 minute** (Ref: Goodman and Gilman 12/e p469)

Duration of action of flumazenil is 30-60 min. So the best answer seems to be 30 min.

2. **Ans. (c) High addiction liability** (Ref: Katzung 11/e p374)

- Ramelteon is non-addictive drug. For details, see text

3. **Ans. (b) It may be used to treat barbiturate poisoning.** (Ref: Katzung 11/e p382-383; KDT 6/e p399-400)

Flumazenil is a specific antagonist of benzodiazepine receptors. It can be used to treat BZD poisoning but not barbiturate poisoning.

4. **Ans. (a) Flumazenil** (Ref: K.D.T. 6/e p399-400 & 5th/362)

5. **Ans. (c) Redistribution** (Ref: Katzung 10/e p407; KDT 6/e p374)

Thiopentone is highly lipid soluble drug. On i.v. administration, it quickly reaches the brain and cause anaesthesia. But due to high lipid solubility, it again crosses the membranes of brain and diffuses to other tissues like fat and muscle. As it is not present in brain, its action is terminated. This is known as re-distribution.

6. **Ans. (d) Diazepam** (Ref: KDT 6/e p450)

Benzodiazepines which are short acting and not metabolized by liver include:

S: Short acting BZD

T: Triazolam, Temazepam

O: Oxazepam

L: Lorazepam

E: Estazolam

7. **Ans. (c) Beta carboline** (Ref: KDT 6/e p395)

8. **Ans. (c) Zolpidem** (Ref: KDT 6/e p398)

9. **Ans. (b) Acute intermittent porphyria** (Ref: KDT 6/e p392)

Barbiturates induce the rate limiting enzyme 'δ-aminolaevulinic acid synthase' in porphyrin synthesis. This increased synthesis of porphyrins can precipitate acute attack of AIP.

10. **Ans (d) Promethazine** (Ref: Katzung 10/e p352, 353, 354; 11/e p377)

11. **Ans. (d) Midazolam; (e) Pethidine** (Ref: Harrison 17/e p2439; KDT 6/e p392, CMDT-2014/1609)

12. **Ans. (c) Diazepam causes lesser respiratory depression than midazolam; (d) Nitrazepam is metabolized in liver** (Ref: KDT 6/e p393-394; Har' 2545)

- Benzodiazepines act on BZD receptors of GABA_A-BZD receptor-chloride channel complex and increase the frequency of Cl⁻ channel opening GABA facilitatory action. Thus these are not GABA agonists.
- Coma, respiratory depression though rare, can occur with ultra short acting agents-like midazolam, triazolam.
- The dependence producing liability of BZDs is low. They are seldom used alone. Agents that are absorbed rapidly and are lipid soluble such as midazolam, have rapid onset of action and higher abuse potential.
- Diazepam has rapid onset of action but prolonged action due to formation of active metabolites.
- Benzodiazepines like nitrazepam, flurazepam, etc. are metabolised in liver by dealkylation and hydroxylation.

13. **Ans. (b) Flumazenil** (Ref: KDT 6/e p395)

14. **Ans. (b) Glycine** (Ref: KDT 6/e p469)

- GABA is the principal inhibitory neurotransmitter in the brain and glycine is the inhibitory amino acid in the spinal cord.
- By antagonizing the glycine receptors, strychnine can result in convulsions and other stimulatory symptoms.

15. **Ans. (c) Alkalinization of the urine will accelerate the elimination of phenobarbital** (Ref: KDT 6/e p391, 394)

- Barbiturates are acidic drugs. These are ionized in the alkaline urine and thus cannot be reabsorbed. Alkalinization of urine can be used to accelerate the elimination of barbiturates in poisoning.
- Other differences between benzodiazepines and barbiturates include.

Benzodiazepines	Barbiturates
GABA facilitatory	GABA mimetic as well as facilitatory
Increase frequency of opening of Cl ⁻ channels	Increase duration of opening of Cl ⁻ channels.
Less addictive potential	Highly addictive
Less toxic due to flat DRC	Highly toxic due to steep DRC
Specific antidote flumazenil is present	No specific antidote
No drug interactions	Decrease the half-life of many drugs due to microsomal enzyme inducing property.

16. **Ans. (c) They increase the frequency of opening of chloride ion channels that are coupled to GABA_A receptors** (Ref: KDT 6/e p394)

17. **Ans. (c) Midazolam** (Ref: KDT 6/e p399, 400)

Flumazenil is an antagonist of benzodiazepine receptors and is used to prevent respiratory depression due to benzodiazepines (like midazolam).

18. **Ans. (c) Melatonin** (Ref: KDT 6/e p400)

19. **Ans. (d) Zaleplon** (Ref: KDT 6/e p398)

- Zolpidem, zaleplon and zopiclone are agonists at BZD receptors.
- These are hypnotic drugs that lack muscle relaxant and anticonvulsant actions.
- These have negligible effect on REM sleep and do not affect sleep architecture.

20. **Ans. (d) Triazolam** (Ref: KDT 7th/405)

Triazolam is a very potent BZD with ultra rapid elimination. Some cases of paranoia and psychiatric disturbances have been noted with this drug.

21. **Ans. (b) Conjugated directly** (Ref: Katzung 6/e p450)

Lorazepam and oxazepam are the benzodiazepines which are excreted from the body by glucuronide conjugation without phase 1 metabolism in the liver. So these can be used safely in hepatic dysfunction.

22. **Ans. (a) Thiopentone** (Ref: KDT 6/e p375)

Barbiturates are contra-indicated in acute intermittent porphyria.

23. **Ans. (d) Antagonist** (Ref: KDT 6/e p395)

24. **Ans. (c) They are weakly acidic and do not ionise in stomach** (Ref: KDT 6/e p12-13)

Barbiturates and salicylates are maximally absorbed in stomach because these are weakly acidic and do not ionize in stomach.

25. **Ans. (c) Oxazepam** (Ref: KDT 6/e p450)

26. **Ans. (a) Midazolam** (Ref: Goodman and Gilman 11/e p411)

27. **Ans. (b) β IFN** (Ref: Harrison 18th/3405, Goodman and Gilman 12th/1026)

The preferred drugs for different type of multiple sclerosis (MS) are

For acute attacks	:	Methylprednisolone pulse therapy
For reducing recurrences in relapsing remitting MS	:	IFN-beta and glatiramer
For resistant cases	:	Natalizumab

28. **Ans. (d) Natalizumab** (Ref: Harrison 18th/3402-3406, Goodman and Gilman 12th/1026)

The statement 'only drug effective in improving EDSS' seems to be wrong because many drugs have shown to reduce disease severity on EDSS scores. Expanded disability status score (EDSS) is a scoring system for MS where high score means worsening neurological dysfunction. Maximum reduction in EDSS is seen in natalizumab group.

29. Ans. (d) Mycophenolate mofetil (Ref: Harrison 18th/3406-3408)

FDA approved therapies for multiple sclerosis include:

- Interferon beta-1a
- Interferon beta-1b
- Glatiramer
- Natalizumab
- Fingolimod
- Mitoxantrone
- Methylprednisolone

30. Ans. (b) Rotigotine (Ref: Katzung 11/e p475)

- **Rotigotine** is a non-ergot dopamine agonist indicated for the treatment of Parkinson's disease (PD) and restless legs syndrome (RLS). It is formulated as a once-daily transdermal patch which provides a slow and constant supply of the drug over the course of 24 hours. However, it was withdrawn in 2008 because of crystal formation on the patches, affecting the bioavailability and efficacy of this drug.

31. Ans. (c) Tricyclic antidepressants (Ref: Katzung 11/e p524; CMDT-2010/987)

- Rivastigmine is used in Alzheimer's disease. It inhibits acetylcholinesterase and increases the level of ACh.
- Tricyclic antidepressants have strong anticholinergic actions. Therefore, these can reduce the efficacy of rivastigmine.
- Depression is commonly seen in patients with Alzheimer's disease. The anti-depressants that are used should have minimum anticholinergic activity, therefore SSRI or MAO-inhibitors are preferred.

32. Ans. (a) It is more potent than penicillamine (Ref: Katzung 11/e p482; Parkinson's disease & movement disorders by Joseph Jankovic/264, Harrison 17/e p2451)

- Penicillamine is the most potent chelating agent useful in Wilson's disease.
- Trientine is not as potent as penicillamine and was used in patients unable to tolerate penicillamine. However, now a days, trientine is preferred because of severe adverse effects of penicillamine.
- Trientine cause fewer adverse effects other than mild anemia due to iron deficiency in few patients.
- Concomitant administration with iron reduces absorption of both. Thus minimum gap of two hours should be given between the administration of trientine and iron salts.

33. Ans. (c) Entacapone (Ref: Katzung 10/e p448-449; KDT 6/e p421)

Levo-dopa is metabolized in the body by two enzymes; MAO and COMT. Thus MAO inhibitors like selegiline and COMT inhibitors like entacapone and tolcapone can increase the bioavailability of dopa.

34. Ans. (d) Domperidone blocks levodopa induced emesis and its therapeutic potential (Ref: KDT 6/e p418)

- Domperidone decreases the vomiting due to levo-dopa without interfering with its therapeutic action. Because domperidone can not cross BBB, it does not inhibit the D₂ receptors in the brain but as CTZ is present outside BBB, it can inhibit the emetogenic potential of levo-dopa.
- L-dopa is a prodrug that acts by conversion to dopamine in the brain.
- Phenothiazines and other D₂ blockers that can cross BBB will interfere with therapeutic actions of levo-dopa.
- Pyridoxine decreases the efficiency of L-dopa therapy as discussed earlier.

35. Ans. (d) Decreased efficiency will result (Ref: KDT 6/e p418)

36. Ans. (a) Parkinson's disease (Ref: KDT 6/e p419)

Ropinirole is a non-ergot dopamine agonist useful for Parkinsonism. It is also used these days for restless leg syndrome.

37. Ans. (c) Amantadine is more effective than levo-dopa (Ref: KDT 6/e p415)

Levo-dopa is very effective in the treatment of Parkinsonism. It initially resolves hypokinesia and rigidity but later on tremors are also reduced. It is more effective than amantadine. Amantadine is an antiviral drug that can be used in Parkinsonism. Central anticholinergic drugs are the agents of choice for the treatment of drug induced Parkinsonism.

38. Ans. (a) Levodopa; (c) Bromocriptine; (e) Benserazide (Ref: KDT 6/e p415)

- **Levodopa, bromocriptine and benserazide** are used in Parkinsonism.
- **Mazindol** is a potent **anorectic** agent. It has an additional peripheral effect of increasing metabolic rate.
- **Acyclovir** is an antiviral agent, not used in parkinsonism.

39. Ans. (b) Phenothiazine; (c) Haloperidol (Ref: KDT 6/e p431)

40. Ans. (b) Decreases formation of 3-OMD (Ref: KDT 6/e p421)

- Levo-dopa is converted to dopamine by dopa decarboxylase (that cannot cross blood brain barrier).
- Carbidopa is an inhibitor of dopa decarboxylase in the periphery. It therefore increases the amount of l-dopa that reaches the brain (due to inhibition of peripheral metabolism to dopamine).
- Due to inhibition of l-dopa metabolism (by dopa decarboxylase), an alternative pathway of metabolism by catechol-o-methyl transferase (COMT) is activated.
- COMT metabolizes l-dopa to 3-o-methyl dopa (3-OMD) that can compete with l-dopa for entry in the brain.
- Entacapone and tolcapone is useful in Parkinsonism by inhibiting COMT.

41. Ans. (a) Involuntary movements (Ref: KDT 6/e p419)

Carbidopa can decrease all the adverse effects of levodopa except

- Involuntary movements
- Behavioural effects

42. Ans. (a) Pramipexole (Ref: KDT 6/e p419, 420)

Directly acting D₂ receptor agonists can be

- Ergot derivatives e.g. bromocriptine and pergolide
- Non-ergot compounds e.g. pramipexole and ropinirole

43. Ans. (c) It is a cerebroselective anticholinesterase that affords symptomatic improvement in Alzheimer's disease (Ref: KDT 6/e p472, 473)

44. Ans. (d) All of the above (Ref: KDT 6/e p419, 420)

Pramipexole and ropinirole are newer non-ergot dopamine agonists. Now, these are first choice drugs for the treatment of Parkinsonism (preferred over levo-dopa).

45. Ans. (d) Catechol-o-methyl transferase inhibition (Ref: KDT 6/e p415)

46. Ans. (d) Reserpine (Ref: KDT 6/e p549)

- Neurotransmitters (like dopamine, serotonin and adrenaline) are stored in the vesicles after their synthesis. These stores of neurotransmitters are released on stimulation of the neuron. Reserpine inhibits the vesicular transport of these neurotransmitters resulting in depletion of dopamine, serotonin and adrenaline.
- Severe depression (due to deficiency of serotonin) leading to suicidal tendencies and extrapyramidal symptoms (due to deficiency of dopamine in the brain) are the adverse effects of this drug.

47. Ans. (b) Vitamin B complex (Ref: KDT 6/e p418, 419)

- Pyridoxine is a component of vitamin B complex.
- Pyridoxine is a cofactor for the enzyme, dopa decarboxylase and therefore, administration of vitamin B complex can stimulate the activity of this enzyme.
- Dopa decarboxylase converts levo-dopa to dopamine. Increased formation of dopamine in the periphery is undesirable because it cannot cross blood brain barrier. Therefore, stimulation of dopa decarboxylase decreases the therapeutic effect of l-dopa.
- If the enzyme, dopa decarboxylase is already inhibited with carbidopa, there will be no interaction with pyridoxine.

48. Ans. (c) Vitamin B complex (Ref: KDT 6/e p418)

49. Ans. (b) Benzhexol (Ref: KDT 6/e p421)

Central anticholinergics like trihexy phenidyl (Benzhexol) are the only drugs effective in drug induced Parkinsonism.

50. Ans. (c) Pyridoxine (Ref: KDT 6/e p418)

Pyridoxine abolishes therapeutic effect of levodopa by enhancing peripheral decarboxylation of levodopa, less is available to cross to the brain.

51. Ans. (a) Tacrine (Ref: KDT 6/e p472)

52. Ans. (c) Ropinirole (Ref: KDT 6/e p472)
53. Ans. (d) To increase crossing of L-Dopa through BBB (Ref: KDT 6/e p418-419)
54. Ans. (d) Piracetam (Ref: KDT 6/e p473)
Nootropic drugs are those that enhance memory. Piracetam is used for this function in patients with head injury.
55. Ans. (a) Centrally acting reversible anticholinesterase (Ref: KDT 6/e p102)
56. Ans. (a) Entacapone (Ref: KDT 6/e p421)
57. Ans. (c) COMT inhibitors prolong the action of L-dopa (Ref: KDT 6/e p421)
58. Ans (a) Amantadine (Ref: KDT 6/e p421)
59. Ans (a) Riluzole (Ref: KDT 6/e p464-465)
60. Ans. (c) Decrease in antidiuretic hormone (Ref: KDT 7/e p416)
- Carbamazepine like other antiepileptic drugs is teratogenic.
 - It can cause neurotoxicity manifested as dizziness, sedation, vertigo, diplopia and ataxia
 - It can result in hypersensitivity reactions like rash, photosensitivity, hepatitis and rarely agranulocytosis
 - It increases the release of ADH from the hypothalamus and thus can result in dilutional hyponatremia particularly in elderly people.
61. Ans. (a) Levetiracetam (Ref: KDT 7/e p421)
- Levetiracetam, lamotrigine, valproate and topiramate are useful in myoclonic epilepsy. Valproate should be avoided in pregnancy.
 - Vigabatrin has no role in this condition whereas carbamazepine and phenytoin are contra-indicated in myoclonic epilepsy.
62. Ans. (d) Lamotrigine mainly acts by causing GABA mediated Cl^- channel opening (Ref: Goodman Gilman 12th/600)
Lamotrigine mainly acts by inhibiting Na^+ and prolonging their recovery from inactivated state. It can also increase GABA-ergic activity, decrease glutamatergic activity and block Ca^{2+} channels.
63. Ans. (d) Oxcarbazepine (Ref: Harrison 18th/3262)
- Carbamazepine and oxcarbazepine (related drug), phenytoin, lamotrigine and topiramate are currently the drugs of choice approved for the initial treatment of partial seizures, including those that secondarily generalize. Overall they have very similar efficacy, but differences in pharmacokinetics and toxicity are the main determinants for use in a given patient.
 - Oxcarbazepine has the advantage of being metabolized in a way that avoids an intermediate metabolite associated with some of the side effects of carbamazepine. Oxcarbazepine also has fewer drug interactions than carbamazepine.
64. Ans. (a) Depression of deep tendon reflexes (Ref: Drug Facts and Comparisons 2010/127, Williams Obstetrics/737)
- Knee jerk (patellar reflex) starts diminishing at plasma magnesium concentration of 4mEq/L and disappears at 10mEq/L, where respiratory paralysis is a potential hazard.
65. Ans. (a) Her decision is wrong, as the risk of teratogenicity was the highest in the first trimester (Ref: Goodman and Gilman 12th/1846)
- Teratogenicity of drugs is maximum in the first trimester during the period of organogenesis.
 - Anti-epileptic drugs should not be stopped during pregnancy
 - The risk of congenital malformations is more if polytherapy is used as compared to single drugs.
66. Ans. (c) Carbamazepine (Ref: Katzung 11/e p418)
- 'Carbamazepine and phenytoin can aggravate juvenile myoclonic epilepsy'
- Drugs useful for myoclonic seizures are:
- Valproic acid (Drug of choice)
 - Benzodiazepines
 - Zonisamide
 - Levetiracetam
 - Topiramate
 - Lamotrigine

67. Ans. (a) Phenytoin (Ref: Katzung 11/e p419)

68. Ans. (d) Cerebellar degeneration occurs on long-term administration (Ref: Katzung 11/e p404-405; CMDT-2010/1431)

- Phenytoin is an anticonvulsant drug that follows zero-order kinetics (also known as saturation kinetics).
- Anti-seizure action of phenytoin depends on plasma concentration. Therapeutic plasma level for most of the patients is 10-20 µg/ml.
- Phenytoin is one of the first non-sedative anti-seizure drugs. It causes CNS depression only at considerably higher levels.
- Phenytoin induced cerebellar degeneration occur at toxic plasma concentration and not necessarily on long-term use.

69. Ans. (b) Absence seizures (Ref: Katzung 11/e p413)

- Ethosuximide is a narrow spectrum anti-epileptic drug mainly used for absence seizures.

70. Ans. (a) It follows zero order kinetics (Ref: Katzung 11/e p404-405; KDT 6/e p403-405)

Phenytoin follows zero order kinetics at therapeutic plasma concentration. Other drugs following zero order kinetics are warfarin, alcohol, aspirin, theophylline and tolbutamide.

- Phenytoin is a powerful microsomal enzyme inducer.
- Phenytoin is metabolized to inactive products by liver.
- Use of phenytoin during pregnancy can cause Fetal hydantoin syndrome characterized by hypoplastic phalanges, cleft lip, cleft palate and microcephaly. It occurs due to a metabolite of phenytoin, arene oxide.

71. Ans. (b) Magnesium sulphate (Ref: CMDT-2010/718)

Prevention of seizures in severe pre-eclampsia and treatment of seizures in eclampsia is done by magnesium sulphate.

72. Ans. (d) Osteomalacia (Ref: Goodman & Gilman 10/e p386-88; KDT 6/e p405-407)

- Osteomalacia is not a side effect of sodium valproate. However, phenytoin on the other hand can cause this problem.
- Other side effects include weight gain, tremors, fulminant hepatitis and polycystic ovarian disease.

73. Ans. (a) Used in trigeminal neuralgia (Ref: K.D.T. 6/e p406-407)

- Carbamazepine is the drug of choice for trigeminal neuralgia and focal seizures.
- Carbamazepine has the ability to induce microsomal enzymes.
- The most common dose related adverse effects of carbamazepine are *diplopia* and *ataxia*. It may also cause *hyponatremia* and *water intoxication*. One more important adverse effect is idiosyncratic blood dyscrasias which may cause *aplastic anemia* and *agranulocytosis*.

74. Ans. (c) Valproate (Ref: Harrison 17/e p2511; K.D.T. 6/e p408)

75. Ans. (b) Flunarizine (Ref: KDT 6/e p172, 402)

Flunarizine is a weak CCB used for prophylaxis of migraine.

76. Ans. (a) Vigabatrin (Ref: KDT 6/e p410)

- Vigabatrin inhibits the metabolism of GABA by inhibition of GABA transaminase enzyme. It has no effect on Na⁺ channels.

77. Ans. (a) Phenytoin (Ref: KDT 6/e p404, 405)

78. Ans. (b) MCV should be estimated (Ref: KDT 6/e p405)

Phenytoin can induce folate deficient megaloblastic anemia that can be diagnosed by measuring MCV.

79. Ans. (d) Sodium valproate (Ref: Harrison 18th/3263-64)

Among the given options, only sodium valproate can be used for myoclonic seizures. Carbamazepine and phenytoin can worsen these seizures whereas phenobarbitone is not effective. However, these days preferred drug is lorazepam.

80. Ans. (b) At very low doses, zero order kinetics occurs (Ref: Katzung 10/e p375, 376, 377, 378)

- Phenytoin follows saturation kinetics (kinetics changes from first order to zero order within therapeutic concentrations). Zero order kinetics are seen at high doses.
- It is also a potent enzyme inducer and can increase the metabolism of various drugs.
- It is 80-90% plasma protein bound.

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81. **Ans. (c) Topiramate** (Ref: KDT 6/e p410)
- Antiepileptic drugs causing weight gain are valproic acid, carbamazepine, oxcarbazepine, gabapentin and vigabatrin
 - Topiramate causes weight loss. It has recently been approved for treatment of obesity.
82. **Ans. (d) Tiagabine** (Ref: KDT 6/e p410)
- Tiagabine is an inhibitor of GAT-1 (GABA-transporter).
83. **Ans. (d) Megaloblastic anemia** (Ref: KDT 6/e p405)
- Phenytoin can cause folic acid deficiency resulting in megaloblastic anemia. This is confirmed by raised MCV and MCH in the blood examination.
84. **Ans. (c) Shift to sodium valproate** (Ref: KDT 6/e p411)
- Hypersensitivity reaction to a drug mandates its discontinuation. Phenytoin is being used for control of GTCS. Valproate can be substituted for phenytoin because it is equally effective against GTCS. Ethosuximide is useful only against absence seizures whereas clonazepam is used to control acute attacks only. Therefore, best course is to change the drug from phenytoin to valproate.
85. **Ans. (c) Hypercalcemia** (Ref: KDT 6/e p405)
- Phenytoin causes osteomalacia and results in hypocalcemia not hypercalcemia.
86. **Ans. (a) Phenytoin** (Ref: KDT 6/e p404, 405)
87. **Ans. (b) Zonisamide – Ca²⁺ channel blocker; (c) Carbamazepine – Na⁺ channel blocker** (Ref: Katzung 11/e p412; KDT 6/e p404)
- Gabapentin acts by increasing the release of GABA from presynaptic neuron.
 - Tiagabine inhibits reuptake of GABA.
 - Zonisamide inhibits T-type Ca²⁺ channels.
 - Carbamazepine and phenytoin inhibits Na⁺ channels and prolongs the inactivated state.
 - Lamotrigine has no action on NMDA receptors but inhibits the AMPA and kainite receptors.
88. **Ans. (e) Nystagmus** (Ref: KDT 6/e p405)
- In toxic doses, phenytoin produces cerebellar symptoms like nystagmus.
 - Other adverse effects like gum hypertrophy, hirsutism, hypersensitivity, hyperglycemia, osteomalacia, megaloblastic anemia and fetal hydantoin syndrome are seen in the normal doses, with prolonged use.
89. **Ans. All** (Ref: Katzung 11/e p244)
- Mg⁺⁺ is used in **Eclampsia and Eclamptic seizure**. It may prevent seizure by interacting with NMDA receptors.
 - Magnesium is used for ventricular tachycardia and Torsades de pointes. It is also used in tetany due to magnesium deficiency.
 - Mg can be used in acute severe asthma in the dose of 2g iv over 20 minutes. (CMDT 2010, 233)
90. **Ans. (b) 10-19 µg/ml** (Ref: Katzung 11/e p404)
- The therapeutic level of phenytoin is 10-20 micro g/ml.
91. **Ans. (b) Sodium-valproate; (c) Lamotrigine** (Ref: KDT 6/e p411)
92. **(a) Gum hypertrophy** (Ref: KDT 6/e p405)
93. **Ans. (d) Visual disturbances can occur** (Ref: KDT 6/e p410)
- Vigabatrin act by inhibiting the enzyme GABA transaminase (involved in breakdown of GABA).
 - It is used for the treatment of partial and generalized seizures. It is also used to treat infantile spasms.
 - Visual disturbances are very important adverse effect of this agent.
94. **Ans. (c) Capacity limited metabolism saturating at higher therapeutic concentration range** (Ref: KDT 6/e p404)
- Phenytoin follows zero order kinetics at high plasma concentration due to saturation of metabolic pathways.
95. **Ans. (a) Ataxia** (Ref: KDT 6/e p404, 405)
- Cerebellar dysfunction (ataxia, nystagmus and vertigo) is seen at toxic plasma concentrations whereas hirsutism and gum hyperplasia is seen at therapeutic concentrations (but on prolonged use).
96. **Ans. (b) Ethosuximide** (Ref: KDT 6/e p406, 407)
- Ethosuximide is useful only in the treatment of absence seizures (petit mal epilepsy).
 - Valproic acid and lamotrigine are broad spectrum antiepileptic drugs.

97. **Ans. (a) Hepatitis** (Ref: KDT 6/e p407)
Sodium valproate is contra-indicated in children less than 3 years due to risk of hepatitis.
98. **Ans. (c) Rectal Diazepam** (Ref: KDT 6/e p409)
Diazepam is the drug of choice for febrile convulsions. It is administered intravenously. If i.v. access is not possible, rectal diazepam can be used.
99. **Ans. (c) It is a broad spectrum antiepileptic drug** (Ref: KDT 6/e p409)
100. **Ans. (a) Intravenous diazepam** (Ref: KDT 6/e p413)
- Benzodiazepines like diazepam and lorazepam are fast acting anti-seizure drugs and can be used to abort the seizures in status epilepticus.
 - Lorazepam is the drug of choice for status epilepticus.
101. **Ans. (c) Lamotrigine** (Ref: KDT 6/e p409, 410)
102. **Ans. (c) Clonazepam** (Ref: KDT 6/e p411, 412)
- Diagnosis of the patient is petit mal epilepsy (absence seizures). Drugs effective against absence seizures are:
 - Ethosuximide
 - Valproate
 - Clonazepam
 - Lamotrigine
 - Clonazepam is a benzodiazepine that can cause sedation and tolerance.
103. **Ans. (d) Valproic acid** (Ref: Harrison 16/e p2367)
Diagnosis of this patient is generalized tonic clonic seizure (GTCS) or grand mal epilepsy. Drug of choice for this condition is valproic acid.
104. **Ans. (b) Gabapentin** (Ref: KDT 6/e p409, 410)
- Gabapentin and pregabalin act by increasing the release of GABA.
 - Gabapentin is the drug of choice for post-herpetic neuralgia and diabetic neuropathy.
105. **Ans. (a) Folic acid** (Ref: KDT 6/e p407, 591)
- Folic acid is administered to prevent the development of neural tube defects in the baby.
 - Risk of neural tube defects is increased with the use of valproic acid in pregnancy.
106. **Ans. (b) Hyponatremia** (Ref: Katzung 11/e p406)
Carbamazepine can cause hyponatremia and water intoxication at high doses. This adverse effect appears to be due to its ADH releasing property (resulting in dilutional hyponatremia). The same adverse effect can be utilized for treatment of diabetes insipidus.
107. **Ans. (a) Phenytoin** (Ref: Katzung 11/e p405)
Phenytoin on long term administration can lead to lymphadenopathy which is sometimes difficult to distinguish from malignant lymphoma. It is known as pseudolymphoma.
108. **Ans. (d) Prophylactic phenobarbitone** (Ref: Current Pediatrics diagnosis and treatment 18th/722,726)
Prophylactic phenobarbitone is indicated for atypical febrile seizures only
109. **Ans. (a) ACTH** (Ref: Katzung 11/e p418)
110. **Ans. (a) Hypoglycemia** (Ref: KDT 6/e p404-405)
- Phenytoin cause hyperglycemia.
111. **Ans. (a) Carbamazepine** (Ref: KDT 6/e p406)
112. **Ans. (b) Sodium Valproate** (Ref: KDT 6/e p411)
- Juvenile myoclonic epilepsy (also known as Janz syndrome) occurs in 12-18 years old children.
 - Valproic acid is drug of choice for this condition whereas carbamazepine can worsen it.
113. **Ans. (d) Valproic acid** (Ref: KDT 6/e p411)
114. **Ans. (b) Gynaecomastia** (Ref: KDT 6/e p404, 405)
115. **Ans. (b) Phenytoin** (Ref: KDT 5th/404, 405)

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116. Ans. (a) Sodium valproate (Ref: KDT 6/e p407)

- It acts by various mechanisms like increase in GABA, blockade of Na⁺ channels and inhibition of T-type Ca²⁺ currents. Valproate increases the formation of GABA (by stimulating glutamic acid decarboxylase) and inhibits the degradation of GABA (by inhibiting GABA transaminase and succinic semialdehyde dehydrogenase).
- Phenytoin and carbamazepine acts by affecting neuronal Na⁺ channels.
- Ethosuximide acts by affecting T-type Ca²⁺ currents.

117. Ans. (c) Diazepam (Ref: KDT 6/e p413)

118. Ans. (b) Sodium valproate (Ref: KDT 6/e p27, 408)

Most anticonvulsants are enzyme inducers except valproate (inhibitor).

119. Ans. (b) Phenytoin (Ref: Katzung 11th./405)

120. Ans. (d) Atropine (Ref: KDT 6/e p402)

121. Ans. (b) Phenytoin (Ref: KDT 6/e p405)

122. Ans. (c) Carbamazepine (Ref: KDT 6/e p412)

123. Ans. (a) Phenytoin (Ref: KDT 6/e p405)

124. Ans. (a) Vigabatrin (Ref: KDT 6/e p404)

125. Ans. (c) Sedation (Ref: KDT 6/e p403, 405)

126. Ans. (c) Carbamazepine and phenytoin (Ref: KDT 405)

127. Ans. (a) Carbamazepine (Ref: KDT 6/e p406)

Carbamazepine releases ADH and causes dilutional hyponatremia.

128. Ans. (a) Ataxia (Ref: KDT 6/e p404, 405)

129. Ans. (a) Valporate (Ref: KDT 6/e p407)

130. Ans. (a) Ethosuximide – K⁺ channel opener (Ref: KDT 6/e p407)

131. Ans. (d) All (Ref: KDT 6/e p591)

132. Ans. (a) Valporate (Ref: KDT 6/e p411)

133. Ans. (a) Antiepileptic drug (Ref: KDT 6/e p402)

134. Ans. (d) Phentermine (Ref: CMDT 2010/1137)

Phentermine was used for treatment of obesity. It decreases appetite and causes weight loss.

135. Ans. (c) Zonisamide (Ref: Goodman and Gilman 11/e p521)

136. Ans. (a) Rash (Ref: Katzung 11/e p409)

137. Ans. (d) Phenytoin (Ref: KDT 6/e p404, 405)

138. Ans. (d) Toxicity may occur with only small increment in dose (Ref: KDT 6/e p404,405)

139. Ans. (c) Valproic acid (Ref: KDT 6/e p407,408)

140. Ans. (c) Inter-nuclear ophthalmoplegia (Ref: K.D.T. 6/e p404-05)

141. Ans. (c) Doxycycline (Ref: K.D.T. 6/e p406, KK Sharma 2nd/527)

142. Ans. (c) Magnesium sulphate (Ref: Principles of pharmacology 1st/542)

143. Ans. (a) M₃ muscarinic receptors (Ref: KDT 7/e p459)

Anticholinergic adverse effects of TCAs include dry mouth, constipation, blurring of vision, urinary retention etc.

144. Ans. (b) Fluoxetine (Ref: Goodman and Gilman 12/e p411)

- All antidepressants including SSRIs and SNRIs can result in discontinuation syndrome. The symptoms of withdrawal include dizziness, headache, nervousness, nausea and insomnia.
- This withdrawal is more intense with paroxetine and venlafaxine because these are relatively short acting.
- This is unlikely with fluoxetine as it produces a very long acting metabolite.

145. Ans (c) SSRI (Ref: *Katzung 12th ed. Pg 533*)

Premenstrual syndrome (PMS) is a collection of emotional symptoms, with or without physical symptoms, related to a woman's menstrual cycle.

- SSRIs can be used to treat severe PMS. Fluoxetine and sertraline have been approved for this indication. Treating for 2 weeks out of a month in luteal phase may be as effective as continuous treatment. The rapid effects of SSRIs in PMS may be associated with rapid increases in pregnenolone levels.
- Hormonal contraception is commonly used as combined oral contraceptive pills and the contraceptive patch. This class of medication may cause PMS-related symptoms in some women, and may reduce physical symptoms in other women. They do not relieve emotional symptoms. Progesterone support has been used for many years but evidence of its efficacy is inadequate.

146. Ans (a) Fluphenazine (Ref: *Goodman Gilman 12th ed/424-426*)

- The common problem of medication nonadherence among schizophrenia patients has led to the development of long-acting injectable (LAI) antipsychotic medications, often referred to as depot antipsychotics.
- There are currently four available LAI forms

- Fluphenazine decanoate
- Haloperidol decanoate
- Risperidone-impregnated microspheres
- Paliperidone palmitate.

147. (c) Atropine sulphate should be administered as an antidote (Ref: *Katzung 12th/1034*)

Amitriptyline is a tricyclic antidepressant. It has anticholinergic properties and thus atropine cannot be used for treatment of its poisoning.

TRICYCLIC ANTIDEPRESSANT POISONING:

The presenting signs of a TCA overdose include cardiac arrhythmias, hypotension, and anticholinergic signs (hyperthermia, flushing, dilated pupils, intestinal ileus, urinary retention, and sinus tachycardia). Central nervous system involvement is also common.

Treatment

- Initial therapy consists of establishing airway and breathing, continuous electrocardiographic monitoring, **gastric lavage**, and the administration of activated charcoal.
- **Intravenous sodium bicarbonate** is the single most effective intervention for the management of TCA cardiovascular toxicity.
- **Lignocaine is the drug of choice for TCA-induced ventricular dysrhythmias.**
- **Diazepam** is the drug of choice in the management of acute-onset seizures. Phenytoin or phenobarbital may be used as second-line drugs.
- **Physostigmine**, a short-acting cholinesterase inhibitor, has been referred to as the antidote for TCAs because of its ability to increase cholinergic tone and reverse anticholinergic effects. It can, however, causes severe bradycardia, seizures, and asystole by overcompensating for cholinergic tone and suppressing supraventricular and ventricular pacemakers. As a result, physostigmine should only be used in patients with coma or those with convulsion or arrhythmias resistant to standard therapy.

148. Ans. (b) Blood level below 350 mg/ml should be maintained to avoid agranulocytosis (Ref: *Drug Facts and Comparisons 2006/1205-1206, Goodman Gilman 12th/427,432*)

High plasma concentration of Clozapine increases the risk of seizures (not agranulocytosis). However, usual plasma concentration required in many persons is 300-600 ng/ml.

- Clozapine is an atypical antipsychotic drug that has high potency to block 5HT₂ receptors as compared to D₂ receptors. However, it also blocks D₄ receptors, Muscarinic receptors, alpha receptors and H₁ receptors. It has high potency to block D₂ (Ki 160nM) as compared to D₁ (Ki 270nM) receptors.
- It should not be used with Carbamazepine due to two reasons:
 - Carbamazepine induces its metabolism and thus decreases the plasma concentration.
 - Carbamazepine has bone marrow suppressant action and can add to agranulocytosis caused by Clozapine.
- Clozapine should be started at low doses (12.5 mg) and gradually dose should be increased. Baseline WBC counts should be measured and then weekly counts should be done atleast for first 6 months. When WBC count becomes less than 3000/mm³ or absolute neutrophil count becomes less than 1500/mm³, Clozapine should be discontinued. After discontinuation, weekly WBC counts should be measured for additional 4 weeks.

- Patients discontinued for WBC count less than 2000/mm³ or absolute neutrophil count below 1000/mm³ should not be started on Clozapine again.

149. **Ans. (a) Doxepin** (*Ref: Katzung 11/e p519*)

- Serotonin and dopaminergic receptor blocking drugs are used for treatment of psychosis. Amisulpiride, sertindole and zotepine are antipsychotic drugs acting by this mechanism. On the other hand, doxepin is an antidepressant and do not block serotonin and dopaminergic receptors, rather it can inhibit the reuptake of serotonin and noradrenaline. It also has strong antihistaminic and anticholinergic property.

150. **Ans. (a) Imipramine** (*Ref: CMDT 2010/966*)

Imipramine is efficacious however, Desmopressin is the first choice drug for nocturnal enuresis.

151. **Ans. (c) Start SSRI treatment based on side effect profile** (*Ref: CMDT 2010/964*)

- Depression associated with reactive disorders usually does not call for drug therapy and can be managed by psychotherapy and the passage of time. In severe cases—particularly when vegetative signs are significant and symptoms have persisted for more than a few weeks—antidepressant drug therapy is often effective. Drug therapy is also suggested by a family history of major depression in first-degree relatives or a past history of prior episodes.
- Drug selection is influenced by the history of previous responses if that information is available. If a relative has responded to a particular drug, this suggests that the patient may respond similarly. If no background information is available, a drug such as sertraline, 25 mg orally daily and increasing gradually up to 200 mg orally, or desipramine, starting with 50 mg orally and gradually increasing to 150 mg daily, can be selected and a full trial instituted. The medication trial should be monitored for worsening mood or suicidal ideation with patient assessments every 1–2 weeks until week 6. If successful, the medication should be continued for 6–12 months at the full therapeutic dose before tapering is considered.

152. **Ans. (d) Diuretics** (*Ref: Katzung 11/e p502-503*)

Most of the renal tubular reabsorption of Li⁺ occurs in the proximal tubule. Nevertheless, Li⁺ retention can be increased by any diuretic that leads to depletion of Na⁺, particularly the thiazides.

153. **Ans. (a) Acute Dystonia** (*Ref: Katzung 11/e p497*)

- **Dystonias** are brief or prolonged contractions of muscles that result in obviously abnormal movements or postures, including oculogyric crises, tongue protrusion, trismus, torticollis, laryngeal-pharyngeal dystonias, and dystonic postures of the limbs and trunk. These are **earliest appearing extrapyramidal symptoms with antipsychotic drugs**.

154. **Ans. (b) Cardiac malformations.** (*Ref: Katzung, 11/e p500, Goodman and Gilman, 11/e p1326*)

- Lithium, if taken during pregnancy, can cause Ebstein's anomaly in the fetus, which is a congenital heart disease presenting as tricuspid atresia.

155. **Ans. (b) Fluoxetine** (*Ref: Harrison 17/e p2715, CMDT 2010/943*)

- SSRIs are drug of choice for most of the neurotic disorders including OCD.

156. **Ans. (a) Clozapine** (*Ref: Goodman and Gilman 12th/440-441*)

- Atypical antipsychotic drugs are implicated in causing adverse metabolic effects like weight gain, hyperlipidemia and insulin resistance. According to their potential to cause these side effects, these can be classified as:

High Potential:	Clozapine, Olanzapine
Intermediate potential:	Quetiapine
Low Potential:	Risperidone, Paliperidone
Least potential:	Iloperidone, Aripiprazole, Asenapine, Ziprasidone

157. **Ans. (d) Tianeptin** (*Ref: KDT 6/e p447*)

- Tianeptin enhances the reuptake of serotonin rather than inhibiting it whereas the other drugs mentioned in the options inhibit the reuptake of serotonin and nor-epinephrine.

158. **Ans. (a) Premature ejaculation** (*Ref: Goodman and Gilman 12th/410-411*)

- SSRIs can result in adverse effects like insomnia, anxiety, irritability and decreased libido due to excessive stimulation of brain 5-HT₂ receptors.
- Excessive activity at spinal 5-HT₂ receptors causes sexual side effects including erectile dysfunction, anorgasmia and ejaculatory delay, these are more prominent with paroxetine.
- Stimulation of 5-HT₃ receptors in the CNS and periphery contributes to GI effects which are usually limited to nausea but can also result in diarrhea and emesis.
- Unlike other SSRIs, paroxetine is associated with an increased risk of congenital cardiac malformations.

159. **Ans. (d) Fluoxetine** (Ref: Goodman and Gilman 12th/444-445)

- Fluoxetine is an anti-depressant drug of SSRI category whereas lithium, valproate and carbamazepine are used for mania and bipolar disorder as mood stabilizers.

160. **Ans. (d) Tyramine containing foods.** (Ref: Katzung 11/e p283, J Clin Psychiatry 1995; 56: 471-5)

'Addition of tyramine containing foods to a patient taking MAO inhibitors cause hypertension and other manifestations of sympathetic excess and not serotonin syndrome'

- Carbamazepine is structurally related to TCAs, its metabolism is inhibited by MAO-inhibitors and concurrent administration can result in serotonin syndrome. Therefore, carbamazepine and MAO-inhibitor concurrent administration is contraindicated. [Ref: Carbamazepine US prescribing information. Novartis Pharmaceuticals Feb.2009]
- For drugs causing serotonin syndrome, refer to chapter of recent topics.

161. **Ans. (c) Alpha 2 receptors** (Ref: KDT 6/e p447, 448)

Mirtazapine blocks presynaptic α_2 receptors on NA and 5-HT neurons. This increases the release of both NA and 5-HT. It also inhibits 5-HT₂ and 5-HT₃ receptors.

162. **Ans. (a) Anxiolytic** (Ref: Katzung 11/e p373; KDT 6/e p451)

Bupirone is 5HT₁ receptor partial agonist useful for treatment of chronic anxiety. It is not useful in acute anxiety.

163. **Ans. (d) Generalized anxiety disorder** (Ref: Kaplan Saddock's Synopsis of Psychiatry, 8th/2499; KDT 6/e p436)

- Lithium is used to treat acute mania and bipolar disorder.
- Lithium is also used as prophylaxis for depression and mania in bipolar disorder.
- It is sometimes used for other psychiatric disorders such as cycloid psychosis and unipolar depression.
- Non-psychiatric uses are limited. However, it is used in the prophylaxis of some headaches related to cluster headaches.
- Leucocytosis is the side effect of lithium. So it is also used for the treatment of drug induced neutropenia especially in patients on anti-cancer therapy.

164. **Ans. (d) Thioridazine** (Ref: K.D.T. 6/e p424, 425)

165. **Ans. (b) Serotonin** (Ref: KDT 6/e p451)

Decreased serotonin levels in brain is associated with depression (and suicidal tendencies) whereas elevated levels of 5-HT are associated with anxiety.

166. **Ans. (a) Amantadine** (Ref: Harrison 17/e p118)

Neuroleptic medications (dopamine blocking agents) are associated with a neuroleptic malignant syndrome (NMS).

- So, metoclopramide and haloperidol which are dopamine blockers and can cross blood brain barrier can be easily ruled out.
- Domperidone cross blood brain barrier much less than metoclopramide but some of it can reach the brain. Many cases of domperidone induced NMS have been reported.
- Amantadine acts by increasing dopamine in the brain, therefore it is indicated in treatment of NMS, however as it is an anti-Parkinsonian drug and withdrawal of such drugs can result in NMS, many cases of amantadine withdrawal induced NMS have also been reported. This lead to confusion.

But according to us, answer should be amantadine due to two reasons:

- Amantadine itself does not cause NMS, only its withdrawal causes this syndrome whereas domperidone itself cause it.
- Amantadine can be used in the treatment of NMS.

167. **Ans. (d) Cause benign and reversible depression of T wave on ECG** (Ref: Katzung 10/e p472)

- Lithium is the drug of choice for prophylaxis of bipolar disorder. For acute mania, usually a sedative agent like lorazepam has to be added because the action of lithium takes minimum one week to manifest.
- Lithium has narrow therapeutic index and therefore therapeutic drug monitoring is done for dose adjustment.
- Electrolyte disturbances particularly sodium depletion can precipitate lithium toxicity.
- It cause benign and reversible depression of T wave on ECG.

168. **Ans. (a) 5-HT** (Ref: Katzung 10/e p475; KDT 6/e p439)

Monoamines like serotonin and nor-adrenaline are deficient in depressive patients, therefore reuptake inhibitors of these monoamines are used for treatment of depression.

169. **Ans. (a) Imipramine** (Ref: *Katzung 10/e p483; KDT 6/e p449*)
170. **Ans. (b) MDP** (Ref: *Katzung 10/e p470; KDT 6/e p436*)
171. **Ans. (c) Schizophrenia** (Ref: *Katzung 10/e p465; KDT 6/e p425*)
172. **Ans. (c) Anti-psychotic drugs** (Ref: *Katzung 10/e p467; KDT 6/e p429-430*)
Atypical antipsychotic drugs are known to cause hyperglycemia, hyperlipidemia, insulin resistance and weight gain. Minimum risk of these metabolic adverse effects is with ziprasidone.
173. **Ans. (b) Anxiety** (Ref: *KDT 6/e p445; Katzung 11/e p524*)
- Nausea and insomnia are the most common adverse effects seen with fluoxetine therapy.
 - Anxiety is the next most frequent adverse effect followed by loose stools.
174. **Ans. (d) Extrapyramidal side effects** (Ref: *KDT 6/e p429*)
Clozapine is an atypical antipsychotic drug. It does not block D₂ receptors, therefore chances of extrapyramidal symptoms are least with this drug.
175. **Ans. (a) Anticholinergics** (Ref: *KDT 6/e p421*)
176. **Ans. (b) Atropine** (Ref: *KDT 6/e p431*)
Oculogyric crisis is a type of acute dystonic reaction (upward deviation of eyes) seen with the use of typical antipsychotic agents (D₂ blockers).
177. **Ans. (b) Selective serotonin reuptake enhancement** (Ref: *KDT 6/e p447*)
178. **Ans. (a) It is a MAO-A inhibitor** (Ref: *KDT 6/e p420*)
Selegiline and rasagiline are selective MAO-B inhibitors useful in Parkinsonism. These drugs inhibit the metabolism of dopamine in the brain and thus can decrease wearing off effect. Cheese reaction (seen with non-selective MAO inhibitors like tranylcypromine) is not associated with these agents.
179. **Ans. (d) Sodium ion is a specific antidote for lithium clearance** (Ref: *KDT 6/e p434, 435, 436, 437*)
- There is no specific antidote for lithium.
 - Lithium is the drug of choice for the treatment of bipolar disorder and prophylaxis of acute mania.
 - It is a narrow therapeutic index drug and requires therapeutic drug monitoring.
 - Amiloride is the drug of choice for lithium induced diabetes insipidus.
180. **Ans. (d) Bromocriptine** (Ref: *KDT 6/e p236*)
Prolactin release inhibitory substance released by hypothalamus is same as dopamine. Thus, dopamine agonists like bromocriptine reduce the secretion of prolactin whereas dopamine antagonists like antipsychotic drugs may result in hyperprolactinemia.
181. **Ans. (d) Akathisia** (Ref: *KDT 6/e p431*)
Continuous purposeless to and fro movement without anxiety is called akathisia. It is an extrapyramidal syndrome caused by D₂ blockers like haloperidol.
182. **Ans. (c) Imipramine** (Ref: *KDT 6/e p444*)
Features are typical of tricyclic antidepressant poisoning. TCAs possess anticholinergic activity that can result in tachycardia. These agents can lead to metabolic acidosis (pH < 7.4, HCO₃⁻ < 24 mmol/L). Seizures and myoclonic jerks are other features of TCA poisoning.
183. **Ans. (c) Furosemide** (Ref: *KDT 6/e p436*)
Loop diuretics and thiazides cause Na⁺ loss in the nephron, this leads to compensatory increase in reabsorption of Na⁺ and Li⁺ in the proximal tubules.
184. **Ans. (c) Ebstein's anomaly** (Ref: *Katzung 10/e p472*)
185. **Ans. (b) Neuroleptic malignant syndrome** (Ref: *KDT 6/e p431*)
186. **Ans. (a) Alprazolam; (b) Paroxetine; (c) Venlafaxine; (d) Buspirone** (Ref: *CMDT 2010/941-942*)
- Benzodiazepines (like lorazepam, oxazepam, temazepam or alprazolam) are usually indicated for generalized anxiety disorder (GAD).
 - Buspirone is a non-sedating anti-anxiety drug.
 - SSRIs (like paroxetine) and venlafaxine are indicated for chronic treatment of GAD.

187. Ans. (b) Extrapyramidal symptoms (Ref: KDT 6/e p429)

- Risperidone is an atypical anti-psychotic agent.
- It carries no risk of blood dyscrasias.
- EPS occur at higher dose (> 6 mg/day)
- It is less epileptogenic than clozapine. It causes rise of prolactin during therapy. It can cause SIADH.
- Associations have been suggested between atypical anti-psychotics and new-onset diabetes, hyperlipidemia, QT_c prolongation and weight gain but data is unclear.

188. Ans. (d) Neuroleptic malignant syndrome (Ref: KDT 6/e p431)

189. Ans. (a) Citalopram; (b) Fluoxetine; (e) Sertraline (Ref: KDT 6/e p446-447)

190. Ans. (c) Olanzapine (Ref: KDT 6/e p429, 430)

All of these drugs can be used for the treatment of bipolar disorder but carbamazepine, lithium and valproic acid are teratogenic. Olanzapine is safe in pregnancy.

191. Ans. (d) Ziprasidone (Ref: KDT 6/e p430)

- Clozapine, olanzapine and ziprasidone are atypical antipsychotic agents that act by blocking 5HT₂ receptors.
- Chlorpromazine is a typical antipsychotic drug. It blocks D₂ receptors in the brain and can cause extrapyramidal symptoms.
- Major adverse effect of clozapine is agranulocytosis (hematotoxic) and seizures.
- Olanzapine causes weight gain.
- Ziprasidone can cause QT prolongation leading to torsades de pointes.

192. Ans. (a) Elevation of seizure threshold (Ref: KDT 6/e p444)

Imipramine is a tricyclic antidepressant. It inhibits the reuptake of serotonin and nor-adrenaline. In addition, it possesses anticholinergic and α -blocking properties are:

- Increased risk of seizures due to lowering of seizure threshold is an adverse effect of this drug.

193. Ans. (b) Extrapyramidal motor disturbances (Ref: KDT 6/e p426, 431)

- Antipsychotic potency of typical antipsychotic drugs is related to their D₂ receptor blocking action.
- D₂ blocking action is also responsible for extrapyramidal adverse effects like muscle dystonia and Parkinsonism etc.

194. Ans. (d) Hypotensive (Ref: KDT 6/e p430, 431)

- Chlorpromazine is a typical antipsychotic (D₂ blocker) with anticholinergic and α -blocking properties.
- D₂ blockade is also responsible for extrapyramidal symptoms and hyperprolactinemia (dopamine acts like prolactin release inhibitory hormone).
- Antiemetic effect of chlorpromazine is due to blockade of D₂ receptors in CTZ.
- Anticholinergic effects manifest as dry mouth, blurring of vision and urinary retention.
- Hypotension and impaired ejaculation may be seen due to α -blocking activity of chlorpromazine.

195. Ans. (a) Prolactin (Ref: KDT 6/e p431)

Dopamine acts like prolactin releasing inhibitory hormone. D₂ blockers decrease the action of dopamine and can result in hyperprolactinemia. Some drugs blocking D₂ receptors are:

- Antipsychotics like chlorpromazine
- Metoclopramide

196. Ans. (a) Its potential to cause agranulocytosis (Ref: KDT 6/e p429)

197. Ans. (d) Akathisia (Ref: KDT 6/e p431, 432)

Treatment of various extrapyramidal symptoms is as follows:

	Symptom	Drug of Choice
1.	Muscular dystonia	Central anticholinergic (e.g. Benhexol)
2.	Parkinsonism	Central anticholinergic (e.g. Benhexol)
3.	Akathisia	Propanolol
4.	Malignant neurolept syndrome	Dantrolene
5.	Tardive dyskinesia	No specific treatment (central anticholinergics are contra-indicated)

198. Ans. (b) Tardive dyskinesia (Ref: KDT 6/e p431)

199. Ans. (d) It has anxiolytic but no anticonvulsant or muscle relaxing property (Ref: KDT 6/e p451)

- Buspirone is a 5HT_{1A} agonist useful for the treatment of anxiety.
- Unlike benzodiazepines, it is non-sedative anti-anxiety drug.
- Due to delay in the onset of its action, it is used for the treatment of chronic anxiety and is ineffective in acute panic attacks.
- Buspirone lacks anticonvulsant and muscle relaxing property.

200. Ans. (d) Selective serotonin reuptake inhibitor (Ref: KDT 6/e p446)

SSRIs are the drugs of choice for long-term management of panic disorder whereas benzodiazepines are DOC for acute panic attacks.

201. Ans. (a) Selegiline (Ref: KDT 6/e p420)

202. Ans. (b) Amitriptyline (Ref: KDT 6/e p443, 444)

Tricyclic antidepressants (TCA) possess anticholinergic and sedative properties. Amitriptyline and trimipramine possess highest sedative and antimuscarinic actions.

203. Ans. (b) Low oral bioavailability (Ref: KDT 6/e p443, 444)

- TCAs have very good oral absorption
- These agents have narrow therapeutic index and thus low safety margin.
- Sedation and anticholinergic adverse effects are seen frequently with the use of TCAs.
- Antidepressant actions of both TCAs as well as SSRIs take several weeks to manifest.

204. Ans. (d) Both (a) and (b) are correct (Ref: KDT 6/e p445)

205. Ans. (d) All of the above (Ref: KDT 6/e p448, 449)

206. Ans. (a) Carbamazepine (Ref: KDT 6/e p437)

207. Ans. (d) Haloperidol does not cause extrapyramidal syndrome (Ref: KDT 6/e p430, 431, 432)

Extrapyramidal adverse effects of antipsychotic drugs are due to blockade of dopamine receptors. These are less often seen with atypical antipsychotics like clozapine and risperidone (and more often with classical drugs like haloperidol and chlorpromazine). These effects can be treated with central anticholinergic drugs like biperiden and trihexiphenidyl.

208. Ans. (c) Lithium (Ref: KDT 6/e p435, 436)

209. Ans. (d) Aspirin (Ref: KDT 6/e p458, 459)

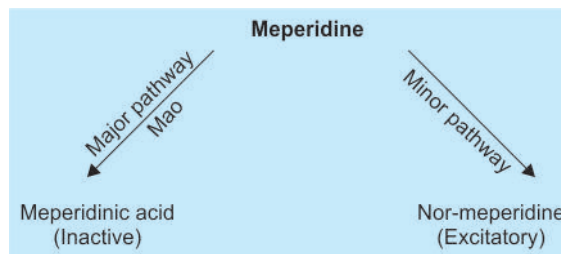
In first three conditions mentioned in the question, MAO inhibitors will lead to hypertensive crisis but these drugs do not interact with aspirin.

210. Ans. (d) Pin point pupil (Ref: KDT 6/e p444)

Amitriptyline is a TCA like imipramine. It causes mydriasis due to anticholinergic activity. Other adverse effects are also similar to imipramine.

211. Ans. (d) Phenelzine (Ref: KDT 6/e p459)

Meperidine (pethidine) is metabolized mainly to meperidinic acid (inactive) by MAO inhibitors. Minor pathway is conversion to nor-meperidine (possesses excitatory properties and shows cumulation)



- MAO inhibitors like phenelzine inhibits the major pathway; therefore minor pathway assumes importance resulting in generation of nor-pethidine that can cause seizures.
- Long term use of meperidine can result in accumulation of nor-meperidine and thus seizures can occur.

- 212. Ans. (a) Thioridazine** (Ref: KDT 6/e p428)
Retinal degeneration and corneal and lenticular opacities are the adverse effects seen most commonly with the use of thioridazine.
- 213. Ans. (c) Haloperidol** (Ref: KDT 6/e p433)
 - Antipsychotic drugs like olanzapine and haloperidol are agents of choice for rapid control of symptoms in acute mania.
 - Lithium is the drug of choice for the treatment of bipolar disorder (MDP) and prophylaxis of mania.
- 214. Ans. (b) Clonidine** (Ref: KDT 6/e p444)
TCAs abolish the antihypertensive effect of guanethidine and clonidine by inhibiting their transport into the adrenergic neurons.
- 215. Ans. (c) Three weeks** (Ref: KDT 6/e p441)
- 216. Ans. (a) Is a muscarinic antagonist** (Ref: KDT 6/e p444)
These symptoms are of anticholinergic drugs. Tricyclic antidepressants have powerful anticholinergic properties and can lead to these symptoms.
- 217. Ans. (d) Sodium bicarbonate** (Ref: Katzung 11/e p525)
Tricyclic anti-depressants (TCAs) can have quinidine-like effect on the cardiac conduction system, potentially causing QRS and QT prolongation and cardiac dysrhythmias. These effects are due to inhibition of fast sodium channels. NaHCO_3 can correct QRS prolongation, reverse hypotension, and treat ventricular dysrhythmias. Sodium bicarbonate is the single most effective agent in treating TCA-associated cardiac abnormalities.
- 218. Ans. (c) Dantrolene** (Ref: Katzung 11/e p499)
Diagnosis in this patient is neuroleptic malignant syndrome (NMS). It is an adverse effect caused by typical antipsychotic drugs like haloperidol. It presents clinically with four primary features: (1) hyperthermia, (2) extreme generalized rigidity, (3) autonomic instability, and (4) altered mental status.
Dantrolene is drug of choice for this condition.
- 219. Ans. (d) Chlorpromazine** (Ref: CMDT-2010/506)
Chlorpromazine is most commonly used drug for intractable hiccups.
Other drugs that can be used are:
 - Anticonvulsants (Phenytoin, carbamazepine)
 - Benzodiazepines (Lorazepam, diazepam)
 - Metoclopramide
 - Baclofen
 - Gabapentin
- 220. Ans. (c) Bromocriptine** (Ref: KDT 6/e p236)
Bromocriptine is used for treatment of hyperprolactinemia (do not cause it).
- 221. Ans. (a) Muscarinic ACh receptors** (Ref: Katzung 10/e p468)
- 222. Ans. (a) Acute Panic attack** (Ref: KDT 6/e p448, 449)
 - SSRIs are drug of choice for depression, sustained treatments of panic disorder and generalized anxiety disorder, obsessive compulsive disorder, post-traumatic stress disorder, social and other phobias and bulimia.
 - In acute panic attacks and for acute treatment of generalized anxiety disorder, benzodiazepines are preferred.
- 223. Ans. (d) 1.0** (Ref: KDT 6/e p436)
Therapeutic plasma concentration of lithium for acute therapy is 0.8-1.2 mEq/L whereas for prophylaxis, its concentration should be 0.5-0.8 mEq/L.
- 224. Ans. (d) Lamotrigine** (Ref: KDT 6/e p437)
Lamotrigine is specifically indicated for depressive phase of bipolar disorder.
- 225. Ans. (b) Valproate** (Ref: KDT 6/e p437)
- 226. Ans. (c) Haloperidol** (Ref: KDT 6/e p431)
 - Akathisia is a side effect of antipsychotic drugs like haloperidol: It is treated with
 - Central anticholinergics like Trihexyphenidyl
 - First generation antihistaminics like promethazine
 - Propanolol
 - Diazepam

Review of Pharmacology

227. Ans. (a) Clozapine (Ref: KDT 6/e p429)
228. Ans. (d) Haloperidol (Ref: KDT 6/e p431)
229. Ans. (d) Weight loss (Ref: KDT 6/e p429)
Clozapine and other atypical antipsychotics result in weight gain.
230. Ans. (d) All of the above (Ref: KDT 6/e p440)
Cheese, beer, wine, pickled meat, fish and yeast extract are rich in sympathomimetic amines (e.g., tyramine). In MAO inhibited patients, these indirectly acting sympathomimetic amines are not degraded in the intestinal wall and liver and reach into systemic circulation where they cause release of large amounts of norepinephrine from adrenergic nerve endings, thus precipitating hypertensive crisis. It is known as cheese reaction.
231. Ans. (c) Clozapine (Ref: KDT 6/e p429)
Clozapine is an atypical neuroleptic with least extrapyramidal side effects among all antipsychotics.
232. Ans. (b) Does not interfere with GABAergic transmission (Ref: KDT 6/e p451)
233. Ans. (d) Flupenthixol (Ref: KDT 6/e p429)
 - Flupenthixol is sometime used for treatment of depression, whereas other drugs mentioned in question can cause depression.
234. Ans. (a) Pemoline (Ref: KDT 5th/471)
Pemoline is used for ADHD whereas other drugs mentioned are antipsychotics.
235. Ans. (c) Weight loss. (Ref: KDT 6/e p444)
'Weight gain (not weight loss) is seen with TCAs.
236. Ans. (a) Tyramine (Ref: KDT 6/e p440)
237. Ans. (b) Thioridazine (Ref: KDT 6/e p427)
238. Ans. (b) Lithium (Ref: KDT 6/e p435)
239. Ans. (c) No individual variation in the rate of excretion (Ref: KDT 6/e p435-436)
240. Ans. (a) Antipsychotics (Ref: KDT 6/e p431)
241. Ans. (a) Clozapine (Ref: KDT 6/e p429)
242. Ans. (c) Dantrolene (Ref: KDT 6/e p397)
243. Ans. (c) Clozapine (Ref: KDT 6/e p429)
244. Ans. (d) Citalopram (Ref: KDT 6/e p442)
245. Ans. (c) Both (Ref: KDT 6/e p429)
246. Ans. (c) Haloperidol (Ref: KDT 6/e p431)
247. Ans. (c) Venlafaxine (Ref: KDT 6/e p447)
248. Ans. (c) 24 hours (Ref: Katzung 11/e p500)
249. Ans. (b) 0.8-1.2 (Ref: KDT 6/e p435)
250. Ans. (c) Tranylcypromine (Ref: KDT 6/e p440)
251. Ans. (b) Benhexol (Ref: KDT 6/e p431)
252. Ans. (b) Increased by decreased serum sodium levels (Ref: KDT 6/e p436)
253. Ans. (a) Imipramine (Ref: KDT 6/e p444)
254. Ans. (b) Fluoxetine (Ref: KDT 6/e p444)
255. Ans. (a) Lithium (Ref: KDT 6/e p435)
256. Ans. (b) Amitriptyline (Ref: KDT 6/e p440)
257. Ans. (c) Fluoxetine (Ref: KDT 6/e p425)

258. Ans. (a) Phenothiazines (Ref: KDT 6/e p431)

259. Ans. (a) Osteoporosis (Ref: KDT 6/e p431-432)

260. Ans. (d) Amoxapine (Ref: KDT 6/e p445)

261. Ans. (d) Loxapine (Ref: KDT 6/e p429)

262. Ans. (a) Chlorpromazine (Ref: Katzung 11/e p482)

263. Ans. (d) Tardive dyskinesia (Ref: KDT 6/e p431)

264. Ans. (c) MAO inhibitors (Ref: KDT 6/e p438)

265. Ans. (d) Quetiapine (Ref: KDT 6/e p431)

All other drugs are typical antipsychotics except quetiapine and release prolactin by blocking hypothalamic dopamine receptors.

266. Ans. (d) Diphenyl butyl piperidine (Ref: Goodman and Gilman 11/e p467)

267. Ans. (a) Aripiprazole (Ref: KDT 6/e p429, 430)

268. Ans. (b) Bupropion (Ref: KDT 6/e p448)

269. Ans. (d) Maprotiline (Ref: KDT 6/e p440)

Maprotiline is a tricyclic antidepressant.

270. Ans. (d) Uncontrolled seizure (Ref: KDT 6/e p448-449)

Tricyclic antidepressants can be used for treatment of

- Depression
- Panic disorder
- Obsessive compulsive disorder
- Chronic neuropathic pain
- Enuresis (incontinence particularly in institutionalized elderly patients)
- Attention deficit hyperkinetic disorder

But currently SSRIs are preferred for most of these indications over tricyclics because of severe adverse effect profile of the latter. Tricyclics are not indicated for seizures, rather some of them like clomipramine can induce convulsions by lowering the seizure threshold.

271. Ans. (c) Antimuscarinic drugs reduces its severity (Ref: Principles of Pharmacology by KK Sharma and HL Sharma 1st/466; KDT 6/e p431-432)

- **Tardive dyskinesia**, a disorder characterized by oro-buccal-lingual dyskinesia (as if patient is chewing chewing-gum), is a common complication of long-term neuroleptic (anti-psychotic) drug treatment.
- It is a late complication that occurs due to increased sensitivity of dopaminergic receptors (due to chronic presence of D₂ antagonists i.e. antipsychotics). Due to increased dopaminergic activity, cholinergic activity decreases that ultimately results in decreased release of GABA from striatal neurons.
- Thus dopaminergic drugs like levo-dopa and anti-cholinergic drugs like trihexyphenidyl will worsen the symptoms.
- A reduction in dose of the dopamine receptor blocker will also worsen the dyskinesia due to same reason, while an increase in dose may suppress it.
- The management of Tardive dyskinesia may involve the following strategies:
 - To decrease dopaminergic activity by increasing the dose of anti-psychotic but it is not advisable as these drugs themselves have resulted in supersensitivity of receptors
 - To increase cholinergic activity by choline or lecithin but the doses required are very high and success rate is limited (only 20%)
 - To increase the GABA activity by diazepam along with neurolept holiday (i.e. stopping anti-psychotic and anticholinergic medications).

272. Ans. (a) Clozapine (Ref: KDT 6/e p429)

273. Ans. (d) Hypercalcemia (Ref: K.D.T. 6/e p435)

274. Ans. (c) Clozapine (Ref: K.D.T. 6/e p429)

275. Ans. (a) Bupropion (Ref: Katzung 11/e p562)

276. Ans. (a) Imipramine (Ref: KDT 6/e p449)

277. Ans (a) Intravenous dantrolene (Ref: Harrison 18th/147)

The current treatment of choice for malignant hyperthermia is the intravenous administration of dantrolene

Other important measures are:

- Discontinuation of triggering agents
- Supportive therapy directed at correcting hyperthermia, acidosis, and organ dysfunction.

278. Ans. (b) Kappa (Ref: KDT 7/e p79)

Dysphoria and psychomimetics effects are caused by kappa receptors.

Actions of mu receptors are:

- S - Sedation
- A - Analgesia
- C - Constipation
- R - Respiratory depression
- U - Euphoria
- M - Miosis

279. Ans. (a) Diazepam (Ref: CMDT 2014/939)

Treatment with anticonvulsants is generally not required for alcohol withdrawal seizures, since they are self limited. Benzodiazepines (diazepam or lorazepam) are effective and safe for preventing further seizures.

280. Ans. (b) Fomepizole acts by inhibiting aldehyde dehydrogenase (Ref: Katzung 12/e p398)

Fomepizole inhibits alcohol dehydrogenase and not aldehyde dehydrogenase

- Serum methanol concentration above 20 mg/dl is an indication to start treatment and above 50 mg/dl is for hemodialysis.
- Metabolic product formaldehyde and formic acid is responsible for blindness and high anion gap metabolic acidosis
- Three specific modalities of treatment are:
 - Inhibit formation of toxic metabolites by inhibiting alcohol dehydrogenase by fomepizole or ethanol
 - Hemodialysis
 - Alkalinization to counter metabolic acidosis.

281. Ans. (b) IV naloxone (Ref: Kaplan & Sadock's Comprehensive Textbook of Psychiatry 9th/1375-76, 1384)

The decreased bowel sounds (constipation), respiratory depression, pin point pupil and history of heroin addiction strongly points toward the diagnosis of acute opioid poisoning. The drug of choice for acute opioid poisoning is intravenous naloxone.

282. Ans. (a) Pethidine (Ref: Goodman Gilman 12th/499, 504)

- Pethidine (meperidine) is metabolized to form nor-pethidine which is excreted by kidneys. It has long half life (15-20 hours) as compared to pethidine (3 hours). Accumulation of this metabolite resulting in excitatory syndrome including hallucinations, tremors, muscle twitches, dilated pupils, hyperactive reflexes and convulsions. Renal failure increases the likelihood of toxicity and thus pethidine should be avoided.
- Morphine produces morphine-6-glucuronide which can accumulate in renal failure. The actions of this metabolite are similar to morphine. In patients with renal failure morphine has more potency and longer duration of action due to accumulation of morphine-6-glucuronide and thus need to be given in lower doses

283. Ans. (c) Seizures (Ref: Goodman and Gilman 12th/511)

Antagonism of opioid effects by naloxone is often accompanied by an 'OVERSHOOT' phenomenon.

- Respiratory rate depressed by opioids transiently becomes higher than before the period of depression.
- Rebound release of catecholamines may cause hypertension, tachycardia and ventricular arrhythmias.
- Pulmonary edema also has been reported after naloxone administration.

284. Ans. (c) Flumazenil (Ref: Katzung, 11/e p395, Goodman and Gilman, 11/e p383- 384)

Flumazenil is a benzodiazepine antagonist used for treat of benzodiazepine overdose and not for alcohol dependence.

285. Ans. (d) Amphetamine (Ref: Katzung 11/e p565)

MDMA is also called Rave drug and ecstasy

286. Ans. (b) Methadone (Ref: Katzung 11/e p560)

Methadone is a synthetic narcotic (an opioid) that substitutes for heroin and can be taken orally. When given to addicts to replace their usual substance of abuse, the drug suppresses withdrawal symptoms. The duration of action for methadone exceeds 24 hours; thus, once-daily dosing is adequate. Methadone maintenance has several advantages.

- It frees persons with opioid dependence from using injectable heroin and, thus, reduces the chance of spreading HIV through contaminated needles.
- Methadone produces minimal euphoria and rarely causes drowsiness or depression when taken for a long time.
- Methadone allows patients to engage in gainful employment instead of criminal activity.

287. Ans. (c) Function of the intestine is not affected (Ref: Katzung 11/e p542)

- Because of their direct action on the superficial neurons of the spinal cord dorsal horn, opioids can also be used as regional analgesics by administration into the epidural or subarachnoid spaces of the spinal column.
- It was initially assumed that the epidural application of opioids might selectively produce analgesia without impairment of motor, autonomic, or sensory functions other than pain. However, respiratory depression can occur after the drug is injected into the epidural space and may require reversal with naloxone.
- Effects such as **pruritus and nausea and vomiting are common after epidural and subarachnoid administration** of opioids and may also be reversed with naloxone if necessary.
- Currently, the epidural route is favored because **systemic adverse effects are less common**

288. Ans. (a) Partial agonist at mu receptor (Ref: Katzung 11/e p546)

- Buprenorphine appears to be a partial agonist at mu receptor and antagonist at kappa receptor.

289. Ans. (a) Miosis (Ref: Katzung 11/e p539)

Tolerance cannot develop to 3Cs

- Constipation
- Constriction of Pupil
- Convulsions

290. Ans. (a) Heroin (Ref: Kaplan and Sadock's Synopsis of Psychiatry/448)

- Opioid withdrawal presents with dysphoric mood, nausea, vomiting, muscle aches, lacrimation, rhinorrhea, pupillary dilatation, sweating, yawning, fever and insomnia. It is also called "Cold Turkey".
- Cocaine withdrawal presents with dysphoric mood, fatigue, vivid and unpleasant dreams, insomnia or hypersomnia, increased appetite, psychomotor agitation or retardation.
- Cannabis is not associated with withdrawal syndrome.
- Alcohol withdrawal presents with sweating, pulse rate > 100, hand tremors, insomnia, transient visual/tactile/auditory hallucinations, psychomotor agitation, anxiety, nausea/vomiting. Later, it can progress to grand mal seizures and delirium tremens.

291. Ans. (a) Opioid (Ref: Goodman and Gilman, 12th/492)

- Morphine, a potent opioid is commonly used in newborn nurseries as a sedative (in this case for postoperative analgesia and sedation) is known to cause respiratory depression.

292. Ans. (c) Strychnine (Ref: Parikh's Textbook of Medical Jurisprudence, 6/e p10.57)

- **Strychnine** stimulates the respiratory centre whereas other drugs given the options like opioids, barbiturates and gelsemium cause respiratory depression
- Gelsemium (a herbal product) has been traditionally been used to treat pain and respiratory ailments. Toxic symptoms include giddiness, weakness, ptosis, dilated pupils and respiratory depression.

293. Ans. (a) Prevention of relapse (CMDT 2010/981-982)

Note:

- Beta-blockers and clonidine **treat** withdrawal symptoms.
- Methadone **prevents** withdrawal symptoms.
- Naltrexone is used to **prevent relapse**.
- Naloxone is used to treat overdose.

294. Ans. (a) Disulfiram (Ref: Goodman and Gilman 12th/660-661)

- Disulfiram is used for alcohol de-addiction and not for opioids.
- Methadone or buprenorphine are used to prevent withdrawal symptoms.
- Alpha 2 agonists like clonidine and lofexidine are used to treat sympathetic withdrawal symptoms of opioid addiction.

295. Ans. (b) Ketamine (Ref: Katzung 11/e p437)

- Ketamine is an NMDA antagonist used as an induction agent in anaesthesia whereas other drugs given in the options are opioids.

296. Ans. (b) Craving for opioids (Ref: Goodman and Gilman 12th/661)

- Naltrexone has no action in the absence of agonists but promptly reverses the opioid effects when administered i.v.
- It can reverse all effects of opioids like sedation, analgesia, constipation, respiratory depression and miosis etc but it do not reduce craving.

297. Ans. (d) Nalmefene is shorter acting than naloxone (Ref: Katzung 11/e p548, KDT 6/e p467)

- Naloxone, naltrexone and nalmefene are opioid antagonists.
- Naloxone is very short acting drug. It is administered i.v. for treatment of acute opioid poisoning but need to be repeated due to its short duration of action.
- Naltrexone is long acting oral drug. It is used to lower craving in alcoholics and to prevent relapse after opioid de-addiction.
- Nalmefene is also used i.v. for opioid overdose but it has longer half life (8-10 hours).

298. Ans. (c) Large proportionate body (Ref: CMDT-2010/979, Nelson 18th/781)

Fetal alcohol syndrome includes one or more of the following developmental defects in the offspring of alcoholic women:

- Low birth weight and small size with failure to catch up in size or weight.
- Mental retardation with an average IQ below 60s.
- A variety of birth defects like
 - Facial abnormalities including short palpebral fissures, epicanthic folds, maxillary hypoplasia, micrognathia, smooth philtrum and a thin smooth upper lip.
 - Cardiac defects, primarily septal defects.
 - Minor joint and limb abnormalities.

299. Ans. (d) Papaverine (Ref: KDT 6/e p453-454; Lee's synopsis of Anesthesia 12th/80)

Papaverine and noscapine are benzoisoquinoline derivatives of opium. These are non-analgesic drugs. These have no central effects. Codeine, morphine and heroin are narcotic drugs.

300. Ans. (a) Lorazepam (Ref: Katzung 11/e p394-395)

- Drugs decreasing craving in alcoholics are:
 - N – Naltrexone
 - O – Ondansetron
 - T – Topiramate
 - A – Acamprosate
- Lorazepam is used for management of alcohol withdrawal symptoms. Long acting benzodiazepines like chlordiazepoxide, clorazepate and diazepam are used to prevent withdrawal symptoms.

301. Ans. (a) Diazepam (Ref: Harrison 17/e p2728; KDT 6/e p385-386)

Medications used in alcohol withdrawal

- The important point to emphasize about the treatment of alcohol withdrawal is that it is caused by the **removal of a CNS depressant i.e. alcohol.**
- So the withdrawal symptoms can be initially controlled by replacing alcohol with *any other C.N.S. depressant drug* and subsequently the dose of the C.N.S. depressant can be tapered.
- Most of the C.N.S. depressant drugs are effective but **benzodiazepenes** have the highest margin of safety and lowest cost and are therefore the preferred class of drugs.
- Most clinicians use long acting benzodiazepenes such as **chlordiazepoxide** or **diazepam** because short acting benzodiazepenes can produce rapidly changing blood levels.
- **Drugs used in Rehabilitation of alcoholism:**
 - Naltrexone
 - Acamprosate
 - Disulfiram

302. Ans. (b) Lacrimation (Ref: Katzung 10/e p502; KDT 6/e p457)

Opioid withdrawal is characterized by yawning, rhinorrhea and lacrimation along with diarrhea.

303. Ans. (c) **Chlordiazepoxide** (Ref: *Katzung 10/e p370*)

Long acting benzodiazepines like diazepam and chlordiazepoxide are drug of choice for alcohol withdrawal.

304. Ans. (a) **Naltrexone** (Ref: *Katzung 10/e p371; KDT 6/e p385*)

305. Ans. (a) **Supraspinal analgesia** (Ref: *KDT 6/e p462*)

Both spinal as well as supraspinal analgesia is mediated by all three opioid receptors i.e., μ , κ and δ . Other actions mentioned in the question are mainly mediated by μ receptors.

306. Ans. (a) **Head injury** (Ref: *KDT 6/e p457*)

Head injury is an absolute contra-indication to morphine use. Hypothyroidism and asthma are relative contra-indications.

307. Ans. (c) **Methadone** (Ref: *Read below*)

- Naloxone is used to reverse neonatal respiratory depression due to opioid use during labour.
- It should not be used in a patient who is dependent on opioids because it can result in withdrawal syndrome.
- When the mother is on opioids, fetus becomes opioid dependent in-utero and the use of naloxone in respiratory resuscitation may result in severe withdrawal symptoms.
- Methadone is an opioid.

308. Ans. (b) **Sufentanil** (See below)

Sufentanil has maximum plasma protein binding (90%) among opioids.

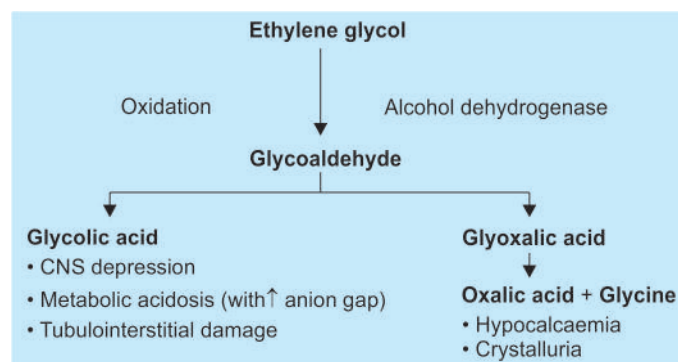
309. Ans. (a) **Miosis** (Ref: *KDT 6/e p462*)

310. Ans. (a) **Morphine** (Ref: *KDT 6/e p457*)

Morphine is contra-indicated in a patient with head injury.

311. Ans. (c) **Fomepizole**; (d) **Ethyl alcohol** (Ref: *KDT 6/e p387; Katzung 11/e p397*)

- The antidote of ethylene glycol poisoning is **ethanol** or **fomepizole**.



- **Ethanol and fomepizole** bind to alcohol dehydrogenase with higher affinity than ethylene glycol and blocks the production of toxic metabolites.

312. Ans. (a) **Ethyl alcohol is used**; (b) **Formation of formic acid produces blindness**; (d) **Gastric lavage done**; (e) **Fomepizole inhibits the formation of formic acid** (Ref: *KDT 6/e p387*)

- **Methyl alcohol** is metabolized to **formaldehyde** and formic acid by alcohol and aldehyde dehydrogenase.
- The toxic metabolite (formic acid) causes retinal damage and blindness.
- *Management:*

- Keep the patient in a quiet, dark room, protect eyes from light.
- **Gastric lavage with sod bicarbonate**, supportive measures to maintain ventilation and BP.
- For acidosis sodium bicarbonate is used.
- **Ethanol** is given orally or IV to saturate alcohol dehydrogenase and thus retard methanol metabolism.
- *Hemodialysis is required in severe cases.*
- **Fomepizole** is a specific inhibitor of alcohol dehydrogenase which inhibits methanol poisoning i.e. formation of formic acid.

313. Ans. (d) **It doesn't increase histamine release** (Ref: *Miller Anaesthesia 5th/348; Goodman & Gilman 10/e p602*)

- Dezocine is slightly **more potent** and **faster acting** opioid than morphine with a **similar duration** of action. It is a partial agonist antagonist opioid.

- It is active at μ receptors and side effects are similar to those of morphine.
- Dezocine doesn't increase plasma histamine and produces less hypotension than morphine or pentazocine.
- Dezocine is effective for moderate to severe pain but can cause myocardial depression.

314. Ans. (d) Subarachnoid (Ref: KDT 6/e p458, 437; Lee 12th/76-77)

- Respiratory depression occurs due to depression of respiratory centre by morphine travelling through the subarachnoid space (intrathecal route)

Routes of administration of morphine are:

- Oral
- Rectal
- Intramuscular
- Intravenous
- Transdermal
- Extradural/Epidural
- Subcutaneous

315. Ans. (b) Rectal; (c) SC; (d) IV; (e) IM (Ref: KDT 6/e p458; Lee 12th/76)

316. Ans. (a) It is an opioid antagonist; (c) It is used in alcohol dependence; (d) It is used to treat opioid dependence (Ref: KDT 6/e p467)

317. Ans. (a) Acetaldehyde (Ref: KDT 6/e p386)

- Disulfiram is an aldehyde dehydrogenase inhibitor that can be used for de-addiction of chronic alcoholics.



Due to inhibition of aldehyde dehydrogenase, there is accumulation of acetaldehyde that leads to several distressing symptoms (which strengthens the resolution of a person to quit alcohol).

318. Ans. (d) Antagonist of opioid receptors (Ref: KDT 6/e p467)

- Naltrexone is used to decrease the craving for alcohol after de-addiction.

319. Ans. (d) Pethidine (Ref: KD Tripathi 6/e p440)

Most of pethidine is metabolized by MAO-A and is inactivated. Small amount is converted to nor-pethidine, which has CNS stimulant properties. Therefore, if combined with MAO inhibitors, most of pethidine will form nor-pethidine and the risk of seizures will increase.

320. Ans. (c) Alcoholics psychologically but not physically dependent on alcohol (Ref: KDT 6/e p387)

- If a patient is physically dependent on alcohol, disulfiram can precipitate severe withdrawal symptoms. It is therefore, not indicated for physically dependent alcoholics.

321. Ans. (c) Inhibits the metabolism of methanol and generation of toxic metabolite (Ref: KDT 6/e p387)

- Methanol produces toxic metabolites (formaldehyde and formic acid) that are responsible for blindness. This metabolism takes place with the help of alcohol and aldehyde dehydrogenase.



- Ethanol is also metabolized by the same enzymes to produce acetaldehyde and acetic acid. It competes with methanol for above enzymes and inhibits the generation of toxic formaldehyde and formic acid.

322. Ans. (d) Fomepizole (Ref: KDT 6/e p387)

323. Ans. (a) Ischemic heart disease patients (Ref: KDT 6/e p457)

- Morphine is used for the treatment of myocardial infarction (ischemic heart disease) and LVF.
- Morphine is contra-indicated in extremes of age i.e., very young and elderly persons.
- It is also contra-indicated in bronchial asthma because it can cause respiratory depression and worsen the condition.
- By increasing intrabiliary pressure, morphine can worsen the pain of biliary colic.

324. Ans. (a) Tramadol (Ref: KDT 6/e p460)

325. Ans. (a) Pentazocine (Ref: KDT 6/e p464, 465)

Pentazocine can cause dysphoric reactions (hallucinations) by stimulating the κ receptors.

326. **Ans. (c) Seizures** (Ref: KDT 6/e p459)

Pethidine is mainly metabolized by hydrolysis to meperidinic acid but a minor pathway of metabolism involving methylation to nor-pethidine is also present. In overdose of pethidine, this minor pathway assumes importance and there is accumulation of nor-pethidine. This compound possesses excitatory properties and can lead to tremors, mydriasis, delirium, myoclonus and convulsions.

327. **Ans. (a) Cefixime** (Ref: KDT 6/e p383)

Drugs showing disulfiram like reaction with alcohol are

- Cefamandole, Cefoperazone, Cefotetan
- Moxalactam
- Chlorpropamide
- Metronidazole
- Griseofulvin
- Procarbazine

328. **Ans. (d) Naltrexone** (Ref: KDT 6/e p467)

- Naltrexone is a long acting, orally effective opioid antagonist that can be used as the maintenance treatment of opioid addicts. It is also used to decrease the craving for alcohol.

329. **Ans. (c) Methadone** (Ref: KDT 6/e p459, 460)

- Methadone is a long acting opioid agonist that has equal potency to morphine.
- It can be used orally for opioid replacement and opioid rotation therapy.
- Due to longer half life, it produces mild withdrawal symptoms.

330. **Ans. (d) Naltrexone** (Ref: KDT 6/e p467)

331. **Ans. (b) Zolpidem** (Ref: KDT 6/e p398)

332. **Ans. (c) Fentanyl** (Ref: KDT 6/e p459)

Fentanyl can be used as a transdermal patch for prolonged treatment of cancer associated pain.

333. **Ans. (a) Formaldehyde and formic acid** (Ref: Katzung 11/e p1024)

Methyl alcohol (methanol) is metabolized to formaldehyde by alcohol dehydrogenase and then to formic acid by aldehyde dehydrogenase. These compounds are responsible for the toxicity. Formic acid can lead to coma and blindness also. Therefore, inhibitor of alcohol dehydrogenase, **Fomepizole** is used for treatment of methanol overdose.

334. **Ans. (b) Naloxone** (Ref: Katzung 11/e p395)

Naloxone is an i.v. opioid antagonist used for acute opioid poisoning. It has no role in alcoholism.

335. **Ans. (a) Rhinorrhea and lacrimation** (Ref: KDT 6/e p457)

- Withdrawal symptoms are opposite of the acute effect of drug. For opioids, these include lacrimation, rhinorrhea, lacrimation, yawning, piloerection, diarrhea, nausea, coughing, mydriasis, sweating and twitching of muscles.

336. **Ans. (a) Morphine** (Ref: Katzung 10/e p499)

Opioids like morphine can be used to treat severe pain associated with terminal cancers.

337. **Ans. (a) Parenterally administered** (Ref: KDT 6/e p467)

- Naltrexone is chemically related to naloxone and is a pure opioid antagonist. It is more potent than Naloxone.
- It differs from Naloxone in being orally active and having a long duration of action (1-2 days) which is used to prevent relapse of heavy drinking.
- Side effects are nausea and headache; high doses can cause hepatotoxicity.

338. **Ans. (b) Kappa** (Ref: KDT 6/e p462)

339. **Ans. (c) Naloxone** (Ref: KDT 6/e p456)

340. **Ans. (a) Heroin** (Ref: KDT 6/e p467)

Naltrexone is an orally effective opioid antagonist. It is useful for the maintenance of the patient of opioid poisoning once it has been treated with naloxone. Heroin is an opioid, whose poisoning can be treated by naloxone and naltrexone.

341. **Ans. (a) Amoxicillin** (Ref: KDT 6/e p386, 706, 799)

342. Ans. (b) Children are more susceptible (Ref: Goodman & Gillman's Pharmacology 10/e p583)
Opioid induced seizures

- In animals high dose of morphine and related opioids can produce convulsions.
 - Morphine excites hippocampal pyramidal cells
 - Selective δ -agonists produce similar effect.
 - These action may contribute to seizures that are produced by some agents at doses only moderately higher than those required for analgesia, esp. in children. However with most opioids seizures occur only at doses far in excess of therapeutic dose.
 - Seizures are not seen when potent μ -agonists are used.
 - Naloxone is potent drug for treatment of opioid poisoning.
 - Anticovulsants (like diazepam) are not always effective in supressing opioid induced seizures.
- So the best answer is (b)

343. Ans. (b) Inhibits oxidation of alcohol (Ref: KDT 6/e p385)

Antabuse (disulfiram) inhibits the enzyme aldehyde dehydrogenase, which causes oxidation of aldehyde.

344. Ans. (d) Maintenance therapy of alcohol abstinence (Ref: KDT 6/e p385)

345. Ans. (b) Pentazocine (Ref: KDT 6/e p465)

346. Ans. (c) Methadone (Ref: KDT 6/e p460)

347. Ans. (d) Mydriasis (Ref: KDT 6/e p462)

348. Ans. (a) Alcohol abstinence (Ref: KDT 6/e p385)

349. Ans. (a) Heroin (Ref: KDT 6/e p458)

350. Ans. (a) It inhibit alcohol dehydrogenase (Ref: KDT 6/e p387)

351. Ans. (b) Epinephrine (Ref: KDT 6/e p467)

352. Ans. (d) All of the above (Ref: KDT 6/e p383)

353. Ans. (b) Nalorphine (Ref: KDT 6/e p464)

354. Ans. (d) All of the above (Ref: KDT 6/e p467)

355. Ans. (b) Fomepizole (Ref: KDT 6/e p387)

356. Ans. (c) Fentanyl (Ref: KDT 7th/476)

In analgesic doses, fentanyl produces little cardiovascular effects. It has less propensity to release histamine.

357. Ans. (d) Opioid analgesic (Ref: KDT 6/e p460)

358. Ans. (c) Codeine (Ref: KDT 6/e p462)

359. Ans. (d) Is an opioid agonist (Ref: KDT 6/e p464)

360. Ans. (d) Causes no constipation (Ref: KDT 6/e p215)

361. Ans. (b) Fentanyl (Ref: KDT 6/e p459)

362. Ans. (d) All of the above (Ref: KDT 6/e p399, 460, 546)

363. Ans. (b) Dorsal horn (Ref: KDT 6/e p454)

364. Ans. (c) Papaver somniferum (Ref: KDT 6/e p453)

365. Ans. (b) Sufentanil (Ref: Goodman Gilman 11/e p571)

366. Ans. (b) Cocaine (Ref: CMDT 2010, 983)

Cocaine is a product of coca plant and it is also a stimulant like amphetamine. Both of these are addictive and sympathomimetic substances.

367. Ans. (d) Sublingual (Ref: KDT 6/e p458, KK Sharma 2nd/500)

368. Ans. (c) Synthetic derivatives (Ref: Principles of Pharmacology by HL Sharma and KK Sharma, 1st/509)

Term Opiate means from 'opium' whereas opioid means opium like analgesics.

369. Ans. (d) Morphine (Ref: Principles of Pharmacology by HL Sharma and KK Sharma 1st/509; KDT 6/e p458)

ANSWERS OF RECENT QUESTIONS ASKED BY NATIONAL BOARD

1. Ans (b) Tardive dyskinesia (Ref: KDT 7/e p444)
2. Ans (b) GABA - agonism (Ref: KDT 7/e p421)
3. Ans (a) Anxiolytic (Ref: KDT 7/e p466)
4. Ans (c) Triazolam (Ref: KDT 7/e p405)
5. Ans (a) Alcohol de-addiction (Ref: KDT 7/e p394)
6. Ans (b) Can be mixed with dextrose (Ref: KDT 7/e p415)
7. Ans (b) Venlafaxine (Ref: KDT 7/e p462)
8. Ans (a) Clozapine (Ref: KDT 7/e p444)
9. Ans (b) Anti-psychotics (Ref: KDT 7/e p444)
10. Ans (c) 2.0 mEq/L (Ref: KDT 7/e p449)
11. Ans. (b) Zolpidem (Ref: KDT 7/e p406)
12. Ans. (b) Fentanyl (Ref: KDT 7/e p478)
13. Ans. (a) Vigabatrin (Ref: KDT 7/e p421)
14. Ans. (d) 5 HT_{2c} (Ref: Goodman Gilman 12/e p435)
 - Antipsychotics cause weight gain due to their antagonistic action on H₁ and 5HT_{2c} receptors.
15. Ans. (d) Valproate (Ref: KDT 7/e p 421)
16. Ans. (c) Retroperitoneal Fibrosis (Ref: KDT 7/e p 431)
 - Adverse effects of ropinirole and pramipexole include nausea, dizziness, hallucinations, postural hypotension and excessive day time sleepiness
 - Their advantage over ergot derivatives like bromocriptine is lack of retroperitoneal fibrosis and gangrene and long duration of action.
 - Ropinirole has been approved by FDA for restless leg syndrome
17. Ans. (d) Pergolide (Ref: KDT 7/e p 430)
18. Ans. (c) Constipation (Ref: KDT 7/e p473)
19. Ans. (a) It is an enzyme inducer (Ref: KDT 7/e p417)
20. Ans. (d) It inhibits microsomal enzymes (Ref: KDT 7/e p413-415)
21. Ans. (a) Amiloride (Ref: KDT 7/e p598)
22. Ans. (c) Lipid soluble (Ref: KDT 7/e p415)
 - Fosphenytoin is water soluble prodrug of phenytoin developed to overcome the difficulties in i.v. administration of phenytoin.
23. Ans. (d) Amitriptyline (Ref: KDT 7/e p454)
24. Ans. (a) Tramadol (Ref: KDT 7/e p477)
 - Tramadol inhibits re-uptake of NA and 5-HT and thus activates monoaminergic spinal inhibition of pain.
25. Ans. (b) Flumazenil (Ref: KDT 7/e p408)

26. Ans. (d) Selegiline (Ref: KDT 7/e p430)
27. Ans. (b) Amoxapine (Ref: KDT 7/e p460)
28. Ans. (d) Buspirone (Ref: KDT 7/e p404)
29. Ans. (b) Ketamine (Ref: KDT 7/e p384)
30. Ans. (d) Nalmefene (Ref: KDT 7/e p484)
31. Ans. (c) Nephrotoxicity (Ref: KDT 7/e p417)
32. Ans. (d) It is longer acting and causes milder withdrawal symptoms (Ref: KDT 7/e p476)
33. Ans. (b) Flumazenil (Ref: KDT 7/e p408)
34. Ans. (c) Methyl alcohol (Ref: KDT 7/e p395)
35. Ans. (c) Gabapentin (Ref: KDT 7/e p419)
36. Ans. (d) Left ventricular failure (Ref: KDT 7/e p471)
37. Ans. (a) Sertraline (Ref: KDT 7/e p464)
38. Ans. (a) Sodium valproate (Ref: CMDT 2014/ p937)
39. Ans. (c) Flumazenil (Ref: KDT 7/e p393-394)
40. Ans. (c) Bromocriptine (Ref: KDT 7/e p430)
41. Ans. (d) Fluphenazine (Ref: KDT 7/e p439)
42. Ans. (c) Pentazocine (Ref: KDT 7/e p481)
43. Ans. (b) Lorazepam (Ref: KDT 7/e p424)
44. Ans. (b) Valproate (Ref: CMDT 2014/ p938)
45. Ans. (c) Increase the release of neurotransmitters (Ref: KDT 7/e p419)
46. Ans. (d) Continue with Phenytoin and add Tab. Folic acid and during the last 2 weeks of pregnancy give oral Vitamin K too (Ref: KDT 7/e p422)
47. Ans. (c) Lithium (Ref: KDT 7/e p450)
48. Ans. (b) Acute dystonia (Ref: KDT 7/e p444)
49. Ans. (b) Labile blood pressure (Ref: KDT 7/e p444)
50. Ans. (d) Dilated pupils (Ref: KDT 7/e p479)
51. Ans. (d) Phenobarbitone (Ref: KDT 7/e p412)
52. Ans. (c) Is secreted by pituitary (Ref: KDT 7/e p409)
53. Ans. (c) Promethazine (Ref: KDT 7/e p444)
54. Ans. (b) Benzodiazepines (Ref: KDT 7/e p398)
55. Ans. (d) Aldehyde dehydrogenase (Ref: KDT 7/e p394)
56. Ans. (b) Anti psychotics (Ref: KDT 7/e p436)
57. Ans. (d) Flumazenil (Ref: KDT 7/e p408)
58. Ans. (a) Lithium (Ref: KDT 7/e p450)
59. Ans. (a) Formic acid (Ref: KDT 7/e p395)

60. Ans. (a) Metoclopramide (Ref: KDT 7/e p666)
61. Ans. (d) Benzhexol (Ref: KDT 7/e p433)
62. Ans. (d) Pentazocine (Ref: KDT 7/e p481)
63. Ans. (d) Chlorpromazine (Ref: KDT 7/e p454)
64. Ans. (d) Fluoxetine (Ref: KDT 7/e p464)
65. Ans. (a) Lithium (Ref: KDT 7/e p450)
66. Ans. (a) Vigabatrin (Ref: KDT 7/e p421)
67. Ans. (d) Haloperidol (Ref: KDT 7/e p465)
68. Ans. (b) Diphenoxylate (Ref: KDT 7/e p686)
69. Ans. (c) Lorazepam (Ref: KDT 7/e p405)
70. Ans. (a) Valproic acid (Ref: KDT 7/e p421)
71. Ans. (a) Olanzapine (Ref: KDT 7/e p446)
72. Ans. (b) Lithium (Ref: KDT 7/e p450)
73. Ans. (c) Ethylene glycol poisoning (Ref: KDT 7/e p396)

NOTES

This image shows a blank sheet of white paper with horizontal ruling lines. On the left side, there is a dark gray vertical band. Inside this band, the words "Central Nervous System" are printed vertically, reading from bottom to top.

LOCAL ANAESTHETICS

These drugs act by blocking the conduction of nerve impulse along the axon. Small diameter and myelinated fibres are blocked first whereas unmyelinated and thick fibres are blocked at last. Thus, the **order of blockade of fibres is B, C, A δ and then A α , β and γ . Autonomic fibres are blocked first, then sensory** (cold temperature sensation is lost first followed by heat, pain and proprioception) **and finally motor** are blocked at last. *Order of recovery is in the reverse order.*

Local anaesthetics (LAs) can be **classified into amide and ester types**. Amides are usually long acting and chances of allergic reactions are less whereas esters are short acting (due to metabolism by esterases present in the plasma). **Ester LAs** can cause allergic reactions and also **antagonize** the action of **sulfonamides** due to degradation of PABA.

Amide class	Ester class
* Lignocaine	* Cocaine
* Prilocaine	* Procaine
* Bupivacaine	* Chlorprocaine (Shortest acting)
* Dibucaine (Longest acting)	* Tetracaine (Amethocaine)
* Mepivacaine	* Benzocaine
* Etidocaine	
* Ropivacaine	

Adrenaline is added to LA to make them long acting whereas sodium bicarbonate makes them fast acting.

MECHANISM OF ACTION

All LAs are **weak bases**. These drugs act by penetrating the axonal membrane (in unionized form) and **blocking the voltage gated sodium channels from within (in ionized form)**. **Sodium bicarbonate speeds the onset of action** of LAs by increasing the unionized form (weak bases are unionized in the alkaline medium) that can penetrate the axonal membrane. Vasoconstrictors like **adrenaline** can **prolong the duration of action and decrease the systemic toxicity**. Alternative vasoconstrictor **felypressin** (synthetic vasopressin) can also be used with LAs in order to avoid cardiovascular complications due to adrenaline.

Lignocaine with adrenaline SHOULD NOT be used for:

- Areas with **end arteries** e.g. for ring block of fingers, toes, penis, pinna (absolute contraindication)
- When an inhalational agent especially **halothane** which sensitizes myocardium to adrenaline is used.
- **Myocardial ischemic** patients
- **Hyperthyroid** patient
- Severe **hypertensives**
- Intravenous regional anaesthesia (**Bier's block**)

IMPORTANT POINTS

- Small diameter axons are **more susceptible** to block than large diameter fibres.
- **Myelinated fibres are more sensitive than non-myelinated.**
- **Sequence of block is type B > type C > type A.**
- In functional terms: **Autonomic > sensory > motor.**
- Among sensory fibres sequence of block is *pain > temperature (cold before heat) > touch > deep pressure > proprioception.*
- **All LAs are vasodilators except cocaine** (act as sympathomimetic due to inhibition of nor-adrenaline reuptake) which is a vasoconstrictor. Therefore all LAs decrease BP except cocaine (increases).
- **Cocaine** should **NEVER** be given by **intravenous route** or with adrenaline.
- **Cocaine** is the only ester which is **not metabolized by pseudocholinesterase**. It is metabolized in the liver.
- **Procaine** is the **local anaesthetic of choice in malignant hyperthermia.**

Contd...



LA causing methemoglobinemia
B – Benzocaine
P – Prilocaine (Max)
L – Lignocaine

Contd...

- **Chlorprocaine** is the **shortest acting** local anaesthetic and is **contra-indicated in spinal anaesthesia** (It may cause paraplegia due to the presence of sodium metabisulphite as preservative, which is neurotoxic).
- **All LAs** if absorbed in systemic circulation can cause **CNS toxicity** that manifests as excitation followed by depression. Initial excitation is due to inhibition of inhibitory neurons. Thus LAs may lead to **seizures followed by coma** at high doses.
- **Dibucaine** is the **most potent, longest acting and most toxic LA** whereas chlorprocaine is the shortest acting LA.
- **Lignocaine** is the **most commonly used LA** and is the **drug of choice for ventricular tachycardia**. It can precipitate **malignant hyperthermia** due to release of calcium. Dose is limited to 7 mg/kg with adrenaline or 4 mg/kg without adrenaline.
- **Bupivacaine** is the **best drug for regional block** but it is also the **most cardiotoxic LA**. Due to cardiotoxic effect, it **should not be used for Bier's block**. It is more potent and longer acting than lignocaine. Addition of adrenaline does not significantly increase the duration of action of this drug. For spinal anaesthesia, 0.5% solution is made hyperbaric with 8.25% dextrose in water. Its *maximum dose is 2mg/kg*. Most common ECG changes in bupivacaine toxicity are slow idioventricular rhythm with broad QRS complex. **Bretylium** is the drug of choice for bupivacaine induced ventricular tachycardia.
- Ropivacaine is less cardiotoxic congener of bupivacaine.
- **Prilocaine** produces a metabolite "**O-toluidine**" which is an oxidizing agent. Latter can oxidize hemoglobin to methemoglobin that can cause **methemoglobinemia**. It is the **most suitable LA for Bier's block**.
- **Oxethazaine** (mucaine) can be used to provide symptomatic relief in gastritis (it remains unionized in the acidic pH of stomach).

USES OF LOCAL ANAESTHETICS

These agents can be used for following types of anaesthesia.

1. Surface Anaesthesia

It is the topical application of LA to mucous membranes and abraded skin. Only superficial area is anaesthetized. **Lignocaine** is the commonly used agent for topical anaesthesia of mucous membranes of nose, ear, eye, mouth and pharynx. It is also used during proctoscopy, catheterization and per rectal examinations. Lignocaine is **ineffective on intact skin**. However a mixture of **2.5% prilocaine and 2.5% lignocaine** in 1:1 ratio can anaesthetize even unbroken skin. Combination of these two agents lowers the melting point of individual drugs and helps to form a semi-solid ointment. This mixture is known as **Eutectic mixture**. Oxethazaine (mucaine) can be used to provide symptomatic relief in gastritis (it remains unionized in the acidic pH of stomach).

2. Infiltration Anaesthesia

LA is infiltrated s.c. in the area of operation site for blocking the sensory nerve endings. It is used in minor surgeries like incisions, excisions, suturing, hydrocele etc. **Adrenaline** can be added to the LA to prolong its duration of action and to prevent systemic side effects.

3. Nerve Blocks

LA is injected around the nerve trunks supplying a particular area to anaesthetize all the nerves coming to or leaving that area. It includes blocks of head and neck (stellate ganglion,



A mixture of 2.5% prilocaine and 2.5% lignocaine in 1:1 ratio can anaesthetize even unbroken skin. Combination of these two agents lowers the melting point of individual drugs and helps to form a semi-solid ointment. This mixture is known as **Eutectic mixture**.

trigeminal nerve, cervical plexus and phrenic nerve block), upper limbs (brachial plexus and wrist block), thorax and abdomen (intercostal nerve, celiac plexus, lumbar sympathetic chain, ilioinguinal nerve, iliohypogastric nerve, penile and paravertebral block) and lower limbs (psoas compartment and perivascular block). Pneumothorax is the most common complication of brachial plexus block.

4. Intravenous Regional Block (Bier's Block)

Intravenous regional anaesthesia (IVRA) is indicated for any procedure on the arm below the elbow or leg below the knee that will be completed within 40-60 minutes. An intravenous cannula is inserted in a distal vein in the limb scheduled for surgery. The tourniquet is then applied to the upper arm or thigh. The local anaesthetic solution is then slowly injected into the cannula. Analgesia will occur within 3-4 minutes and surgery can then commence. The **pressure in the tourniquet must be maintained at least 50 mm Hg above the patient's systolic blood pressure**. The **drug of choice for IVRA is prilocaine** as it is the least toxic local anaesthetic and has the largest therapeutic index. If prilocaine is not available, lignocaine is an acceptable alternative. It is essential that *plain and not adrenaline-containing solutions are used*. **Bupivacaine should never be employed** as it is too toxic, particularly to the myocardium.

IVRA should be avoided in a patient with sickle cell disease

The drug of choice for IVRA is prilocaine

5. Spinal Anaesthesia

It is the injection of LA in the subarachnoid space (between pia and arachnoid; also known as intrathecal space) in lumbar spinal cord. **Spinal cord ends at lower border of L₃ vertebrae in children and at lower border of L₁ vertebrae in adults**. Thus, spinal anaesthesia can be performed safely in L₂₋₃ intervertebral space in adults and L₄₋₅ space in children. Spinal anaesthesia leads to creation of a **zone of differential blockade** in which autonomic fibres are blocked at two segments higher and motor fibres are blocked at two levels lower than sensory blockade. It is due to different sensitivity of various types of nerve fibres.

Maximum dose of lignocaine

- With adrenaline : 7 mg/kg
- Without adrenaline : 4.5 mg/kg
- For IVRA : 4 mg/kg

Structures encountered during lumbar puncture

1. Skin
2. Subcutaneous tissue
3. Supraspinous ligament
4. Interspinous ligament
5. Ligamentum flavum
6. Duramater
7. Arachnoidmater

Drugs used for Spinal Anaesthesia

- Lignocaine - 5% in 7.5% dextrose (heavy or hyperbaric)
- Bupivacaine - 0.5% in 8% dextrose

Indications

- Orthopaedic surgery of lower limbs and pelvis.
- Surgery of lower abdomen (all pelvic and perineal surgeries, hernia, hydrocele, appendix, testicular surgeries).
- Gynaecological and obstetrics surgeries (hysterectomy, myomectomy, cervical surgeries, tubectomy, tuboplasty, caesarean section).

Complications

- **Hypotension** is the **most common intraoperative complication**. It can be prevented by preloading with crystalloids or colloids and treated by head low position (**Trendelenburg position**), fluids, vasopressors and ionotropic agents. Other intraoperative complications include bradycardia, respiratory depression, and cardiac arrest.
- **Most common postoperative complication is headache**, known as **post dural puncture headache (PDPH)**. It is mainly occipital headache that occurs **after 12-24**

Concentration (In %) of LA for different uses:

	Lignocaine	Bupivacaine
Infiltration	0.5 – 2	0.25 – 0.5
Spinal	5	0.5
Epidural	2	0.5

Hypotension is the most common intraoperative complication of spinal anaesthesia whereas most common postoperative complication is headache, known as post dural puncture headache (PDPH).

Management of LA Toxicity

(*ASRA guidelines)

1. 20% Intralipid I.V. at first sign of toxicity
2. Benzodiazepines are DOC for seizures. If not able to control, give SCH. If not available, use propofol.
3. Lignocaine and other class Ib drugs avoided for arrhythmias.
4. NaHCO₃ for severe acidosis

* ASRA: American Society of Regional Anesthesia

hours. It is different from any headache previously experienced by the patient and is initiated or **made worse** by the adoption of **sitting or erect posture**. It is **relieved** by **abdominal compression**, which raises the venous pressure. Most common cause of PDPH is **leakage of CSF** through the hole in the duramater. It can be **prevented** by using **small bore needle** (25G). Treatment of PDPH consists of lying down for 24 hours, plenty of fluids, abdominal compression and sealing the hole by epidural blood patch. Other post-operative complications include *urinary retention, paralysis of cranial nerves (most commonly involved nerve is abducens, sixth cranial nerve), meningitis, arachnoiditis, paraplegia and cauda equina syndrome*.

Contraindications

Absolute	Relative
• Raised intracranial tension • Uncooperative patient • Shock • Bleeding disorders/coagulopathy • Patients on anticoagulants, thrombolytic therapy • Infection at local site • Septicemia	• Aortic stenosis • Mitral stenosis • Recent MI, heart block • Spinal deformity – Psychiatric disorders – CNS disorders.

6. Epidural Anaesthesia

Epidural anaesthesia is given in **epidural space** (between duramater and bone) with **Tuohy's needle**. Epidural space extends from foramen magnum to sacral hiatus (triangular in shape) and contains anterior and posterior nerve roots, epidural veins, spinal nerves, lymphatics and fat.

Indications

- **Mainly used for controlling postoperative pain** (by continuous epidural through a catheter).
- All surgeries which can be performed under spinal anaesthesia.
- Upper abdominal surgeries, thoracic surgeries and even neck surgeries.
- Painless labour.
- Chronic pain due to cancer and other conditions.

Spinal Versus Epidural Anaesthesia

Spinal anaesthesia is *highly reliable, easier* to place (because it can be confirmed by the presence of CSF in the needle and loss of resistance) and has *very quick onset*. However, it can be performed *only for the surgeries of limited duration*. *Re-dosing cannot be done* if the procedure takes longer time than expected. PDPH is a very common problem.

Epidural anaesthesia is *difficult* to perform (requires expert persons) and therefore is less reliable. Further, onset of analgesic effect is *slower*. But it can be used for *surgeries of any duration* by inserting an epidural catheter. Chances of PDPH is *very less* because it is quite superficial procedure (no CSF leak).

SKELETAL MUSCLE RELAXANTS

These drugs are used in anesthesia to relax lower limbs and abdominal wall muscles so that operative manipulation becomes easy. These can also be used to facilitate endotracheal intubation by relaxing laryngeal musculature. Some of these drugs are useful in the spastic conditions also. Skeletal muscle relaxants may be **divided into centrally acting and peripherally acting agents**.

Centrally Acting Muscle Relaxants

These drugs cause muscle relaxation by their action in the CNS. All these drugs can cause **sedation**. Important drugs in this class are:

- **Mephenesin** group includes *carisoprodol* (its metabolite meprobamate is used as a CNS depressant), *chlorzoxazone*, *chlormezanone* and *methocarbamol*. These drugs **selectively inhibit polysynaptic reflexes** and are useful in local muscle spasms like sprains and spasms due to spondylitis.
- **Benzodiazepines** like diazepam and clonazepam **inhibit both polysynaptic** as well as **monosynaptic reflexes** and are useful in muscle spasms of almost any origin. They are mainly used in spinal injuries and tetanus.
- **GABA_B** (It is a G protein coupled receptor unlike GABA_A, which is an ionotropic receptor) **agonists** like *baclofen* **increase K⁺ conductance and can inhibit monosynaptic as well as polysynaptic reflexes**. Baclofen is used to relieve spasticity in multiple sclerosis and spinal injuries. It is **not useful in cerebral palsy**.
- **Tizanidine** is a centrally acting α_2 **agonist** but unlike clonidine, has **no effect on blood pressure**. It inhibits the release of excitatory neurotransmitters in the spinal cord (by its presynaptic action). It can be used to relieve spasms in multiple sclerosis, amyotrophic lateral sclerosis, other neurological disorders and spinal injuries.

Dantrolene is the drug of choice for the treatment of malignant hyperthermia and is also useful in neurolept malignant syndrome.

Peripherally Acting Muscle Relaxants

These drugs do not enter the CNS and cause muscle relaxation by blocking neuromuscular junction (neuromuscular blockers) or by acting directly on the muscle.

A. DIRECTLY ACTING SKELETAL MUSCLE RELAXANTS

- **Dantrolene** and **quinine** act directly on the skeletal muscles.
- Dantrolene inhibits the release of Ca⁺⁺ from sarcoplasmic reticulum via inhibition of *ryanodine receptors*. It is used to relieve spasticity due to multiple sclerosis, cerebral palsy and spinal cord injuries but is ineffective in spasms due to musculoskeletal injuries. It is **the drug of choice** for the treatment of **malignant hyperthermia** and is also useful in **neurolept malignant syndrome**. Major adverse effects of this drug are **muscle weakness** and **hepatitis**.
- **Quinine** acts by decreasing the excitability of motor end plate and can be used in patients with **nocturnal leg cramps**.

B. DRUGS ACTING ON NEUROMUSCULAR JUNCTION (NMJ)

These drugs decrease the transmission of impulse across NMJ either by inhibiting nicotinic N_M receptors or by consistently depolarizing the muscle end plate.

(a) Depolarizing Blockers

Succinylcholine (SCh) or suxamethonium is the only depolarizing SMR in use at present. It is an ACh analogue and thus **stimulates nicotinic N_M receptors** resulting in depolarization of the membrane. This effect is responsible for **initial fasciculations** seen on administration of this agent (results in post operative muscle pain or soreness). Constant depolarization makes the end plate refractory to other impulses and muscle relaxation results. It is a type of **flaccid paralysis** that **cannot be reversed with neostigmine (Phase I block)**. On prolonged use, this block may be converted to **phase II block** that can be **reversed with anticholinesterases**.

Succinylcholine can cause hyperkalemia especially in patients with nerve and muscle disorders. Therefore it is contra-indicated in patients with nerve diseases (like paraplegia, hemiplegia and Guillain barre syndrome) and muscle diseases (muscular dystrophy, myasthenia gravis, crush injury, burns and rhabdomyolysis).

- SCh is the **shortest and the fastest acting SMR**. Due to its quick onset of action, it is the **preferred SMR for endotracheal intubation**. It is metabolized by pseudocholinesterase that may be non-functioning (**atypical pseudocholinesterase**) in some individuals. This is a **genetic condition** and may result in **prolonged apnea on SCh administration** (due to decreased metabolism, action of SCh is prolonged). **Activity of atypical enzyme can be assessed by dibucaine number**.
- SCh can **stimulate the autonomic ganglia** whereas non-depolarizing blockers inhibit the ganglia.
- It can cause **hyperkalemia** especially in patients with **nerve and muscle disorders**. Therefore it is **contra-indicated** in patients with nerve diseases (like *paraplegia, hemiplegia and Guillain barre syndrome*) and muscle diseases (*muscular dystrophy, myasthenia gravis, crush injury, burns and rhabdomyolysis*).
- **SCh increases all pressures** i.e. intraocular pressure (**C/I in glaucoma**), intracranial tension (**C/I in head injury**), blood pressure (due to **stimulation of sympathetic ganglia**) and intragastric pressure (responsible for **nausea and vomiting**).
- It may trigger **malignant hyperthermia** specially when given in combination with *halothane*.

(b) Non Depolarizing Blockers or Competitive Skeletal Muscle Relaxants

These drugs act by **competitively inhibiting N_M receptors** and thus cause muscle relaxation without any fasciculations (no postoperative muscle soreness). Further, due to competitive nature of inhibition, effect of these drugs can be **reversed by anticholinesterases** like neostigmine. These are divided into two major groups (benzylisoquinolines and steroidal) on the basis of chemical structure.

(i) Steroidal skeletal muscle relaxants

Pancuronium, vecuronium, pipecuronium, rocuronium and rapacuronium are the drugs in this group. These drugs have very little histamine releasing action and no effect on autonomic ganglia.

- **Pancuronium** can produce **tachycardia** due to its **vagolytic action** (M_2 blocker).
- **Rocuronium** is the **fastest acting non depolarizing skeletal muscle relaxant** and can be used for rapid sequence endotracheal intubation as an alternative to SCh.
- **Rapacuronium** has been withdrawn due to reports of **severe bronchoconstriction**. It was the **fastest acting** non-depolarizing skeletal muscle relaxant.
- **Vecuronium** is preferred in cardiac patients because of **better cardiovascular stability**. It is **contra-indicated in hepatic disease and biliary obstruction**.
- **Gantacurium** is **shortest (< 10 min.) and fastest** acting non-depolarizing neuromuscular blocker in phase 3 clinical trials. It is being investigated as an alternative to SCh. It causes less release of histamine. Its metabolism is carried out non-enzymatically by cysteine.

Sugammadex is a modified gamma cyclodextrin that can be used to reverse neuromuscular blockade by rocuronium. It is the first **selective relaxant binding agent** (SRBA). It encapsulates rocuronium and inhibits its access to N_M receptors at neuromuscular junction. It can also be used to reverse vecuronium and pancuronium induced muscle relaxation. *It is ineffective against SCh and benzylisoquinolines (curiums)*. Major advantage of sugammadex over neostigmine is that it produces reliable and rapid reversal without producing autonomic instability. However, it has not been granted approval by FDA due to risk of hypersensitivity reactions.

(ii) Benzylisoquinoline derivatives

This group includes d-Tubocurarine (d-TC), metocurine, doxacurium, atracurium, cis-atracurium and mivacurium.

Rapacuronium has been withdrawn due to reports of severe bronchoconstriction

Sugammadex is first selective relaxant binding agent (SRBA).

- These drugs **release histamine** (maximum with d-TC and minimum with cis-atracurium) and block autonomic ganglia (maximum with d-TC and metocurine).
- **d-TC** causes **hypotension** due to histamine releasing and ganglionic blockade property. It can also cause **bronchospasm** due to histamine release.
- **Doxacurium** is the **longest acting** and most potent SMR.
- **Mivacurium** is the **shortest acting** non-depolarizing SMR because it is **metabolized by an esterase**. It can be used as an alternative to Sch for endotracheal intubation.
- **Atracurium and cis-atracurium** undergo **Hoffmann's elimination** (spontaneous non-enzymatic molecular rearrangement) and are the **agents of choice for patients with hepatic or renal insufficiency**. **Atracurium is metabolized to laudanosine that is responsible for seizures**. Cis-atracurium is relatively safe in this regard. Cis-atracurium release **much less histamine** as compared to atracurium.
- **Gantacurium** is undergoing phase III clinical trials. It is **fastest** (even rapid than rapacuronium) **and shortest** (shorter than mivacurium) acting non-depolarizing neuromuscular blocker. If approved, it can be used as an alternative to succinylcholine for endotracheal intubation.

Atracurium and cis-atracurium undergo Hoffmann's elimination (spontaneous non-enzymatic molecular rearrangement) and are the agents of choice for patients with hepatic or renal insufficiency.

Elimination of muscle relaxants:

Renal	Hepatic	Both	None
Doxacurium	Rapacuronium	Pipecuronium	Atracurium
Tubocurarine		Vecuronium	Cis-atracurium
Pancuronium		Rocuronium	Mivacurium
			SCh

(iii) Gallamine

The **least potent** skeletal muscle relaxant. It is rarely used now a days because of its **nephrotoxic and teratogenic** potential. It possesses **vagolytic** action and can lead to **tachycardia**.

Note:

- **Shortest acting SMR is succinylcholine** whereas *shortest acting non-depolarizing SMR is mivacurium*.
- **Fastest acting SMR is succinylcholine** whereas *fastest acting non-depolarizing SMR is rapacuronium* but next is rocuronium (because rapacuronium has been withdrawn).
- **Doxacurium is the longest acting and most potent** skeletal muscle relaxant whereas **gallamine is the least potent** skeletal muscle relaxant.
- Neostigmine reverses the effect of non depolarizing SMRs whereas it potentiates the effects of depolarizing SMRs.

GENERAL ANAESTHETICS

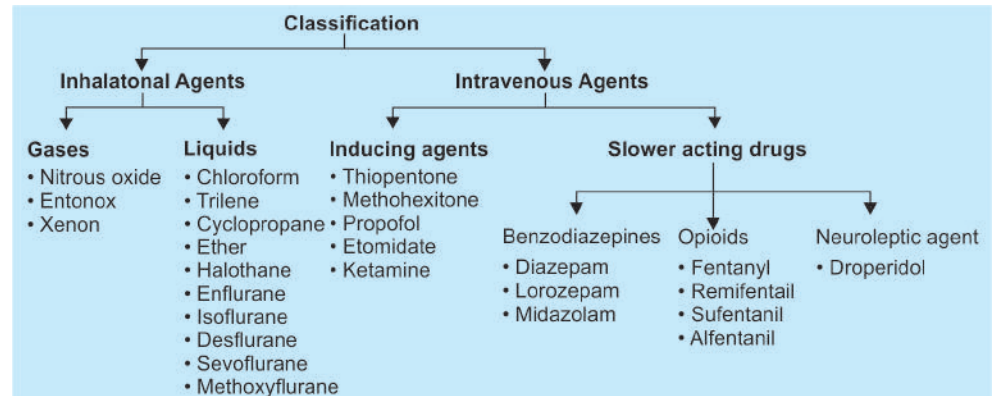
Anaesthesia is the reversible loss of response to a noxious stimuli. It may be **general anaesthesia** (if associated with loss of consciousness) or **local anaesthesia** (consciousness is maintained). Four main features of balanced anaesthesia are:

Unconsciousness

Muscle relaxation

Analgesia

Abolition of compensatory reflex responses



Inhalational Agents

These agents are stored in cylinders and are delivered to the patient through Boyle's machine. Colour coding of the cylinders (for identification) and the Pin index system is present for the safety (so that only the required cylinder can fit in the machine at that site).

COLOUR CODING OF CYLINDERS

N ₂ O	Blue
Cyclopropane	Orange
Air	Grey body with white shoulders
O ₂	Black body with white shoulders
CO ₂	Grey
Helium	Brown
Entonox	Blue body with white shoulders

PROPERTIES

Two important properties of an inhalational agent is its minimum alveolar concentration (MAC) and blood gas partition coefficient.

- **Minimum Alveolar Concentration (MAC):** It is the minimum concentration of an inhalational agent required in the alveoli to produce unresponsiveness to the skin incision in 50% of the patients. It is the **measure of potency** of an agent. *Greater is the MAC, lesser is the potency.*

- **Nitrous oxide** is a gas with **maximum MAC** and thus **least potency**. Its MAC is 104% i.e. even with pure (100%) nitric oxide alone, we cannot get complete anaesthesia. This is thus, not a complete anaesthetic agent.
- **Methoxyflurane** is the **most potent** agent (having least MAC).

- **Blood gas partition coefficient:** It is determined by solubility of an agent in the blood. It **determines the speed of onset and recovery** of an anaesthetic drug. *Greater is blood gas partition coefficient, lesser is the speed of onset and recovery and vice versa..*

- **Desflurane** is the **fastest acting** agent as it has *minimum blood gas partition coefficient*.
- **Methoxyflurane** is the **slowest acting** agent (*maximum blood gas partition coefficient*).
- **Ether** also has a very high value of this coefficient; therefore it is also a **slow acting** agent. Due to its slow onset of action, we can differentiate the four stages of general anaesthesia whereas with modern anaesthetics like desflurane, these stages are hardly discernible.

Pin Index System

Air	1,5
O ₂	2,5
N ₂ O	3,5
CO ₂ (>7.5%)	1,6
CO ₂ (<7.5%)	2,6
Cyclopropane	3,6
Entonox	7

MAC is inversely related to potency whereas blood gas partition coefficient is inversely related to speed of onset and recovery of an inhalational agent.

Nitrous oxide is a gas with maximum MAC (least potent) whereas methoxyflurane is the most potent agent (having least MAC)

Anaesthetic	MAC (% atm)	Blood gas partition coefficient
Halothane	0.74	2.3
Enflurane	1.68	1.8
Isoflurane	1.15	1.4
Desflurane	6.0	0.42
Sevoflurane	2.05	0.69
Cyclopropane	9.2	0.44
Nitrous oxide	104	0.47
Trilene	0.2	9
Ether	1.92	12
Chloroform	0.8	8
Methoxyflurane	0.16	15
Xenon	70	0.115

BREATHING CIRCUITS

- *Open*: Ether, chloroform and ethyl chloride may be used.
- *Semi-closed (Mapelson circuits)*:
 Type A (Magill): *Circuit of choice for spontaneous ventilation* [fresh gas flow (FGF) = Respiratory minute volume (RMV)]
 Type B: Not used
 Type C (Water's): Not used
 Type D (Bain's): *Most commonly used circuit and circuit of choice for controlled ventilation* (FGF = $1.6 \times \text{RMV}$)
 Type E (Ayre's T piece): *Paediatric circuit*
 Type F (Jackson Rees'): *Most commonly used paediatric circuit.*
- *Closed*: Sodalime or barylime are used to absorb CO_2 . Barylime do not contain silica and is less efficient than sodalime. It is preferred in conditions with high production of CO_2 (e.g. malignant hyperthermia). *Trilene, sevoflurane and methoxyflurane should not be used in closed circuit.*

SYSTEMIC EFFECTS

Respiratory System

- All inhalational anaesthetic agents result in **respiratory depression (maximum with Enflurane)**. These also *blunt the ventilatory response to hypercapnea and hypoxia (maximum with halothane)*.
- All inhalational agents cause **bronchodilation** (thus increase anatomical dead space). **Maximum** bronchodilation is seen **with halothane** in asthmatics and with sevoflurane in non-asthmatics.
- All of these agents **reduce the ciliary activity** in respiratory system **except ether**.

Cardiovascular System

- All inhalational agents **reduce cardiac output except isoflurane and desflurane**. **Maximum** decrease in cardiac output is seen **with enflurane**.
- Blood pressure is reduced by all of these agents. **Maximum reduction in blood pressure** is seen with **isoflurane**. It is therefore used as an **agent of choice for producing controlled hypotension**. **Cyclopropane** results in increase in blood pressure. It is therefore **preferred in patients having shock**.
- All agents reduce cardiac contractility (maximum with halothane).
- **Baroreceptor reflexes** are also **blunted** by all inhalational anaesthetic agents (*maximum with halothane*). **Isoflurane** does not blunt these reflexes; therefore is the **drug of choice for cardiac patients**.



Maximum bronchodilation is seen with halothane in asthmatics and with sevoflurane in non-asthmatics.

Liver

- **Halothane, chloroform and methoxyflurane** can result in hepatotoxicity on long term use.

Kidney

- **Methoxyflurane** can result in **vasopressin resistant polyuric renal failure** due to the presence of high content of **fluoride** in it (*maximum*). *Fluoride is added to decrease the inflammability of these agents.*

Blood

- **Nitrous oxide** can result in **megaloblastic anemia** due to vitamin **B₁₂ deficiency**. It can also lead to *bone marrow suppression*.

Skeletal Muscles

- All inhalational agents are good **skeletal muscle relaxants** except **nitrous oxide**. **Maximum** muscle relaxation is caused by **ether**.

Analgesia

- **Newer** anaesthetic agents like halothane and isoflurane **are not** very good **analgesic** agents. **Maximum analgesia** is caused by **trilene** (ether is also a good analgesic agent).

Metabolic Effects

- Chloroform (*maximum*), ether and cyclopropane can cause hyperglycemia.

Inflammability

- **Ether and cyclopropane** are highly **inflammable** agents. *Cautery should not be used* when these agents are used to induce the anaesthesia.
- **Reaction with soda lime**
- Sevoflurane, trilene and methoxyflurane should not be used in closed circuit.
- **Sevoflurane** reacts with soda lime to produce **compound A**, which is highly **nephrotoxic**.
- **Trilene** reacts with soda lime in the closed circuit to produce **dichloroacetylene** (neurotoxic) and **phosgene** (can cause ARDS).
- **Methoxyflurane** reacts with **rubber tubing** of the closed circuit.

INDIVIDUAL DRUGS**Nitrous Oxide**

- It is also called '**laughing gas**'.
- It is colourless, non-irritating and non-inflammable.
- Colour of N₂O cylinder is **blue**.
- It is a very **good analgesic** but *weak* anaesthetic agent (**Highest MAC**).
- It is a **poor muscle relaxant**.
- It shows **faster induction & recovery** of anaesthesia (low blood gas partition coefficient).
- It is used in a concentration of 50 to 65% with 33% oxygen.
- **Entonox** is a *mixture of 50% N₂O + 50% O₂*.

- **Concentration effect** is seen with agents like N₂O, which are administered in high concentrations. Due to high concentration, when diffusion occurs from alveoli to blood, there is generation of negative pressure in the alveoli that leads to more removal of anaesthetic gas from the cylinder.
- **Second gas effect** is seen when another inhalational agent (like halothane) is administered along with N₂O. Due to generation of negative pressure, second gas is also taken in from the cylinder.
- **Diffusion hypoxia** occurs when supply of N₂O is stopped **while recovery** from anaesthesia. It can be **prevented by 100% oxygen** inhalation for a few minutes before discontinuing N₂O.

Halothane sensitizes the heart to arrhythmogenic action of adrenaline and nor-adrenaline. It is therefore contra-indicated in patients with pheochromocytoma.

Sevoflurane, trilene and methoxyflurane should not be used in closed circuit.

Diffusion hypoxia occurs when supply of N₂O is stopped during recovery from anaesthesia. It can be prevented by 100% oxygen inhalation for a few minutes before discontinuing N₂O.

Methemoglobinemia and laryngospasm may occur due to the presence of impurities like nitric oxide (NO) and nitrogen dioxide (NO₂).

- Bone marrow depression and megaloblastic anemia due to vitamin B₁₂ deficiency may also occur. Latter can result in subacute combined degeneration of spinal cord.
- N₂O use is **contraindicated in pneumothorax and volvulus** because it may lead to development of high pressure in the closed cavities in the body (like gut, pneumothorax and pneumoperitoneum).
- It is used as a supplement to anaesthesia (because it is not a complete anaesthetic).
- It is also used as a carrier gas for inhalational agents like halothane.

N₂O use is contraindicated in pneumothorax and volvulus because it may lead to development of high pressure in the closed cavities in the body.

Halothane

- It is a colourless, volatile liquid.
- It is a non-irritant, non explosive and pleasant smelling agent.
- It is stored in amber coloured bottles and contains thymol (0.01%) as preservative.
- It is a **good anaesthetic but very poor analgesic** agent.
- It can cause **hepatitis** on repeated use.
- It can also result in **malignant hyperthermia**, which can be treated with dantrolene.
- It can result in **post-anaesthetic chills and shivering**. **Pethidine is used for treatment** of this condition.
- Halothane relaxes the uterus. Due to this property, it is the **agent of choice in internal version and manual removal of placenta** (version can be accomplished easily in a relaxed uterus). However due to its uterine relaxing property, it is **contra-indicated in labour**, because if post-partum hemorrhage results, it will be difficult to control (contraction of uterus stops bleeding after labour).
- It sensitizes heart to the arrhythmogenic action of catecholamines. It is therefore **contra-indicated in patients with pheochromocytoma**.
- It is also a cardiodepressant drug that causes hypotension, bradycardia and arrhythmias.
- It is the inhalational **agent of choice in bronchial asthma** due to its bronchodilator action.
- It is an excellent agent for induction in **children**.

Halothane can result in post-anaesthetic chills and shivering. Pethidine is used for treatment of this condition.

Ether

- It is a **pungent smelling and irritant** liquid (can result in excessive secretions).
- It is a highly **inflammable and explosive** agent. Cautery should not be used with ether anaesthesia.
- It is a **very good analgesic and muscle relaxant**.
- It is very **slow in induction** of anaesthesia. Guedel's four stages of anaesthesia are based on ether.
- It **does not affect the ciliary action and is also a good bronchodilator**. Therefore it is safe in asthmatic patients.
- It is **very economical** and can be used as a sole agent for anaesthesia.
- It is the **safest agent in unskilled hands**.
- It can result in **hyperglycemia**, therefore is contra-indicated in diabetic patients.

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Properties of Halothane

- H – Hyperthermia [malignant hyperthermia]
- A – Arrhythmias (sensitize heart to adrenaline)
- L – Liver toxic
- O – Orthostatic hypotension
- T – Tocolytic
- H – Heart [inhibits heart; decreases cardiac output]
- A – Asthma [bronchodilator]
- N
- E ☐ Non-explosive
- C – Chills [post-anaesthetic shivering]
- C – Catecholamines [sensitizes heart to arrhythmogenic action]
- C – Children [safe in children]

Enflurane

- It is a halogenated ether.
- It is inflammable at high concentrations (> 5%)
- It is **contra-indicated in epilepsy** as it can raise intracranial tension and produce tonic clonic seizures.
- Like other newer agents, it is also **not a good analgesic**.

Enflurane is contra-indicated in **epilepsy** as it can raise intracranial tension and produce tonic clonic seizures.

Isoflurane is inhalational agent of choice for producing **controlled hypotension**.

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Inhalational anaesthetics that can precipitate seizures

S – Sevoflurane
E – Enflurane (Maximum)
I – Isoflurane
ZURE

Sevoflurane should not be used in closed circuit because it can produce a nephrotoxic metabolite, **Compound A**.

Desflurane has lowest boiling temperature (~24°C) whereas methoxyflurane has highest boiling point (~104°C)

Isoflurane

- It is an isomer of enflurane.
- It is not a good analgesic agent.
- Cardiac output is maintained with isoflurane. Therefore, it is the **inhalational agent of choice for cardiac surgery**.
- It produces least increase in intra-cranial tension, therefore is the **agent of choice for neurosurgery**.
- It produces maximum decrease in blood pressure, therefore is **inhalational agent of choice for producing controlled hypotension**.
- It can be used in **day care surgery**.
- It is **safe in pheochromocytoma** (does not sensitize the heart to catecholamines).
- It can cause **coronary steal phenomenon**.

Desflurane

- It has minimum blood gas partition coefficient and therefore is the **fastest** inducing agent.
- It has **very high vapour pressure**. Its boiling point is 23°C; therefore it boils at room temperature. It requires special vaporizers due to this property.
- It produces cardiovascular effects similar to isoflurane except coronary steal phenomenon.
- Induction with desflurane is unpleasant as it can lead to coughing, breath holding and laryngospasm.
- It can **also be used in day care surgery**.

Sevoflurane

- It is the **inhalational agent of choice for induction in children**.
- It is a very good muscle relaxant but poor analgesic agent.
- It should not be used in **closed circuit** because it can produce a **nephrotoxic metabolite, Compound A**.

Methoxyflurane

- It is the **most potent** inhalational agent (least MAC).
- It has the **slowest induction and recovery** (highest B/G partition coefficient).
- It can lead to **high output renal failure** (highest amount of fluoride content).
- It **should not be used in closed circuit** (reacts with rubber tubing of the closed circuit).

Trielene (Trichlorethylene)

- It is the **most potent analgesic agent**.
- It should not be used in **closed circuit** because reaction with soda lime can result in the production of **phosgene gas** (responsible for Acute Respiratory Distress Syndrome), and **dichloroacetylene** (neurotoxic to Vth and VIIth cranial nerves).
- It can be used for analgesia in labour.

Cyclopropane

- It is **highly inflammable and explosive agent**.
- Colour of its **cylinder is orange**
- It is the **inhalational agent of choice in hemorrhagic shock** (increases BP by increasing sympathetic tone).
- It should be stopped slowly because sudden discontinuation may result in hypotension (**cyclopropane shock**).

Chloroform

- It is a cardiotoxic agent and can result in **ventricular fibrillation**.
- It is also a **hepatotoxic** drug.
- It can cause profound **hyperglycemia**.

Carbon Dioxide

- 5% concentration is used for creating **pneumoperitoneum in laparoscopy**.
- Colour of its cylinder is **grey**.

Helium

- It is **lighter than air**.
- Mixture of 80% helium and 20% oxygen is used in cases of **tracheal obstruction**.

Xenon

Xenon is Greek for stranger. It was discovered in 1898 and found to be the **only noble gas to be anaesthetic under normobaric conditions**. Xenon is *extremely scarce* with an average room containing only 4ml. It is *very close to the 'ideal agent'*.



Xenon can be considered as ideal inhalational anaesthetic

- It is a *colourless and odourless* gas with no irritation to the respiratory tract. Well tolerated with gas induction.
- It has **lowest blood/gas partition co-efficient** (0.115) allowing rapid induction and reversal of anaesthesia.
- It produces unconsciousness with analgesia and a degree of muscle relaxation
- It has a MAC of 60-70% that allows a reasonable inspired oxygen concentration
- It **does cause respiratory depression**, to the point of apnoea.
- It has **no effect on cardiovascular function**.
- It is *not metabolised in the body* and is eliminated rapidly and completely via the lungs.
- It is *non toxic* and is not associated with allergic reactions
- It is *stable in storage*, has *no interaction with anaesthesia circuits or soda lime*. However, it should not be used with rubber anaesthesia circuits as there is a high loss through the rubber.
- It is *non-inflammable*
- Major problem with xenon is that it is **highly expensive** and routine usage will only be possible with a closed circuit delivery system that recycles xenon.

SUMMARY OF PROPERTIES OF INHALATIONAL AGENTS

Agent	Induction		Heart rate	BP	CMO ₂	Ventilation	B D
	Onset	Smoothness					
Halothane	Intermediate	Very smooth	↓	↓↓	↓	↓	++
Isoflurane	Intermediate	Slightly irritable	↑ (reflex)	↓↓↓	↓↓↓	↓	+
Enflurane	Intermediate	Slightly irritable	↓	↓↓	↓	↓	+
Nitrous oxide	Fast	Not used for induction	0	0	0	↓	0
Sevoflurane	Fast	Very smooth	↓	↓	↓	↓	+
Desflurane	Fastest	Slightly irritable	↑	↓↓	↓	↓	+
Ether	Slow	Highly irritable	↑	↑	↑↑	↑	++
Trielene	Slow	Smooth	0	0	–	↑↑	+
Methoxyflurane	Slowest	Smooth	↓	↓	–	↓	+
Cyclopropane	Fast	Smooth	↑	↑↑	–	↓	+
Choloroform	Slow	Smooth	↓	↓	–	↓	+

*BP: mean arterial pressure, CMO₂: O₂ consumption of brain, BD: bronchodilation

Note:

- Trielene has maximum analgesic activity.
- Ether has maximum muscle relaxant activity.
- All inhalational agents increase cerebral blood flow (maximum with halothane) as well as intracranial tension (maximum with halothane and ether).
- Halothane, chloroform and methoxyflurane are hepatotoxic whereas methoxyflurane and sevoflurane are nephrotoxic.

Intravenous Agents

These may be fast acting (used for induction) or may be slow acting.

1. INDUCING AGENTS**A. Thiopentone**

- It is an *ultra short acting barbiturate* and is the *most commonly used intravenous inducing agent*. It is used as a 2.5% solution.
- *Sulphur* is added to pentobarbitone to *increase the lipid solubility*.
- Due to high lipid solubility, it is very fast acting drug.
- Action of this drug terminates very quickly due to **redistribution** (although half life is longer).
- It also possesses **anticonvulsant** action (another barbiturate *methohexitone* increases the risk of convulsions, therefore *used for electroconvulsive therapy*).
- It is the *agent of choice for cerebral protection* (decreases cerebral oxygen consumption, decreases intra-cranial tension and decreases cerebral metabolic rate).
- It causes peripheral vasodilatation and also depresses cardiovascular system, therefore can cause *hypotension*.
- Instead of producing analgesic effect, it can *produce hyperalgesia* at subanaesthetic doses.
- *Respiratory depression* and transient apnea are other problems seen with this agent.
- On **accidental injection** of thiopentone **in the arteries**, it can lead to thrombosis and vasoconstriction that may progress to **ischemia and gangrene**. It is accompanied by very severe pain. This condition is treated by **leaving the needle in situ** (*needle should not be withdrawn*), dilution of injected thiopentone with saline, immediate heparinization and papaverine injection to relieve spasm. Vasodilators, steroids, lignocaine and urokinase can also be employed. Brachial plexus and stellate ganglion block should be performed.
- Barbiturates are absolutely **contra-indicated in acute intermittent porphyria**.

B. Methohexitone

- It is also an ultra short acting barbiturate.
- It is 3 times more potent than thiopentone.
- It induces seizures; therefore, it is the agent of choice for electroconvulsive therapy.

C. Ketamine

- It is a *phencyclidine (hallucinogenic) derivative* that is administered in a dose of 2 mg/kg.
- Its onset of action is 30-60s whereas action terminates in 15-20 min. due to *redistribution*.
- It acts by **blocking NMDA receptors** of glutamate.
- It is a **very strong analgesic** agent but *lacks muscle relaxant property*.
- It is used for producing **dissociative anaesthesia** (state of profound analgesia, amnesia with light sleep, immobility, feeling of dissociation from one's own body and the surroundings).

Contd...

Thiopentone is used as a 2.5% solution for i.v. induction of anaesthesia

Action of thiopentone terminates very quickly due to redistribution.

Contd...

- It does not depress pharyngeal and laryngeal reflexes; therefore is the **agent of choice** for emergency anaesthesia with **full stomach** (because vomiting will prevent aspiration).
- It **increases all pressures** (blood pressure, intracranial tension, intraocular pressure) in the body. It is therefore intravenous *anaesthetic of choice for shock* (increases blood pressure). Further it is *contraindicated in glaucoma* (increases IOP) and *head injuries* (increases ICT).
- It is a powerful bronchodilator agent and is therefore **intravenous anaesthetic of choice in bronchial asthma** (*halothane is the inhalational anaesthetic agent of choice for bronchial asthma*).
- It is the **intravenous anaesthetic agent of choice for induction in children** (*Sevoflurane is inhalational agent of choice in children*).
- On discontinuation of ketamine anaesthesia, several adverse effects may be seen (known as **emergence reaction**). **Hallucinations are the most common side effect**. Other effects include *vivid dreams, illusions and excitement*.

M

- K** Kids (i.v. anaesthetic of choice in children)
- E** Emergence reaction [hallucinations, illusions, vivid dreams etc. seen while recovery from anaesthesia]
- T** Thalamocortical junction [site of action, responsible for dissociative anaesthesia]
- A** Analgesic [maximum among anaesthetics]
- M** Meals [can be given in full stomach]
- I** Increases all pressures [BP, IOP, ICT]
- N** NMDA antagonist
- E** Excellent for asthmatics.

D. Propofol

- It is a **milky white powder** that is **preservative free**. Therefore, it must be used within 6 hours.
- It is an **oil based preparation**, therefore injection is *painful*.
- Its onset of action is within 15 seconds and last for 5-10 min. (due to redistribution)
- It possesses very **strong antiemetic and antipruritic action**.
- It *decreases blood pressure* and impairs baroreceptor reflexes.
- It produces more severe and prolonged *respiratory depression* than thiopentone.
- It has *no muscle relaxant property*.
- It has cerebroprotective activity but does not possess anticonvulsant activity. Rather, **myoclonic jerking and muscle twitching** can be seen with the use of propofol.
- It is the intravenous anaesthetic of choice for **day care surgery**.
- It is also the intravenous anaesthetic of choice for *sedation in ICU*.
- Propofol is the intravenous anaesthetic of choice in the patients with **malignant hyperthermia**.
- This agent is intravenous anaesthetic of choice, and is used with alfentanil for **total intravenous anaesthesia** (TIVA).

A

Propofol is the intravenous anaesthetic of choice for:

- Day care surgery
- Total Intravenous anaesthesia (TIVA)
- Sedation in ICU
- Malignant Hyperthermia

DISH

E. Etomidate

- It does not interfere with cardiovascular functions; therefore is **the agent of choice for aneurysm surgeries and cardiac disease**.
- It causes minimal respiratory depression.
- Maximum incidence of **nausea and vomiting** is seen with the use of this agent.
- It can also produce **myoclonus**.
- Injection of etomidate is **painful** and may result in thrombophlebitis.
- It can lead to **adrenocortical suppression**.
- **Vitamin C deficiency** can also develop with the use of etomidate.

SUMMARY OF SYSTEMIC EFFECTS OF INTRAVENOUS ANAESTHETICS							
Agent	Cardiovascular system		Central nervous system			Respiratory system	
	Heart rate	Mean arterial	O ₂ of consumption brain	ICT	Cerebral blood flow	Ventilation	Bronchial muscles
Thiopentone	↑ (reflex)	↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓	Constriction (tachycardia)
Methohexital	↑	↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓	Constriction
Ketamine	↑↑	↑↑	↑↑	↑↑	↓↓↓	↑	Dilatation
Propofol	0	↓↓↓	↓↓↓	↓↓↓	↓↓↓	↓↓	0
Etomidate	0	↓	↓↓	↓↓	↓↓	↓	0

2. SLOW ACTING AGENTS

A. Benzodiazepines

- Important benzodiazepines are diazepam, lorazepam and midazolam.
- These are not analgesic agents.
- However, these possess muscle relaxing and anticonvulsant property.
- Lorazepam is the most commonly used benzodiazepine in pre-anaesthetic medication.
- Midazolam is used for day care surgery.
- These agents may cause sedation and anterograde amnesia.

B. Opioids

- **Fentanyl, alfentanil, sufentanil and remifentanyl** are the opioids used in anaesthesia.
- These are 100 times **more potent than morphine**. **Sufentanil is the most potent** opioid.
- These drugs possess very **strong analgesic** activity.
- **Fentanyl** is used along with droperidol for **neurolept analgesia**.
- If nitrous oxide is also added, the combination can be used as **neurolept anaesthesia** (N₂O + fentanyl + droperidol).
- These agents can lead to **post operative muscle rigidity** (SCH causes post operative muscle pain and fasciculations).
- **Alfentanil** is used for day care surgery and for **total intravenous anaesthesia**.
- **Remifentanyl** is the **shortest acting** opioid (due to its metabolism by esterases).

C. Neuroleptic agent

- **Droperidol** is a D₂ receptor blocker.
- It is used along with fentanyl to produce **neurolept analgesia and neurolept anaesthesia**.
- It can produce **extrapyramidal symptoms**.

Drugs Useful for Day Care Surgery

Dr	Desflurane
Manmohan	Midazolam (Benzodiazepine)
Singh	Sevoflurane
Is	Isoflurane
A	Alfentanil
Prime	Propofol
Minister	Mivacurium (Muscle relaxant)

ANAESTHETIC AGENTS OF CHOICE FOR VARIOUS CONDITIONS

Day care:	Propofol
Ischemic heart disease:	Etomidate
<i>Congenital heart disease</i>	
– Left to right shunt:	Isoflurane
– Right to left shunt:	Ketamine
CHF:	Ketamine
Shock:	Ketamine
To produce deliberate hypotension:	Isoflurane
Asthma and COPD:	Ketamine
Epilepsy:	Thiopentone
For electroconvulsive therapy:	Methohexitone
Thyrotoxicosis:	Thiopentone
Cardiac surgery:	Isoflurane
Neurosurgery:	Isoflurane

DRUG OF CHOICE	
Condition	Drug of choice
• Neurolept analgesia	Droperidol + Fentanyl
• Neurolept anaesthesia	Droperidol + Fentanyl + N ₂ O
• GA for internal version	Halothane
• GA for asthma	
– Inducing agent	Ketamine
– Inhalational	Halothane
• GA to produce controlled hypotension	Isoflurane
• GA for cardiac surgery	
– Inducing agent	Etomidate
– Inhalational	Isoflurane
• GA for neurosurgery	Isoflurane
• Day care surgery	Propofol
• Total Intravenous Anaesthesia	Propofol
• GA for malignant hyperthermia	Propofol
• GA in patients with shock	Ketamine
• LA in patients with malignant hyperthermia	Procaine
• Intravenous Regional Anaesthesia (IVRA; Bier's block)	Prilocaine
• Malignant hyperthermia	Dantrolene
• Malignant Neuroleptic Syndrome	Dantrolene
• MR in patients with asthma	Vecuronium
• MR in liver and kidney disease	Atracurium or Cis-atracurium
• MR for endotracheal intubation	Succinylcholine

Note:

- GA : General Anaesthetic
- LA : Local Anaesthetic
- MR : Muscle Relaxant

MULTIPLE CHOICE QUESTIONS

LOCAL ANAESTHESIA

- All of the following statements about lignocaine are true EXCEPT:** (AIIMS Nov 2012)
 - It blocks active sodium channels with more affinity than resting sodium channels
 - It can cause cardiotoxicity
 - It is given orally for treatment of cardiac arrhythmias
 - Adrenaline increases the duration of action of lignocaine when used for infiltration anaesthesia.
- Maximum dose of lignocaine given with adrenaline for infiltration anaesthesia is:** (AIIMS May 2012)
 - 3 mg/kg
 - 5 mg/kg
 - 7 mg/kg
 - 10 mg/kg
- Anaesthetic agent with vasoconstrictor is contraindicated in?** (AI - 2011)
 - Digital block
 - Spinal block
 - Epidural block
 - Regional anaesthesia
- Methemoglobinemia is caused by:** (AIIMS May 2010) (AIIMS May 2009 Karnataka 2004)
 - Prilocaine
 - Ropivacaine
 - Bupivacaine
 - Procaine
- First local anesthetic used in clinical anaesthesia was:** (AIIMS Nov 2009)
 - Bupivacaine
 - Procaine
 - Lidocaine
 - Cocaine
- From which of the following routes, absorption of local anaesthetic is maximum?** (AIIMS Nov 2008)
 - Intercostal
 - Epidural
 - Brachial
 - Caudal
- Blockade of nerve conduction by a local anesthetic is characterized by:** (DPG 2009)
 - Greater potential to block a resting nerve as compared to a stimulated nerve
 - Need to cross the cell membrane to produce the block
 - Large myelinated fibers are blocked before the unmyelinated fibers
 - Cause consistent change of resting membrane potential
- In spinal anaesthesia the drug is deposited between:** (DPG 2009)
 - Dura and arachnoid
 - Pia and arachnoid
 - Dura and vertebra
 - Into the cord substance
- Cardiac or central nervous system toxicity may result when standard lignocaine doses are administered to patients with circulatory failure. This may be due to the following reason:** (AI 2003)
 - Lignocaine concentration is initially higher in relatively well perfused tissues such as brain and heart.
 - Histamine receptors in brain and heart get suddenly activated in circulatory failure
 - There is a sudden outburst of release of adrenaline, noradrenaline and dopamine in brain and heart
 - Lignocaine is converted to a toxic metabolite due to its longer stay in the liver.
- Bupivacaine poisoning is treated with:** (PGI Dec. 2007)
 - Esmolol
 - Sotalol
 - Lignocaine
 - 5% dextrose
 - Diazepam
- Which of the following statements is not true of local anaesthetics?**
 - The local anaesthetic is required in the unionized form for penetrating the neuronal membrane
 - The local anaesthetic approaches its receptor only from the intraneuronal face of the Na⁺ channel
 - The local anaesthetic binds to its receptor mainly when the Na⁺ channel is in the resting state
 - The local anaesthetic combines with its receptor in the ionized cationic form
- The following local anaesthetic raises BP instead of tending to cause a fall:**
 - Cocaine
 - Dibucaine
 - Lignocaine
 - Procaine
- The local anaesthetic with the longest duration of action is:**
 - Procaine
 - Chlorprocaine
 - Lignocaine
 - Dibucaine
- Eutectic lignocaine-prilocaine has the following unique property:**
 - It causes motor blockade without sensory block

- (b) By surface application, it can anaesthetize unbroken skin
- (c) It is not absorbed after surface application
- (d) It has strong vasoconstrictor action

15. The segmental level of spinal anaesthesia depends on:

- (a) Volume of the local anaesthetic injected
- (b) Specific gravity of the local anaesthetic solution
- (c) Posture of the patient
- (d) All of the above

16. In spinal anaesthesia the segmental level of:

- (a) Sympathetic block is lower than the sensory block
- (b) Sympathetic block is higher than the sensory block
- (c) Motor block is higher than the sensory block
- (d) Sympathetic, motor and sensory block has the same level

17. The duration of spinal anaesthesia depends on all of the following EXCEPT:

- (a) Local anaesthetic that is used
- (b) Concentration of the local anesthetic used
- (c) Posture of the patient
- (d) Whether adrenaline has been added to the local anaesthetic

18. Intravenous regional anaesthesia is suitable for:

- (a) Orthopedic manipulation on the upper limb
- (b) Vascular surgery on the lower limb
- (c) Head and neck surgery
- (d) Caesarian section

19. Most cardiotoxic local anaesthetic is:

- (a) Procaine
- (b) Bupivacaine
- (c) Prilocaine
- (d) Tetracaine

20. A patient receives a toxic dose of lignocaine i.v., the patient is likely to exhibit:

- (a) Excessive salivation
- (b) Mydriasis and diarrhea
- (c) Respiratory paralysis
- (d) Seizures and coma

21. An agent added to local anesthetics to speed the onset of action is:

- (a) Methylparapben
- (b) Bicarbonate
- (c) Fentanyl
- (d) Adrenaline

22. Epinephrine added to a solution of lignocaine for a peripheral nerve block will:

- (a) Increase risk of convulsions
- (b) Increase the duration of action of the local anesthetic
- (c) Both (a) and (b)
- (d) None of these

23. All of the following are properties of local anesthetics EXCEPT:

- (a) Blockade of voltage dependent Na^+ channels
- (b) Preferential binding to resting channels

- (c) Slowing of axonal impulse conduction
- (d) Increase in the membrane refractory period

24. The most important adverse effect of i.v. administration of large dose of an amide anesthetic is:

- (a) Bronchoconstriction
- (b) Hepatic damage
- (c) Renal failure
- (d) Seizures

25. Ram has a 4 ml lignocaine vial of 2% solution. How much lignocaine is present in 1 ml?

- (a) 2 mg
- (b) 8 mg
- (c) 20 mg
- (d) 200 mg

26. Which of the following drugs has a high surface activity and vasoconstrictor actions that reduce bleeding in mucus membranes?

- (a) Bupivacaine
- (b) Cocaine
- (c) Lidocaine
- (d) Procaine

27. All are vasodilators except:

(DPG 2010)

- (a) Procaine
- (b) Lidocaine
- (c) Cocaine
- (d) Chlorprocaine

28. Which of the following local anaesthetics belongs to the ester group?

(DPG 2010)

- (a) Procaine
- (b) Bupivacaine
- (c) Lignocaine
- (d) Mepivacaine

29. The following statements about Bupivacaine are true except:

(DPG 2010)

- (a) Must never be injected into a vein
- (b) More cardiotoxic than lignocaine
- (c) 0.5 percent is effective for sensory block
- (d) It produces methaemoglobinemia

30. Local anesthetics act by:

(DPG 2006)

- (a) Affecting at the spinal level
- (b) Affecting the Na^+ channels
- (c) Affecting the K^+ channels
- (d) Blocking axonal transport

31. Local anesthetics:

(MPPG 2002)

- (a) Block the release of neurotransmitters
- (b) Block the influx of sodium into the cell
- (c) Increase the release of inhibitory neurotransmitters
- (d) Inhibit the efflux of sodium from neurons

32. All are true about bupivacaine Except:

(UP 2007)

- (a) Less cardiotoxic than lignocaine
- (b) Dose increases with adrenaline
- (c) Long acting
- (d) Cannot given in vein

33. **Post dural (Spinal) puncture headache is due to:** (UP 2007)
 (a) Seepage of CSF
 (b) Fine needle
 (c) Toxic effects of the drugs
 (d) Traumatic damage to nerve roots
34. **True statement regarding Bupivacaine is:** (UP 2005)
 (a) Used intravenously along with lignocaine
 (b) More cardiotoxic than lignocaine
 (c) Contraindicated in pregnancy
 (d) All of the above
35. **Percentage of lignocaine used in spinal anesthesia is:** (RJ 2001)
 (a) 0.5%
 (b) 1%
 (c) 2%
 (d) 5%
36. **The mechanism of action of local anesthetics is that they act on Na⁺ channels in their:** (Kolkata 2008)
 (a) Activated state
 (b) Inactivated state
 (c) Resting state
 (d) Any state
37. **The most potent and longest acting anaesthetic agent is:** (Karnataka 2008)
 (a) Dibucaine
 (b) Tetracaine
 (c) Bupivacaine
 (d) Lignocaine
38. **Adrenaline is added to lignocaine to prolong its effect and decrease its absorption into blood stream in a ratio of:** (Karnataka 2006)
 (a) 1:50,000
 (b) 1:100,000
 (c) 1:200,000
 (d) 1:500,000
- (b) Dantrolene
 (c) Diazepam
 (d) Tizanidine
42. **Which one of the following skeletal muscle relaxants causes pain on injection?** (AIIMS Nov 2011) (AI 2012)
 (a) Succinyl choline
 (b) Vecuronium
 (c) Rocuronium
 (d) Pancuronium
43. **Cis-atracurium is preferred over atracurium, because:** (AIIMS May 2011)
 (a) It has rapid onset of action
 (b) It causes less release of histamine
 (c) It has short duration of action
 (d) It has less depressant action on heart
44. **Laudanosine is a metabolite of:** (AIIMS May 2011)
 (a) Atracurium
 (b) Cis-atracurium
 (c) Pancuronium
 (d) Vecuronium
45. **Muscular rigidity caused by opioids is due to the agonistic effect on which receptor?** (AIIMS May 2011)
 (a) Mu
 (b) Kappa
 (c) Delta
 (d) Sigma
46. **A 70 kg young athlete was planned for surgery. During anaesthesia, vecuronium was not available, so repeated doses of succinylcholine was given intermittently up to 640 mg. During recovery, patient was not able to spontaneously respire and move limbs. What is the cause?** (AIIMS Nov 2010)
 (a) Pseudocholinesterase deficiency
 (b) Phase II blockade
 (c) Muscle weakness due to repeated fasciculations
 (d) Undiagnosed muscular dystrophy

■ SKELETAL MUSCLE RELAXANTS

39. **Which of the following skeletal muscles is relaxed first by tubocurarine?** (AIIMS Nov, 2013)
 (a) Respiratory
 (b) Fingers
 (c) Limbs
 (d) Head and neck
40. **Central muscle relaxants act by:** (PGI June, 2002)
 (a) Decreasing nerve conduction
 (b) Inhibiting spinal polysynaptic reflexes
 (c) Blocking conduction across NM junction
 (d) Causing CNS depression
 (e) Decreasing muscle excitation
41. **Which of the following drugs has spasmolytic activity and could also be used in the management of seizure caused by overdose of a local anesthetic?** (AIIMS May 2012)
 (a) Baclofen
 (b) Dantrolene
 (c) Diazepam
 (d) Tizanidine
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 (a) Pseudocholinesterase deficiency
 (b) Phase II blockade
 (c) Muscle weakness due to repeated fasciculations
 (d) Undiagnosed muscular dystrophy
47. **The administration of succinylcholine to a paraplegic patient led to appearance of dysarrhythmias, conduction abnormalities and finally cardiac arrest. The most likely cause is:** (DPG 2011)
 (a) Hypercalcemia
 (b) Hyperkalemia
 (c) Anaphylaxis
 (d) Hypermagnesemia
48. **Muscle relaxant of choice in liver disease is?** (AI 2010)
 (a) Atracurium
 (b) Pipecuronium
 (c) Rocuronium
 (d) Vecuronium
49. **Which of the following is a metabolite of carisoprodol?** (AIIMS Nov 2009)
 (a) Doxylamine
 (b) Meprobamate
 (c) Dimethadione
 (d) Amphetamine

50. A child presents with bladder exstrophy and chronic renal failure. The muscle relaxant of choice to be used during surgery of exstrophy in this child is:
(a) Atracurium (AIIMS Nov 2009)
(b) Mivacurium
(c) Pancuronium
(d) Rocuronium
51. All of the following can aggravate Myasthenia gravis except:
(a) Azathioprine (AIIMS May 2009)
(b) d- Tubocurarine
(c) Tetracycline
(d) Aminoglycoside
52. Shortest acting non-depolarizing muscle relaxant is:
(a) Succinyl choline (AIIMS May 2008)
(b) Rapacurium
(c) Atracurium
(d) Pancuronium
53. d-Tubocurarine acts by:
(a) Inhibiting nicotinic receptors at myoneural junction (DPG 2009)
(b) Inhibiting nicotinic receptors at autonomic ganglion
(c) Producing depolarizing block
(d) By inhibiting reuptake of acetylcholine
54. Muscle relaxant of choice in renal and hepatic failure is:
(a) Cis-atracurium (AIIMS May 2007)
(b) Vecuronium
(c) Rocuronium
(d) Rapacurium
55. Neostigmine antagonizes non-depolarizing blockade by all of the following mechanisms EXCEPT:
(a) Decreasing the breakdown of acetylcholine at the motor end plate (AIIMS May 2006)
(b) Preventing the K⁺ efflux from the cell
(c) Increasing the release of acetylcholine at the motor end plate
(d) Depolarization at the motor end plate
56. Bradycardia is common after injection of:
(a) Midazolam (AIIMS Nov, 2005)
(b) Succinylcholine
(c) Dopamine
(d) Isoprenaline
57. Hepatotoxic drugs are:
(a) Chloroform (PGI June, 2003)
(b) Ether (diethyl)
(c) N₂O
(d) Halothane
(e) Enflurane
58. The fall in blood pressure caused by d-tubocurarine is due to:
(a) Reduced venous return
(b) Ganglionic blockade
(c) Histamine release
(d) All of the above
59. Pancuronium differs from tubocurarine in that:
(a) It is a depolarizing blocker
(b) Its action is not reversed by neostigmine
(c) It can cause rise in BP on rapid I.V. injection
(d) It causes marked histamine release
60. The neuromuscular blocker that does not need reversal of action by neostigmine at the end of the operation is:
(a) d-Tubocurarine
(b) Doxacurium
(c) Pipecuronium
(d) Mivacurium
61. The most rapidly acting nondepolarizing neuromuscular blocking agent which can be used as an alternative to succinylcholine for tracheal intubation is:
(a) Rocuronium
(b) Pancuronium
(c) Doxacurium
(d) Pipecuronium
62. The following antibiotic accentuates the neuromuscular blockade produced by pancuronium:
(a) Streptomycin
(b) Erythromycin
(c) Penicillin G
(d) Chloramphenicol
63. Dantrolene sodium reduces skeletal muscle tone by:
(a) Reducing acetylcholine release from motor nerve endings
(b) Suppressing spinal polysynaptic reflexes
(c) Inhibiting the generation of muscle action potential
(d) Reducing Ca²⁺ release from sarcoplasmic reticulum in the muscle fibre
64. Which of the following is a skeletal muscle relaxant that acts as a central α_2 adrenergic agonist:
(a) Tizanidine
(b) Brimonidine
(c) Chlormezanone
(d) Quinine
65. One of the following statements about succinylcholine is true:
(a) It may induce life threatening hyperkalemia
(b) It has a long duration of action
(c) It is the drug of choice in non traumatic rhabdomyolysis
(d) It is useful in patients with spinal cord injuries with paraplegia
66. Which of the following drugs has caused hyperkalemia leading to cardiac arrest in patients with neurological disorders?
(a) Baclofen
(b) Dantrolene
(c) Succinylcholine
(d) Tubocurarine
67. Which of the following drugs is most effective in the management of malignant hyperthermia?
(a) Baclofen

- (b) Dantrolene
(c) Succinylcholine
(d) Vecuronium
68. Patient undergoing surgery was given a muscle relaxant. It produced marked fall in B.P. and increase in airway resistance which were reversed with diphenhydramine. The muscle relaxant was most probably:
(a) Atracurium
(b) Diazepam
(c) Tubocurarine
(d) Vecuronium
69. Which of the following drugs is hydrolyzed by a plasma esterase that is abnormally low in activity in about 1 in every 2500 humans?
(a) Ethanol
(b) Rifampicin
(c) Cimetidine
(d) Succinylcholine
70. While performing a rapid sequence intubation in the operation theatre, a patient was given a standard intravenous dose of muscle relaxant "A." To maintain the muscle relaxation during surgery, another muscle relaxant vecuronium was given. At the end of the surgery, neostigmine was used to reverse the residual muscle relaxation. However, the patient did not respond and continued to display too much muscle paralysis to permit safe extubation. Drug A was most likely to be?
(a) Pancuronium
(b) Succinylcholine
(c) Midazolam
(d) Tubocurarine
71. The enzyme pseudocholinesterase acts on:
(a) Decamethonium (DPG 2010)
(b) Tubocurarine
(c) Gallamine
(d) Suxamethonium
72. Hoffman's elimination is seen with:
(a) Atracurium (DPG 2007, DPG 2003)
(b) Vecuronium (MPPG 2005, RJ 2001)
(c) Pancuronium (Karnataka 2004)
(d) Rocuronium
73. Non-depolarizing blockade is potentiated by:
(a) Hyperkalemia (DPG 2007)
(b) Hypomagnesemia
(c) Chronic phenytoin therapy
(d) Quinidine
74. The drug causing curare like effect are all, EXCEPT:
(a) Chloramphenicol (DPG 2001)
(b) Polymyxin
(c) Tetracycline
(d) Streptomycin
75. Which of the following muscle relaxants is free of cardiovascular effects over the entire clinical dose range?
(a) Pancuronium (MPPG 2007)
(b) Vecuronium
(c) Atracurium
(d) Pipecuronium
76. Suxamethonium is:
(a) Non depolarizing muscle relaxant
(b) Depolarising muscle relaxant
(c) Direct acting muscle relaxant
(d) All of the above (UP 2008)
77. Baclofen is:
(a) Centrally acting muscle relaxant
(b) Peripherally acting muscle relaxant
(c) Both centrally and peripherally acting muscle relaxant
(d) Direct acting muscle relaxant (UP 2005)
78. True statement regarding depolarizing neuromuscular blocking drugs is:
(a) The depolarized muscles fibres are unresponsive to other stimuli
(b) Causes muscular fasciculations
(c) Not reversed by neostigmine
(d) All of the above (UP 2005)
79. Shortest acting neuromuscular blocker is:
(a) Gallamine (RJ 2004)
(b) Pancuronium
(c) Succinylcholine
(d) d-TC
80. Long acting non-depolarizing muscle relaxants is:
(a) Succinylcholine (Bihar 2004)
(b) Mivacurium
(c) Pancuronium
(d) Phenylephrine
81. In case of spasticity, the drug not used is:
(a) Diazepam (Kolkata 2008)
(b) Baclofen
(c) Tizanidine
(d) Amitriptyline
82. The drug inactivated in plasma by spontaneous non-enzymatic degradation is:
(a) Atracurium (Karnataka 2008)
(b) Vecuronium
(c) Pipecuronium
(d) Pancuronium
83. Which one of the following drugs is not a long acting neuromuscular blocking agent?
(a) Doxacurium (Karnataka 2006)
(b) Mivacurium
(c) Pancuronium
(d) Pipecuronium
84. The following is the feature of depolarizing blockade?
(a) Tetanic fade (DPG 2007)
(b) Post tetanic potentiation
(c) Progression to dual blockade
(d) Antagonism by anticholinesterases

85. Drug not acting on neuromuscular junction is:

- (a) Baclofen (Bihar 2006)
- (b) Carisoprodol
- (c) Haloperidol
- (d) All of the above

GENERAL ANAESTHESIA

86. A patient with ruptured spleen is taken for laparotomy. His blood pressure is 80/50 and heart rate is 125/min. Induction agent of choice for this patient is:

- (a) Sodium Thiopentone (AIIMS May 2012)
- (b) Fentanyl
- (c) Ketamine
- (d) Halothane

87. Which of these can be safely stopped before an abdominal surgery? (AI 2012)

- (a) ACE inhibitors
- (b) Beta blocker
- (c) Statins
- (d) Steroids

88. Xenon anesthesia all are true except: (AI 2012)

- (a) Slow induction and recovery
- (b) Non explosive
- (c) Minimal cardiovascular side-effects
- (d) Low blood solubility

89. A 32 year old male is a known hypertensive and is being planned for cholecystectomy. Which of the following anaesthetic agents is contraindicated in this person? (AI - 2011)

- (a) Propofol
- (b) Ketamine
- (c) Midazolam
- (d) Etomidate

90. Which anaesthetic modality is to be avoided in sickle cell disease? (AI - 2011), (AIIMS May 2010)

- (a) General Anaesthesia
- (b) Brachial Plexus Block
- (c) Intravenous Regional Anaesthesia
- (d) Spinal Anaesthesia

91. Anaesthetic having epileptogenic potential is:

- (a) Desflurane (AI - 2011)
- (b) Sevoflurane
- (c) Ether
- (d) Halothane

92. A patient with mitral stenosis had to undergo surgery. Pre-anaesthetic checkup revealed the increased liver enzymes. Which of the following inhalational agent should be preferred in this patient? (AIIMS Nov 2010)

- (a) Xenon
- (b) Enflurane
- (c) Halothane
- (d) Sevoflurane

93. Which of the following intravenous induction agent suppress steroidogenesis?

- (a) Thiopentone (AIIMS Nov 2010)
- (b) Propofol
- (c) Ketamine
- (d) Etomidate

94. The following causes increased intra ocular pressure:

- (a) Thiopentone (DPG 2011)
- (b) Althesin
- (c) Ketamine
- (d) Barbiturate

95. Nitrous oxide is contraindicated in patients with pneumothorax, pneumopericardium or intestinal obstruction, because it: (DPG 2011)

- (a) Depresses an already compromised myocardium
- (b) Permits the use of limited FIO₂ only
- (c) Is less soluble than nitrogen
- (d) Causes the expansion of air filled body cavities

96. Anaesthesia contraindicated in volvulus of gut is:

- (a) Halothane (DPG 2011)
- (b) Nitrous oxide
- (c) Ketamine
- (d) Pancuronium

97. A 5 years old child is suffering from cyanotic heart disease. He is planned for corrective surgery. The induction agent of choice would be: (DPG 2011)

- (a) Thiopentone
- (b) Ketamine
- (c) Halothane
- (d) Midazolam

98. Which of the following induction agent produce cardiac stability? (AIIMS May 2009)

- (a) Ketamine
- (b) Etomidate
- (c) Propofol
- (d) Midazolam

99. Anaesthetic agent which is explosive in the presence of cautery: (DPG 2009)

- (a) Nitrous oxide
- (b) Ether
- (c) Trilene
- (d) Halothane

100. Best uterine relaxation is seen with: (DPG 2009)

- (a) Chloroform
- (b) Nitrous oxide
- (c) Ether
- (d) Halothane

101. Hallucinations are seen after anaesthesia:

- (a) Ketamine (DPG 2009)
- (b) Thiopentone
- (c) Fentanyl
- (d) Nitrous oxide

102. Anaesthetic that has a smooth induction is:

- (a) Diethyl ether (DPG 2009)
- (b) Isoflurane
- (c) N₂O
- (d) Halothane

103. Which of the following drugs are believed to be effective in the treatment of post operative shivering?
(a) Ondansetron (DPG 2009)
(b) Diclofenac sodium
(c) Pethidine
(d) Paracetamol
104. "MAC" of desflurane is: (DPG 2009)
(a) 1.15
(b) 2
(c) 4
(d) 6
105. Which of the following should be considered as the cause of generalized convulsions 20 minutes postoperatively?
(DPG 2009)
(a) Halothane
(b) Enflurane
(c) Isoflurane
(d) Sevoflurane
106. Remifentanyl is: (PGI Dec. 2007)
(a) Long acting anaesthetic
(b) Useful for short painful procedures
(c) Administered by intravenous bolus dose
(d) Metabolized by plasma esterases
(e) Equipotent as fentanyl
107. The minimal alveolar concentration of an inhalational anaesthetic is a measure of its:
(a) Potency
(b) Therapeutic index
(c) Diffusibility
(d) Oil: water partition coefficient
108. Which general anaesthetic selectively inhibits excitatory NMDA receptors:
(a) Thiopentone
(b) Halothane
(c) Desflurane
(d) Ketamine
109. 'Second gas effect' is exerted by which of the following gas when coadministered with halothane:
(a) Nitrous oxide
(b) Cyclopropane
(c) Nitrogen
(d) Helium
110. Which of the following general anaesthetics has poor muscle relaxant action?
(a) Ether
(b) Nitrous oxide
(c) Halothane
(d) Isoflurane
111. Select the correct statement about nitrous oxide:
(a) It irritates the respiratory mucosa
(b) It has poor analgesic action
(c) It is primarily used as a carrier and adjuvant to other anaesthetics
(d) It frequently induces post anaesthetic nausea and retching
112. Ether is still used as a general anaesthetic in India, specially in peripheral hospitals because:
(a) It is non-explosive
(b) It is pleasant smelling and non irritating
(c) It induces anaesthesia rapidly
(d) It is cheap and can be administered without anaesthetic machine
113. As a general anaesthetic, halothane has the following advantages EXCEPT:
(a) Very good analgesic action
(b) Non-inflammable and non-explosive
(c) Reasonably rapid induction of anaesthesia
(d) Pleasant and non-irritating
114. Malignant hyperthermia is a rare complication of the use of the following anaesthetic:
(a) Ketamine
(b) Thiopentone sodium
(c) Halothane
(d) Ether
115. 'Dissociative anaesthesia' is produced by:
(a) Ketamine
(b) Fentanyl
(c) Propofol
(d) Both (a) and (b) are correct
116. Ketamine is the preferred anaesthetic for the following EXCEPT:
(a) Hypertensives
(b) Trauma cases that have bled significantly
(c) Burn dressing
(d) Short operations on asthmatics
117. If ketamine is the only agent used in reducing a dislocated shoulder, its actions will include:
(a) Analgesia
(b) Bradycardia
(c) Hypotension
(d) Respiratory depression
118. Postoperative vomiting is uncommon with this intravenous anaesthetic agent and patients are able to ambulate sooner than those who receive other anaesthetic agents:
(a) Ketamine
(b) Enflurane
(c) Propofol
(d) Remifentanyl
119. A young man having pheochromocytoma has BP of 188/92 mm Hg and a hematocrit of around 50%. Pulmonary function tests and renal functions are normal. His catecholamines are elevated. Which of the following drugs should not be included in the anesthesia protocol?
(a) Desflurane
(b) Fentanyl
(c) Halothane
(d) Midazolam

120. A patient, Tina was anesthetized with halothane and nitrous oxide and tubocurarine was used for skeletal muscle relaxation. She became hypertensive along with marked muscle rigidity and hyperthermia. Lab reports showed that she has developed hyperkalemia and acidosis. This complication was caused by:
- Block of autonomic ganglia by tubocurarine
 - Pheochromocytoma
 - Activation of brain dopamine receptors by halothane
 - Excessive release of calcium from the sarcoplasmic reticulum
121. An i.v. bolus dose of thiopentone leads to loss of consciousness within 10-15 sec. The patient regains consciousness in just a few minutes. This is because it is:
- Renally excreted
 - Exhaled rapidly
 - Rapidly metabolised by hepatic enzymes
 - Redistributed from brain to other body tissues
122. Ketamine should be avoided in:
- The presence of increased arterial pressure
 - Pregnancy
 - Hypovolemic shock
 - Asthmatic
123. The drug for OPD analgesia is:
- Morphine
 - Pethidine
 - Fentanyl
 - Alfentanil
124. Shivering is observed in the early part of postoperative period due to:
- Chloroform
 - Halothane
 - Trichloroethylene
 - Ether
125. Following accidental intra-arterial injection of thiopentone, which should not be done?
- Remove the needle
 - Intra-arterial heparin
 - Intra-arterial papaverine
 - Do a stellate ganglion block
126. An anaesthetic agent with boiling temperature more than 75°C is:
- Ether
 - Halothane
 - Cyclopropane
 - Methoxyflurane
127. True statement about sevoflurane is:
- It is nephrotoxic at high doses
 - It has maximum risk of causing convulsions
 - It is cardiostable
 - It can cause fulminant hepatitis
128. Which of the following does not have analgesic action:
- Ether
 - Ketamine
 - Halothane
 - Morphine
129. Induction agent of choice in day care surgery is:
- Ketamine
 - Propofol
 - Methohexitone
 - Thiopentone sodium
130. True statements regarding halothane is:
- Hepatitis occurs in susceptible individuals after repeated dose
 - It potentiates competitive neuromuscular blockers
 - Causes respiratory depression
 - All of the above
131. Which of the following agents is most commonly used to induce anaesthesia:
- Thiopentone sodium
 - Methohexitone sodium
 - Propofol
 - Etomidate
132. All of the following are halogenated anaesthetic agents except:
- Halothane
 - Propofol
 - Enflurane
 - Isoflurane
133. In raised ICT, anesthetic agent of choice is:
- Enflurane
 - Isoflurane
 - Ketamine
 - Ether
134. Which anesthetic agent is contraindicated in epilepsy?
- Isoflurane
 - Enflurane
 - Halothane
 - Ether
135. In patients with liver disease, anesthetic of choice is:
- Halothane
 - Ether
 - Isoflurane
 - None
136. Dissociative anesthesia is seen on administration of:
- Ether
 - Halothane
 - Enflurane
 - Ketamine
137. Profound analgesia is produced by which parenteral anesthetic?
- Thiopental
 - Propofol
 - Ketamine
 - Etomidate

138. Thiopental sodium is administered intravenously as:
(a) 25% solution (MP 2009), (RJ 2001)
(b) 2.5% solution
(c) 0.25% solution
(d) 0.025% solution
139. Which of the following increase the speed of induction with an inhalational agent?
(a) Opiate pre-medication (Karnataka 2008)
(b) Increased alveolar ventilation
(c) Increased cardiac output
(d) Reduced FIO_2
140. The recommended time for prophylactic antibiotic is:
(a) 30 min. prior to induction of anaesthesia (DPG 2007)
(b) 15 min. after the initiation of surgery
(c) At the time of induction
(d) At the time of skin incision
- RECENT QUESTIONS ASKED BY NATIONAL BOARD**
1. Trilene when used with soda lime causes:
(a) Renal damage
(b) ARDS
(c) Myocardial depression
(d) Reaction with rubber tubing of closed circuit
2. Short acting non-depolarizing blocker is:
(a) Rocuronium
(b) Suxamethonium
(c) Mivacurium
(d) Pancuronium
3. Drug used in day care anaesthesia is
(a) Propofol
(b) Enflurane
(c) Xenon
(d) Thiopentone
4. Which opioid does not require kidney and liver for metabolism?
(a) Remifentanyl
(b) Sufentanil
(c) Alfentanil
(d) Fentanyl
5. In pseudocholinesterase deficiency, drug to be used cautiously is
(a) Barbiturate
(b) Succinylcholine
(c) Halothane
(d) Gallamine
6. Mechanism of action of curare is:
(a) Reducing end plate potential
(b) Reducing presynaptic potential
(c) Inhibits K^+ channels
(d) Inhibits Na^+ channels
7. The term "balanced anaesthesia" has been given by:
(a) Simpson
(b) Fischer
(c) Lundy
(d) Mortan
8. Regarding propofol, which one of the following is false:
(a) It is used as an intravenous induction agent
(b) It causes severe vomiting
(c) It is painful on injecting intravenously
(d) It has no muscle relaxant property
9. Eutectic mixture of local anaesthetic (EMLA) cream is:
(a) Bupivacaine 2.0% + Prilocaine 2.5%
(b) Lidocaine 2.5% + Prilocaine 2.5%
(c) Lidocaine 2.5% + Prilocaine 5%
(d) Bupivacaine 0.5% + Lidocaine 2.5%
10. Ketamine produces:
(a) Emergence delirium
(b) Pain on injection
(c) Bronchoconstriction
(d) Depression of cardiovascular system
11. Cocaine overdose presents with all of the following except:
(a) Diaphoresis
(b) Hypertension
(c) Constricted pupils
(d) Agitation
12. Baclofen is used in the treatment of:
(a) Schizophrenia
(b) Depression
(c) Anxiety
(d) Spasticity
13. All of the following are the true for post lumbar puncture headache except:
(a) Presents 12 hours after procedure
(b) Pain is relieved in standing position
(c) Pain is worsened by headshaking
(d) Pain is occipito-frontal in location
14. Which one of the following inhalational anesthetics is most likely to cause fluoride ion nephrotoxicity?
(a) Methoxyflurane
(b) Enflurane
(c) Halothane
(d) Isoflurane
15. Regarding muscle relaxants which one of the following is true:
(a) Atracurium is contraindicated in renal failure
(b) Pancuronium causes bradycardia
(c) Cis - atracurium is a depolarizing muscle relaxant
(d) Vecuronium induced muscle relaxation can be reversed by neostigmine

16. Local anaesthetic used as an antiarrhythmic agent is:

- (a) Bupivacaine
- (b) Lignocaine
- (c) Cocaine
- (d) Chlorprocaine

17. Pin index of oxygen is which one of the following:

- (a) 2, 5
- (b) 3, 5
- (c) 1, 5
- (d) 3, 6

18. All of the following are intravenous anesthetic induction agents except:

- (a) Thiopentone sodium
- (b) Ketamine
- (c) Etomidate
- (d) Bupivacaine

EXPLANATIONS

1. **Ans (c) It is given orally for treatment of cardiac arrhythmias** (Ref: *Katzung 12/e p453, 457, 458*)
 - All local anaesthetics (LA) are weak bases. These drugs act by penetrating the axonal membrane (in unionized form) and **blocking the voltage gated sodium channels from within (in ionized form)**. Resting sodium channels are less sensitive to block than active and inactive channels.
 - Vasoconstrictors like **adrenaline can prolong the duration of action and decrease the systemic toxicity**.
 - **Lignocaine is the most commonly used LA and is the drug of choice for ventricular tachycardia**. However because of very high first pass metabolism, it is not effective orally.
 - All LA can cause cardiotoxicity and neurotoxicity. Bupivacaine is most cardiotoxic LA.
2. **Ans. (c) 7mg/kg** (Ref: *Goodman and Gilman 12/e p576*)
 - For normal healthy adults, the individual maximum recommended dose of lignocaine HCl with epinephrine should not exceed **7 mg/kg** of body weight, and in general it is recommended that the maximum total dose not exceed 500 mg.
 - When used without epinephrine the maximum individual dose should not exceed **4.5 mg/kg** of body weight, and in general it is recommended that the maximum total dose does not exceed 300 mg.
 - For **intravenous** regional anaesthesia, the dose administered should not exceed **4mg/kg** in adults.
3. **Ans (a) Digital block** (Ref: *Katzung 11/e p446*)
Vasoconstrictors are contraindicated if LAs are used **for organs with end arteries** (tips of fingers, toes, nose, pinna and penis) due to risk of ischemia and necrosis.
4. **Ans (a) Prilocaine** (Ref: *Katzung 11/e p449*)
 - The administration of large doses (> 10 mg/kg) of prilocaine during regional anesthesia may lead to accumulation of the metabolite o-toluidine, an oxidizing agent capable of converting hemoglobin to methemoglobin.
 - The treatment of methemoglobinemia involves the intravenous administration of reducing agents (eg, methylene blue or ascorbic acid), which rapidly convert methemoglobin to hemoglobin.
5. **Ans. (d) Cocaine** (Ref: *Ajay Yadav 3/e p105*)
 First local anaesthetic to be used clinically was cocaine by Carl Koller.
6. **Ans. (a) Intercostal** (Ref: *Miller's Anaesthesiology/591*)
 - The greater the blood supply to the area injected, the greater is the systemic absorption. Sites of absorption from greatest to least include:
 - Interpleural > Intercostal > Pudendal > Caudal > Epidural > Brachial plexus > Infiltration
7. **Ans. (b) Need to cross the cell membrane to produce the block** (Ref: *Katzung 10/e p417; KDT 6/e p353*)

- Local anaesthetics cross the neuronal membrane in un-ionized state and become ionized again in the neuron to block sodium channels. Due to this reason, sodium bicarbonate increases the rapidity of onset of action (LA are weak bases and in alkaline medium easily cross the membrane).
 - Un-myelinated and weakly myelinated fibres are blocked first and then the myelinated ones.
 - These do not affect the resting membrane potential rather inhibit the depolarization.
 - Resting nerves are less sensitive to block by LA than the stimulated nerves.
8. **Ans. (b) Pia and arachnoid** (Ref: *Katzung 10/e p419; KDT 6/e p359*)
 In spinal anaesthesia, drug is deposited in sub-arachnoid space (i.e. between pia and arachnoid) whereas in epidural anaesthesia, it is given outside the duramater.
9. **Ans. (a) Lignocaine concentration is initially higher in relatively well perfused tissues such as brain and heart** (Ref: *KDT 6/e p355*)
 - Lignocaine has very high first pass metabolism.
 - Its metabolism is dependent on hepatic blood flow. Its $t_{1/2}$ increases in patients with CHF.
 - It is initially distributed rapidly to well perfused tissues (like brain and heart) but action terminates rapidly due to redistribution.

10. Ans. (a) Esmolol; (b) Sotalol; (e) Diazepam (Ref: Ajay yadav 2/e p110)

- Bupivacaine is most cardiotoxic local anaesthetic.
- At toxic doses, local anaesthetics can result in CNS (convulsions) or CVS (hypotension, bradycardia, arrhythmias) symptoms.
- Diazepam is used to treat convulsions. If not responding, thiopentone may be used.
- Arrhythmias should be promptly treated using bretylium, amiodarone, disopyramide, magnesium sulphate, esmolol or sotalol.
- Lignocaine should be avoided as anti-arrhythmic because it can exacerbate the CNS toxicity.
- In refractory arrhythmias, intravenous lipid emulsion (like intralipid) has been found to be extremely useful.
- Bupivacaine induced cardiotoxicity is enhanced by acidosis, hypercarbia and hypoxemia.

11. Ans. (c) The local anaesthetic binds to its receptor mainly when the Na⁺ channel is in the resting state (Ref: KDT 6/e p352, 353)

- All LAs are weak bases.
- LAs act by blocking Na⁺ channels from inside the neuron (intraneuronal face).
- These can cross the membrane only in unionized (lipid soluble) form. Sodium bicarbonate is therefore added to make the LA rapid acting.
- Once inside the neuron, LAs again gets ionized and bind to Na⁺ channels.
- Binding to Na⁺ channels is more in repetitively firing neurons than in resting neurons.

12. Ans. (a) Cocaine (Ref: KDT 6/e p356, 357)

- All LAs cause hypotension except cocaine.
- Cocaine increases blood pressure by inhibiting the reuptake of catecholamines.

13. Ans. (d) Dibucaine (Ref: KDT 6/e p358)

- Longest acting, most potent and most toxic LA is dibucaine.
- Chlorprocaine is the shortest acting LA.

14. Ans. (b) By surface application, it can anaesthetize unbroken skin (Ref: KDT 6/e p357)

- Lignocaine or prilocaine cannot anaesthetize intact skin.
- Eutectic mixture is the combination of equal proportions of lignocaine and prilocaine at 25 °C. This mixture has a lower melting point than any of the two ingredients. It helps to make the preparation oily that can be applied on the intact skin.
- Eutectic mixture can be used to anaesthetize intact skin.

15. Ans. (d) All of the above (Ref: KDT 6/e p359, 360)

- **Factors affecting the height of block**
 - Volume of drug
 - Baricity (Ratio of specific gravity of an agent to that of CSF).
 - Position of the patient
 - Intra-abdominal pressure
 - Curvature of spine
- **Factors affecting duration of block**
 - Dose
 - Concentration
 - Drug (LA used)
 - Added vasoconstrictors

16. Ans. (b) Sympathetic block is higher than the sensory block (Ref: KDT 6/e p360)

Spinal anaesthesia creates a zone of differential blockade in which sympathetic fibres are blocked two segments higher and motor fibres are blocked two segments lower than the level of sensory block.

17. Ans. (c) Posture of the patient (Ref: KDT 6/e p360)

Posture of the patient determines the height of block, not the duration.

18. Ans. (a) Orthopedic manipulation on the upper limb (Ref: KDT 6/e p361)

IVRA is indicated for procedures on upper limb or lower limb of less than one hour duration.

19. Ans. (b) Bupivacaine (Ref: KDT 6/e p357, 358)

20. **Ans. (d) Seizures and coma** (Ref: KDT 6/e p356)

- If LA reaches the blood stream, most prominent adverse effects are related to CNS and CVS.
- In CNS, stimulation (convulsions) followed by depression (coma) is seen. Initial stimulation is due to inhibition of the inhibitory neurons.

21. **Ans. (b) Bicarbonate** (Ref: KDT 6/e p412)

- LAs are weak bases. These require penetration inside the neuron for their action. For entry in the neuron, LAs have to cross the neuronal membrane.
- Unionized drugs (lipid soluble) can easily cross the membrane, therefore addition of NaHCO_3 in the local anaesthetic solution (weak bases are un-ionized in the alkaline medium) makes them rapid acting.
- Adrenaline increases the duration of action by causing vasoconstriction.
- Methylparaben is the preservative added in LA solution.

22. **Ans. (b) Increase the duration of action of the local anaesthetic** (Ref: KDT 6/e p354)

- Adrenaline and felypressin are the vasoconstrictors that are added to LA solution.
- By causing vasoconstriction, these drugs
 - decrease the systemic absorption resulting in less CNS adverse effects (decreased chances of seizures).
- Prolong the stay of drug at the site of action resulting in the increase in duration of action of LA.

23. **Ans. (b) Preferential binding to resting channels** (Ref: KDT 6/e p415)

LAs act from within the neuron and are more active when the neuron is rapidly firing (i.e., Na^+ channels are open).

24. **Ans. (d) Seizures** (Ref: KDT 6/e p356, Katzung, 10/e p420, 421)

25. **Ans. (c) 20 mg** (See below)

- 1% solution means 1g (1000 mg) of a drug is present in 100 ml of the solution.
- 2% means 2000 mg in 100 ml of solution.
- Therefore 1 ml will contain 20 mg.

26. **Ans. (b) Cocaine** (Ref: KDT 6/e p356, 357)

- All LAs are vasodilators except cocaine. It possesses vasoconstrictor activity.
- Cocaine also has good surface activity.

27. **Ans. (c) Cocaine** (Ref: Katzung 11/e p448)

All local anaesthetics cause vasodilation except cocaine. It blocks reuptake of nor-adrenaline and result in sympathetic overactivity. Therefore, cocaine can cause hypertension and cardiac arrhythmias.

28. **Ans. (a) Procaine** (Ref: Katzung 11/e p441)

29. **Ans. (d) It produces methemoglobinemia** (Ref: Katzung 11/e p448-450)

- Bupivacaine is the most cardiotoxic local anaesthetic, therefore should never be given intravenously. Most common ECG findings in patients with bupivacaine toxicity are slow idioventricular rhythm with broad QRS complexes and eventually electromechanical dissociation.
- Methemoglobinemia is caused by prilocaine and not by bupivacaine.

30. **Ans. (b) Affecting the Na^+ channels** (Ref: KDT 6/e p353)

31. **Ans. (b) Blocks the influx of sodium into the cell** (Ref: KDT 6/e p353)

LA block nerve conduction by inhibiting Na^+ entry during upstroke of action potential.

32. **Ans. (a) Less cardiotoxic than lignocaine** (Ref: KDT 6/e p357)

33. **Ans. (a) Seepage of CSF** (Ref: KDT 6/e p360)

34. **Ans. (b) More cardiotoxic than lignocaine** (Ref: Katzung 11/e p448)

35. **Ans. (d) 5%** (Ref: KDT 7/e p368)

36. **Ans. (a) Activated state** (Ref: Katzung 11/e p443)

37. **Ans. (a) Dibucaine** (Ref: KDT 6/e p358)

38. **Ans. (c) 1:200,000** (Ref: KDT 6/e p354)

39. **Ans. (b) Fingers** (Ref: KDT 7/e p350)

- Tubocurarine is a Non-depolarizing muscle relaxant (NDMR). The order of relaxation of muscles with NDMR like d-Tubocurarine is
- Fingers, Eye > Limbs > Neck > Trunk > Respiratory

40. Ans. (b) Inhibiting spinal polysynaptic reflexes: (Ref: KDT 6/e p348)

- Centrally acting muscle relaxants reduce skeletal muscle tone by a selective action in the cerebrospinal axis, without altering consciousness.
- *They selectively depress spinal and supraspinal polysynaptic reflexes involved in the regulation of muscle tone* without significantly affecting monosynaptically mediated stretch reflex.
- Polysynaptic pathways in the ascending reticular formation which are involved in the maintenance of wakefulness are also depressed, though to a lesser extent.
- All centrally acting muscle relaxants do have some sedative property. They have no effect on neuromuscular transmission and on muscle fibres, but reduce decerebrate rigidity, upper motor neuron spasticity and hyperreflexia.

41. Ans. (c) Diazepam (Ref: KDT 6/e p396, 409, 450)

Diazepam possesses following activities:

- Muscle relaxing
- Anticonvulsant
- Antianxiety
- Sedative-hypnotic

42. Ans. (c) Rocuronium (Ref: Pharmacology for Nurse Anaesthesiology/110)

- Rocuronium causes pain on injection. It can be minimized by alkalinizing the solution.
- Propofol is also responsible for pain on injection
- Remember, post-operative muscular pain is caused by succinylcholine and post-operative muscle rigidity is caused by fentanyl group of drugs.

43. Ans. (b) It causes less release of histamine (Ref: Miller's 7/e p869)

- Both atracurium and cis-atracurium are non-depolarizing neuromuscular blockers.
- Both of these are intermediate acting agents (both have same duration of action).
- Both of these agents are cardiostable
- Atracurium has faster onset of action as compared to cis-atracurium.
- Both are eliminated by Hoffman's elimination. Atracurium is also metabolized by liver to some extent and result in production of a metabolite laudanosine that can cause CNS toxicity including seizures. On the other hand cis-atracurium is almost completely eliminated by Hoffman's elimination and produce negligible laudanosine.
- Major advantage of cis-atracurium over atracurium is that the former do not release histamine.

Note: Only cis-atracurium and doxacurium are the drugs in this category (whose name ends with curium) that don't release histamine.

44. Ans. (a) Atracurium (Ref: Miller 7/e p880)

Both atracurium and cis-atracurium are eliminated by Hoffman's elimination. Atracurium is also metabolized by liver to some extent and result in production of a metabolite, laudanosine that can cause CNS toxicity including seizures. On the other hand cis-atracurium is almost completely eliminated by Hoffman's elimination and produce negligible laudanosine.

45. Ans. (a) Mu (Ref: Miller 7/e p781)

Truncal rigidity caused by highly lipid soluble opioids like fentanyl is supraspinal in origin. It is mainly caused by stimulation of mu receptors whereas kappa and delta receptors tend to reduce the rigidity.

46. Ans (b) Phase II blockade (Ref: Wiley 7/584-586, Lee 12/223)

Succinylcholine produces a characteristic depolarizing block that is associated with absence of fade in response to train-of-four and tetanic stimulation, the absence of post-tetanic facilitation and increased block in the presence of anticholinesterase drugs. The type of block may change into a non-depolarizing type following prolonged administration of the drug (phase II block). Transition from a depolarizing to phase II block is gradual and usually occurs after administration of 7-10 mg/kg of succinylcholine.

47. Ans. (b) Hyperkalemia (Ref: Katzung 11/e p460)

Succinylcholine can cause hyperkalemia especially in patients with nerve and muscle disorders. Therefore it is contraindicated in patients with nerve diseases (like paraplegia, hemiplegia and Guillain barre syndrome) and muscle diseases (muscular dystrophy, myasthenia gravis, crush injury, burns and rhabdomyolysis).

48. Ans. (a) Atracurium (Ref: Katzung 11/e p456)

Atracurium and cis-atracurium are degraded spontaneously by Hoffman's elimination. These do not require liver or kidney for elimination and thus are muscle relaxant of choice in a patient with renal and hepatic dysfunction.

- Other drugs mentioned in the question are metabolized by liver and thus should be avoided in hepatic failure.

49. **Ans. (b) Meprobamate** (Ref: Goodman and Gilman 11/e p422)

Meprobamate was used as a CNS depressant drug but is rarely indicated now due to its addictive properties. It is a metabolite of carisoprodol, which is used as a centrally acting skeletal muscle relaxant.

50. **Ans. (a) Atracurium** (Ref: Katzung 11/e p453)

Atracurium is eliminated by Hoffman's elimination i.e. it does not require liver or kidney. It is the muscle relaxant of choice in hepatic and renal failure.

51. **Ans. (a) Azathioprine** (Ref: Harrison 17/e p2677, Ajay yadav 2/e p94)

- 'Azathioprine is used for treatment of myasthenia gravis'

Drugs that may exacerbate myasthenia gravis and potentiate the action of non-depolarizing muscle relaxants are:

- Antibiotics
 - Aminoglycosides e.g Streptomycin
 - Tetracyclines
 - Quinolones e.g ciprofloxacin
 - Macrolides e.g erythromycin
- Non-depolarizing muscle relaxants e.g d-Tubocurarine
- Beta-blockers like propranolol, atenolol, metoprolol
- Local anaesthetics
- Botulinum toxin
- Quinine derivatives like quinine, quinidine, chloroquine, mefloquine
- Magnesium
- Penicillamine

52. **Ans. (b) Rapacuronium** (Ref: Miller's anaesthesia 5/e p892; Drugs and equipment in Anaesthesia 5/e p78 Arun Kumar Paul)

- Among the given options Rapacuronium is the shortest acting drug.
- Rapacuronium has been withdrawn from the market because it produces intense bronchospasm in a significant number of patients.
- Mivacurium is shortest acting NDMR.
- SCh is shortest acting muscle relaxant.

53. **Ans. (a) Inhibiting nicotinic receptors at myoneural junction** (Ref: Katzung 10/e p429; KDT 6/e p342)

D-tubocurarine is a skeletal muscle relaxant that acts by competitive inhibition of NM receptors at neuron-muscular junction.

54. **Ans. (a) Cis-atracurium** (Ref: Katzung 9/e p432; KDT 6/e p345)

Atracurium and cis-atracurium are muscle relaxants of choice for renal and hepatic failure patients.

55. **Ans. (b) Preventing the K⁺ efflux from the cell** (Ref: Katzung 10/e p436; KDT 6/e p99-101)

Neostigmine is an anti-cholinesterase. It inhibits the breakdown of ACh at the motor end plate. This results in the increased activity of ACh that causes depolarization of motor end plate by opening Na⁺ channels (increasing the influx of Na⁺). It possesses some direct agonistic activity on NM receptors resulting in depolarization. In addition, a minor effect to increase the release of ACh at motor end plate is also present.

56. **Ans. (b) Succinylcholine** (Ref: KDT 6/e p343, 344)

- Succinylcholine is a depolarizing neuromuscular blocker. In contrast to ganglionic blocking properties of competitive neuromuscular blockers (like d-TC), it stimulates the ganglia.
- Initially bradycardia is seen due to stimulation of parasympathetic ganglion which is followed by tachycardia and hypertension due to stimulation of sympathetic ganglia.
- Dopamine and isoprenaline possess β_1 agonistic activity and thus can cause tachycardia.
- Midazolam is a benzodiazepine. It does not affect CVS at therapeutic dose but produces bradycardia at toxic levels.

57. **Ans. (a) Chloroform; (d) Halothane** (Ref: Lee 12/e p167, KDT 6/e p372; Ajay yadav 2/e p61,66)

- Massive liver necrosis following halothane anaesthesia is seen in some cases.
- N₂O is nontoxic to liver, kidney and brain.
- Ether does not sensitize the heart to Adr and is not hepatotoxic.
- Enflurane is eliminated mostly via the lungs, although about 3% is metabolised in body and resultant fluoride ions are excreted by kidney. Hepatic necrosis is seen in very rare instances. (Lee/165)
- If chloroform is given for long period, liver damage occurs (Parikh 5/e p877)

58. **Ans. (d) All of the above** (Ref: KDT 6/e p343, 344)
- d-tubocurarine is a competitive NM blocker. It produces fall in BP due to:
 - Blockade of sympathetic ganglia.
 - Histamine release.
 - Reduced venous return as a result of paralysis of limb and respiratory muscles.
59. **Ans. (c) It can cause rise in BP on rapid i.v. injection** (Ref: KDT 6/e p345)
- Ancuronium possesses vagolytic activity and can cause hypertension and tachycardia on rapid i.v. injection.
 - Pancuronium is a competitive NM blocker (Non-depolarizing NM blocker). Its actions can be reversed by anticholinesterases like neostigmine.
 - Unlike d-TC, histamine release is not seen with pancuronium.
60. **Ans. (d) Mivacurium** (Ref: KDT 6/e p345)
- Long acting non-depolarizing (competitive) NM blocking agents require reversal with neostigmine.
 - Mivacurium is the shortest acting NDMR. It does not require reversal due to its short duration of action.
 - Mivacurium can be used in day care surgery.
61. **Ans. (a) Rocuronium** (Ref: KDT 6/e p345)
- Rocuronium is the fastest acting non-depolarizing muscle relaxant (NDMR). It can be used for the rapid sequence endotracheal intubation in patients having contra-indications to the use of SCh.
 - Mivacurium is the shortest acting NDMR.
 - SCh is the shortest and fastest acting skeletal muscle relaxant. It is a depolarizing NM blocker.
62. **Ans. (a) Streptomycin** (Ref: KDT 6/e p721, 722)
- Aminoglycosides (like streptomycin and gentamicin) can accentuate the neuromuscular blockade produced by competitive blockers (like pancuronium).
 - Mechanism of neuromuscular blockade produced by aminoglycosides is the inhibition of presynaptic release of ACh.
63. **Ans. (d) Reducing Ca^{2+} release from sarcoplasmic reticulum in the muscle fibre** (Ref: KDT 6/e p347)
- Dantrolene is the drug of choice for the treatment of malignant hyperthermia and neurolept malignant syndrome.
 - It acts as an antagonist of ryanodine receptors (present on smooth endoplasmic reticulum). It inhibits the release of Ca^{2+} from sarcoplasmic reticulum in the muscle fibre.
64. **Ans. (a) Tizanidine** (Ref: KDT 6/e p349)
- Tizanidine and brimonidine are α_2 adrenergic agonists. Tizanidine is used as a centrally acting muscle relaxant whereas brimonidine is used topically for the treatment of glaucoma.
 - Chlormezanone is a centrally acting muscle relaxant that acts by inhibiting the spinal internuncial neurons.
 - Quinine is a directly acting peripheral muscle relaxant.
65. **Ans. (a) It may induce life threatening hyperkalemia** (Ref: KDT 6/e p344)
- SCh is the shortest and fastest acting muscle relaxant.
 - SCh is contra-indicated in patients with nerve or muscle disorders due to the risk of hyperkalemia
 - **Nerve disorders:** Hemiplegia, paraplegia, Guillain Barre syndrome etc.
 - **Muscle disorders:** Myopathy, myasthenia gravis, rhabdomyolysis, crush injury etc.
66. **Ans. (c) Succinylcholine** (Ref: KDT 6/e p344)
67. **Ans. (b) Dantrolene** (Ref: KDT 6/e p347)
68. **Ans. (c) Tubocurarine** (Ref: KDT 6/e p344)
- Hypotension and bronchoconstriction (increase in airway resistance) are important adverse effects caused by histamine. This is confirmed to be due to histamine because of reversal with diphenhydramine.
 - Maximum histamine release is caused by d-tubocurarine.
 - Atracurium causes minimum histamine release, therefore is preferred agent in asthmatic patients.
69. **Ans. (d) Succinylcholine** (Ref: KDT 6/e p344)
- SCh is the shortest acting muscle relaxant due to its metabolism by pseudocholinesterase.
 - Some patients contain an atypical pseudocholinesterase (which has abnormally low activity) and are susceptible to develop apnea with the use of this drug.
70. **Ans (b) Succinylcholine** (Ref: Katzung 11/e p454)
- There are two clues to the correct answer in this scenario.

- The patient underwent rapid sequence intubation (RSI). A depolarizing neuromuscular blocking drug is commonly administered for RSI, because onset of action is generally more rapid (within 60 seconds) than for most available non-depolarizing blockers.
- The patient still exhibits residual muscle paralysis even after neostigmine, an anti-cholinesterase. The persistence of paralysis indicates that Drug A is a depolarizing blocker. Anticholinesterases do not reverse the action of depolarizing and may, in fact, enhance them.

The only depolarizing blocker listed among the options is succinylcholine. In patients with atypical pseudocholinesterase, SCh may produce prolonged paralysis and apnea.

71. **Ans. (d) Suxamethonium** (Ref: *Katzung 11/e p454*)

Suxamethonium is the other name of succinylcholine. It is the shortest acting muscle relaxant due to metabolism by pseudocholinesterase

72. **Ans. (a) Atracurium** (Ref: *KDT 6/e p345*)

73. **Ans. (d) Quinidine** (Ref: *Clinical Anesthesiology by Murray and Morgan/189; KDT 6/e p346*)

Non-depolarizing blockade is potentiated by

Hypothermia	Respiratory acidosis
Hypokalemia	Hypocalcemia
Hypermagnesemia	Neonatal period
Aminoglycosides, Tetracyclines, Polymyxin B	Quinine, Lignocaine, CCBs, Procainamide
Trimethaphan	Dantrolene
MgSO ₄	Local Anaesthetics
Ketamine	

74. **Ans. (a) Chloramphenicol** (Ref: *KDT 6/e p346*)

Drugs causing curare like effect are:

- Aminoglycosides
- Polypeptide antibiotics:
 - Polymyxin B
 - Bacitracin
 - Colistin
 - Tyrothricin
- Tetracycline
- Clindamycin, lincomycin

75. **Ans. (b) Vecuronium** (Ref: *KDT 5/e p345*)

It does not cause ganglion blockade or histamine release and is having good cardiovascular stability.

76. **Ans. (b) Depolarising muscle relaxant** (Ref: *KDT 6/e p339*)

77. **Ans. (a) Centrally acting muscle relaxant** (Ref: *Katzung 11/e p463*)

78. **Ans. (d) All of the above** (Ref: *Katzung 11/e p457*)

79. **Ans. (c) Succinylcholine** (Ref: *KDT 6/e p343*)

80. **Ans. (c) Pancuronium** (Ref: *KDT 6/e p343*)

81. **Ans. (d) Amitriptyline** (Ref: *Katzung 11/e p462-464*)

82. **Ans. (a) Atracurium** (Ref: *KDT 6/e p345*)

83. **Ans. (b) Mivacurium** (Ref: *KDT 6/e p339*)

84. **Ans. (c) Progression to dual blockade** (Ref: *Katzung 11/e p457*)

85. **Ans. (d) All of the above** (Ref: *KDT 6/e p348*)

86. **Ans. (c) Ketamine** (Ref: *Goodman and Gilman 12/e p538-539*)

Ketamine increases all pressures (blood pressure, intracranial tension, intraocular pressure) in the body. It is therefore intravenous anaesthetic of choice for shock (increases blood pressure).

87. Ans. (a) ACE inhibitors (Ref: CMDT 2014/45-47)

- All antihypertensives should be continued in peri-operative period except ACE inhibitors, Angiotensin receptor blockers and diuretics. ACE inhibitors and ARBs should be stopped 24 hours before surgery to prevent intraoperative hypotension. Diuretics should be stopped once the patient is kept NPO (Nil per oral) to prevent intraoperative volume depletion and electrolyte abnormalities.
- Statins should be continued if the patient is taking them, especially because preoperative withdrawal has been associated with a 4.6-fold increase in troponin release and a 7.5-fold increased risk of myocardial infarction (MI) and cardiovascular death following major vascular surgery.
- Corticosteroid therapy in excess of prednisone 5 mg/day or equivalent for more than five days in the 30 days preceding surgery might predispose patients to acute adrenal insufficiency in the perioperative period. Surgical procedures typically result in cortisol release of 50-150 mg/day, which returns to baseline within 48 hours. Therefore, the recommendation is to continue a patient's baseline steroid dose and supplement it with stress-dose steroids tailored to the severity of operative stress.

General principles are

- Perioperative medication use should be tailored for each patient.
- Medications should be continued to avoid perioperative disease decompensation and withdrawal.
- Medications that interact with anesthesia or increase the risk of perioperative complications might need to be stopped.
- Stop ACEI/ARB 24 hours before surgery.
- Stop diuretics once NPO.
- Continue statins.
- Continue CNS-active drugs.
- Insulin may require adjustment.
- Stop metformin 24 hours before surgery.
- Stop sulfonylureas the night before surgery.
- Stop OCPs and HRT four weeks before surgery, if possible.
- Stop nonselective NSAIDs two to three days before surgery, but continue COX-2 inhibitors.
- Continue outpatient dosing of corticosteroids and add a stress dose.
- Stop DMARDs and biologics one week before surgery.
- Stop herbal medicines one to two weeks before surgery.

88. Ans. (a) Slow induction and recovery (Ref: Goodman and Gilman 12/e p547-548)

Xenon is very close to the 'ideal agent'.

Advantages of Xenon Anesthesia

- Inert (probably nontoxic to liver and kidney with no metabolism)
- Minimal effect on CVS function
- Lowest blood solubility (Lowest blood gas partition coefficient) therefore rapid induction and recovery.
- Does not trigger malignant hyperthermia
- Environmental friendly
- Non-explosive.

89. Ans. (b) Ketamine (Ref: Katzung 11/e p437)

Ketamine **increases all pressures** (blood pressure, intracranial tension, intraocular pressure) in the body. It is therefore intravenous anaesthetic of choice for shock and should be avoided in hypertensive patients (increases blood pressure). Further it is contraindicated in glaucoma (increases IOP) and head injuries (increases ICT).

90. Ans. (c) Intravenous Regional Anaesthesia (Ref: Short textbook of Anaesthesia by Ajay Yadav 2/e p148)

Prevention of conditions that favor sickling is the basis of peri-operative management.

- Supplemental oxygen is recommended during and after regional anaesthesia/GA.
- Circulatory stasis can be prevented with hydration and anticipation of intraoperative blood loss in order to avoid acute hypovolemia
- Normothermia is desirable because hyperthermia increases the rate of gel formation, and hypothermia produces vasoconstriction that impairs organ blood flow.
- The use of a tourniquet and hence Bier's block (intravenous regional anaesthesia) is contraindicated because blood stasis can cause local acidosis, hypoxia with sickling of cells.
- Drugs commonly used for anaesthesia should not have significant effects on the sickling process.

91. **Ans. (b) Sevoflurane** (Ref: *Katzung 11/e p432L*)
Sevoflurane, Enflurane and Isoflurane have epileptic potential.
92. **Ans (a) Xenon** (Ref: *Goodman and Gilman 12/e p547-548, Morgan's Clinical Anaesthesiology, 11/e p166-167, Wiley 7/e p527-532*)
Halothane is hepatotoxic and all fluorinated anesthetic agents can cause dose dependent decrease in arterial BP and depression of heart. Xenon has minimal effect on CVS function.
93. **Ans (d) Etomidate** (Ref: *Goodman and Gilman, 12/e p538*)
Etomidate
- It does not interfere with cardiovascular functions; therefore is the agent of choice for aneurysm surgeries and cardiac disease.
 - It can also produce myoclonus.
 - It can lead to adrenocortical suppression.
 - Vitamin C deficiency can also develop with the use of etomidate.
94. **Ans. (c) Ketamine** (Ref: *Goodman and Gilman 12/e p538*)
95. **Ans. (d) Causes the expansion of air filled body cavities** (Ref: *Goodman and Gilman 12/e p547*)
N₂O use is contraindicated in pneumothorax and volvulus because it may lead to development of high pressure in the closed cavities in the body (like obstructed loop of bowel, intraocular air bubble, a pulmonary bulla, pneumothorax, obstructed middle ear, air embolus, intracranial air and pneumoperitoneum).
96. **Ans. (b) Nitrous oxide** (Ref: *Goodman and Gilman 12/e p547*)
97. **Ans (b) Ketamine** (Ref: *Ajay Yadav 2/e p215*)
98. **Ans. (b) Etomidate** (Ref: *Katzung 11/e p437*)
- 'Major advantage of etomidate over other intravenous anaesthetics is that it causes minimum cardiovascular and respiratory depression.'
 - Propofol has greatest negative inotropic action among all intravenous anaesthetics.
 - Ketamine has cardiostimulatory properties and can cause hypertension.
 - Midazolam is not used as an inducing agent.
99. **Ans. (b) Ether** (Ref: *Goodman & Gilman 11/e p341; KDT 6/e p371*)
Ether is an explosive agent and should not be used with cautery.
100. **Ans (d) Halothane** (Ref: *Katzung 10/e p405; KDT 6/e p372*)
Halogenated inhalational anaesthetic agents like halothane are powerful tocolytic agents. Halothane is anaesthetic of choice for internal version and manual removal of placenta.
101. **Ans. (a) Ketamine** (Ref: *Katzung 10/e p409; KDT 6/e p376*)
102. **Ans. (d) Halothane** (Ref: *Katzung 10/e p404; KDT 6/e p372*)
Halothane and sevoflurane have smooth induction, so these are preferred agents for anaesthesia in children.
103. **Ans. (c) Pethidine** (Ref: *Anaesthesiology by Longnecker/1485; KDT 6/e p459*)
Pethidine is most effective drug for treatment of post-operative shivering. Other drugs that can be used for this purpose are clonidine, doxapram, ketanserin and alfentanil.
104. **Ans. (d) 6** (Ref: *Anaesthesiology by Longnecker/744; KDT 6/e p371*)
105. **Ans. (b) Enflurane** (Ref: *Anaesthesiology by Longnecker/761; KDT 6/e p372*)
Enflurane is known to produce seizures.
106. **Ans. (b) Useful for short painful procedures; (d) Metabolized by plasma esterases; (e) Equipotent as fentanyl** (Ref: *Goodman and Gilman 11/e p572*)
- Remifentanyl is shortest acting opioid due to its metabolism by plasma esterases.
 - Due to its short duration of action, it is indicated for short term painful procedures.
 - Intravenous bolus dosing is not practical because of short duration of action, rather it is administered by constant i.v. infusion.
 - Potency is equal to fentanyl and similarly it can also cause post operative muscle rigidity.
107. **Ans. (a) Potency** (Ref: *KDT 6/e p365*)
- MAC is inversely related to potency of an inhalational agent.

- N₂O has maximum MAC (104%) and is thus the least potent agent.
- Methoxyflurane is the most potent drug due to minimum value of MAC.

108. Ans. (d) Ketamine (Ref: KDT 6/e p376)

- Ketamine is an intravenous inducing agent. It acts by blocking NMDA receptors.
- Hallucinations, delirium and vivid dreams are important adverse effects that are seen during recovery from anaesthesia (emergence reaction).
- It increases blood pressure, intraocular pressure and intracranial tension.

109. Ans. (a) Nitrous oxide (Ref: KDT 6/e p369)

Concentration effect, second gas effect and diffusion hypoxia are seen with inhalational agents used in high concentrations (like N₂O).

110. Ans. (b) Nitrous oxide (Ref: KDT 6/e p371)

- Nitrous oxide is not a complete anaesthetic (MAC 104%).
- It is a good analgesic but poor muscle relaxant.

111. Ans. (c) It is primarily used as a carrier and adjuvant to other anaesthetics (Ref: KDT 6/e p371)

112. Ans. (d) It is cheap and can be administered without anaesthetic machine (Ref: KDT 6/e p371)

- Ether is the only complete anaesthetic agent.
- It is highly inflammable and explosive.
- It has good analgesic and muscle relaxant action.
- It can be delivered by open method.
- It is a pungent smelling liquid.
- Induction of anaesthesia with ether is quite slow. All the four stages can be seen.

113. Ans. (a) Very good analgesic action (Ref: KDT 6/e p372)

- Newer inhalational anaesthetic agents like halothane, isoflurane etc. lack analgesic activity.
- All other advantages listed in the question are present in halothane.

114. Ans. (c) Halothane (Ref: KDT 6/e p372)

Rarely, halothane can cause malignant hyperthermia, which is treated with dantrolene

115. Ans. (a) Ketamine (Ref: KDT 6/e p376)

- Ketamine produces dissociative anaesthesia
- Neurolept analgesia is produced by fentanyl + droperidol

116. Ans. (a) Hypertensives (Ref: KDT 6/e p376)

- Ketamine is contra-indicated in hypertensives because it increases the blood pressure.
- It is the induction agent of choice for:
 - Asthmatics
 - Shock
 - Children
 - Full stomach
- It possesses very powerful analgesic action.
- It can be used as a sole agent for minor procedures.

117. Ans. (a) Analgesia (Ref: KDT 6/e p376)

- Ketamine is a powerful analgesic agent.
- It increases blood pressure, intraocular pressure and intracranial tension.
- It does not depress CVS and respiratory system.

118. Ans. (c) Propofol (Ref: KDT 6/e p375)

Propofol is the most commonly used anaesthetic agent for 'day care surgery'.

119. Ans. (c) Halothane (Ref: KDT 6/e p372)

- Halothane sensitizes the heart to arrhythmogenic action of catecholamines.

- In pheochromocytoma, there are elevated levels of catecholamines.
- Therefore, halothane should not be used in patients with pheochromocytoma.

120. **Ans. (d) Excessive release of calcium from the sarcoplasmic reticulum** (Ref: KDT 6/e p347, 372)

- The symptoms of the patient (muscle rigidity, hypertension, hyperthermia, hyperkalemia and acidosis) suggests the diagnosis of malignant hyperthermia.
- Halothane can precipitate malignant hyperthermia in susceptible individuals. SCh increases this incidence.
- Malignant hyperthermia is due to excessive release of Ca^{2+} from the sarcoplasmic reticulum.
- Drug of choice for malignant hyperthermia is dantrolene that inhibits the release of Ca^{2+} (by blocking ryanodine receptors in the sarcoplasmic reticulum).

121. **Ans. (d) Redistributed from brain to other body tissues** (Ref: KDT 6/e p374)

Thiopentone and other highly lipid soluble agents first reach the highly perfused organs like brain. Therefore, onset of action of these agents is very quick. However, action also terminates quickly because of redistribution to less well perfused tissues like fat and muscle.

122. **Ans. (a) The presence of increased arterial pressure** (Ref: Katzung 11/e p437)

123. **Ans. (d) Alfentanil** (Ref: Katzung 11/e p546)

124. **Ans. (b) Halothane** (Ref: Ajay yadav 2/e p61)

Post-operative shivering (halothane shakes) and hypothermia is maximum with halothane. Pethidine is used for treatment of this condition.

125. **Ans. (a) Remove the needle** (Ref: Ajay yadav 2/e p73)

Treatment of accidental intra-arterial injection of thiopentone is:

- Immediately stop further injection.
- Leave the needle at site.
- Inject heparin through this needle.
- Inject papaverine through this needle.
- If vasodilators like papaverine are not available, xylocaine can be used.
- Brachial plexus or stellate ganglion block should be done to relieve vasospasm.

126. **Ans. (d) Methoxyflurane** (Ref: Anesthesiology by Longnecker 2008/777)

Boiling point of methoxyflurane is 104.7°C whereas other fluorinated inhalational anaesthetics have boiling point between 50°C to 60°C (except desflurane: 22.9°C)

127. **Ans. (a) It is nephrotoxic at high doses** (Ref: Goodman & Gilman 11/e p360; KDT 6/e p74)

- Sevoflurane is a general anaesthetic used by inhalational route.
- It is very good agent for children and asthmatic patients.
- It can produce dose dependent hypotension and decrease in cardiac output.
- It high doses, it can release fluoride resulting in nephrotoxicity. Also, it can interact with soda lime (in closed circuit) to produce nephrotoxic, compound A.
- It is not known to cause hepatotoxicity.
- Enflurane has maximum potential to induce seizures.

128. **Ans. (c) Halothane** (Ref: KDT 6/e p372)

Halothane and newer fluorinated inhalation anaesthetic agent are devoid of analgesic property.

129. **Ans. (b) Propofol** (Ref: KDT 6/e p375)

130. **Ans. (d) All of the above** (Ref: Katzung 11/e p432,461)

131. **Ans. (a) Thiopentone sodium** (Ref: Katzung 11/e p434)

132. **Ans. (b) Propofol** (Ref: KDT 6/e p375)

133. **Ans. (b) Isoflurane** (Ref: KDT 6/e p373)

134. **Ans. (b) Enflurane** (Ref: KDT 6/e p372)

135. **Ans. (c) Isoflurane** (Ref: KDT 6/e p373)

136. **Ans. (d) Ketamine** (Ref: KDT 6/e p376)

137. Ans. (c) Ketamine (Ref: KDT 6/e p377)
138. Ans. (b) 2.5% solution (Ref: Morgan 4/e p187)
139. Ans. (b) Increased alveolar ventilation (Ref: Katzung 11/e p427)
140. Ans. (a) 30 min. Prior to induction of anaesthesia (Ref: Katzung 11/e p898)
- Antibiotic should be present in adequate concentration at the operative site before incision and throughout the procedure.
 - Parenteral agents should be administered during the interval beginning 60 minutes before incision; administration up to the time of incision is preferred.

ANSWERS OF RECENT QUESTIONS ASKED BY NATIONAL BOARD

1. Ans. (b) ARDS (Ref: KK Sharma 2/e p122)
2. Ans (c) Mivacurium (Ref: KDT 7/e p352)
3. Ans. (a) Propofol (Ref: KDT 7/e p382)
4. Ans. (a) Remifentanyl (Ref: KK Sharma 2/e p440)
5. Ans. (b) Succinylcholine (Ref: KDT 6/e p344)
6. Ans. (a) Reducing end plate potential (Ref: KDT 7/e p348)
7. Ans. (c) Lundy (Ref: Goodman Gilman 12/e p528)
 - Term 'balanced anaesthesia' was introduced by Lundy in 1926.
8. Ans. (b) It causes severe vomiting (Ref: KDT 7/e p382)
9. Ans. (b) Lidocaine 2.5% + Prilocaine 2.5% (Ref: KDT 7/e p366)
10. Ans. (a) Emergence delirium (Ref: KDT 7/e p384)
11. Ans. (c) Constricted pupils (Ref: KDT 7/e p365)
12. Ans. (d) Spasticity (Ref: KDT 7/e p358)
13. Ans. (b) Pain is relieved in standing position (Ref: Evidence-Based obstetric Anesthesia p75)
 - Post-dural-puncture headache (PDPH) or post-lumbar-puncture headache occurs 12-24 hours after dural puncture.
 - It presents with headache (occipito frontal) and nausea that typically worsens when the patient assumes upright position.
 - Incidence is higher in younger patients.
14. Ans. (a) Methoxyflurane (Ref: Nurse Anaesthesia by John J. Nagelhout p77)
15. Ans. (d) Vecuronium induced muscle relaxation can be reversed by neostigmine (Ref: KDT 7/e p353-354)
16. Ans. (b) Lignocaine (Ref: KDT 7/e p366)
17. Ans. (a) 2, 5 (Ref: KDT 7/e p513)
18. Ans. (d) Bupivacaine (Ref: KDT 7/e p378)

HAEMATINICS

These are the agents required for the formation of blood and treatment of anemia. Main haematinics include iron, folic acid and vitamin B₁₂. Other substances like copper, pyridoxine etc. are also required in small quantities for the formation of blood.

Iron

- Daily requirement of iron is

Adult male	1 mg
Menstruating female	2 mg
Pregnant female	3-5 mg

- Liver, egg yolk, beans and dry fruits are good source of iron whereas **milk and its products are poor sources**.
- Iron is **absorbed** mostly in the **duodenum** in the **ferrous form (Fe²⁺)**. Heme contains the iron in ferrous form and most of the inorganic iron is in ferric form (Fe³⁺). This must be reduced to ferrous form for absorption. Thus reducing substances like **ascorbic acid** and also gastric acid (**HCl**) **increases the absorption**. On the other hand, substances like *alkalies, phosphates, phytates and tetracyclines* *decrease the absorption*.
- After absorption, iron can either be stored as ferritin or it is transported with transferrin to be utilized in the formation of blood. When there is **excess of iron** in the body, it combines with apoferritin to form **ferritin**, which remains stored in the mucosal cells and is removed from the body when these cells are shed. In case of **iron deficiency, number of transferrin receptors increase** on erythropoietic cells (so, iron selectively goes to these cells) resulting in brisk erythropoiesis.
- Iron is used for *prophylaxis or treatment of iron deficiency anemia (microcytic hypochromic anemia)*. It can be given by oral route or parenteral route. **Parenteral route (i.v., i.m.) is indicated only when oral iron is not tolerated, not absorbed or along with erythropoietin**. *Rate of hematopoietic response with parenteral iron is not faster than that with optimal doses of oral iron therapy.*
- Oral preparations include ferrous sulphate, gluconate, succinate etc. **Ferrous sulphate** contains **20% elemental iron**. For treatment of iron deficiency, the dosage recommended is 200 mg elemental iron daily that can be obtained by giving 1000 mg of ferrous sulphate in three divided doses providing around 60 mg elemental iron per dose [maximum tolerated dose]. *Iron absorption increases in response to low iron stores or increased iron requirements. The reticulocyte count should begin to increase in two weeks and peak in 4 weeks. This suggests good response to treatment. Treatment with oral iron should be continued for 3-6 months. This will correct the anemia and replenish iron stores.*
- Rise of hemoglobin level of blood by 0.5-1 g/dl per week** is considered **adequate response** to iron therapy. For prophylaxis of iron deficiency, 200 mg ferrous sulphate once daily is enough. In pregnancy, iron should be started in the **second trimester**.
- Major *adverse effects* of oral iron that result in poor compliance are gastrointestinal problems like *epigastric pain, nausea, vomiting and metallic taste* etc. These are **related to elemental iron content in the iron preparation**.

Iron is absorbed mostly in the duodenum in the ferrous form (Fe²⁺).

Parenteral route (i.v., i.m.) is indicated only when

- Oral iron is not tolerated
- Oral iron is not absorbed
- Along with erythropoietin

- **Ferric citrate** has the capacity to bind phosphate and form non-absorbable complex. It is indicated to control **hyperphosphatemia** in patients with chronic kidney disease on dialysis. It is given orally.
- **Parenteral** iron preparations are **iron-dextran** and **iron-sorbitol-citrate**. Former can be given by either i.v. or i.m. routes whereas the **latter should not be used intravenously** because it will cause rapid saturation of transferrin receptors, which can cause iron toxicity due to more free iron. **Total iron requirement** can be calculated by the formula:

$$4.3 \times \text{Body weight (kg)} \times \text{Hemoglobin deficit (g/dl)}$$

This formula includes iron required for replenishment of stores also.

- Intramuscular injections are usually given by z-technique to avoid staining and pigmentation of skin. Major problem with parenteral route is pain at injection site and pigmentation of skin.

	Iron-dextran	Iron-sorbitol-citrate
1.	Can be given i.v. or i.m.	* Only i.m.
2.	Not excreted.	* about 30% excreted in urine.
3.	Absorbed through lymphatics.	* Absorbed directly in the circulation.
4.	Not bound to transferrin.	Not bound to transferrin.

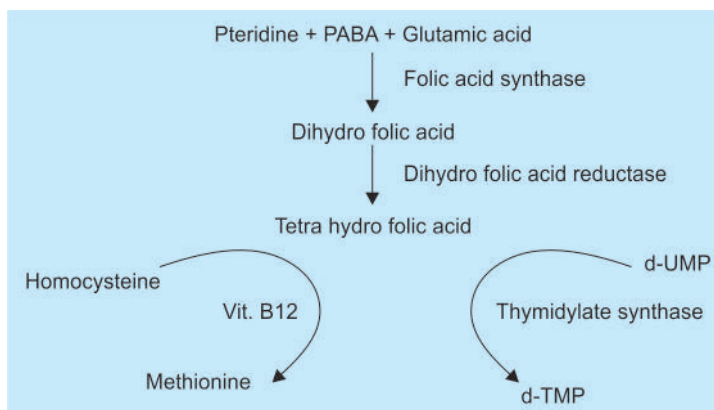
IRON POISONING

- Acute iron poisoning can occur in children due to accidental intake of large number of the iron tablets. The **antidote** of acute iron poisoning is **desferrioxamine**. It is given by i.m. injection. DTPA and calcium disodium EDTA may also be used but dimercaprol (**BAL**) is **contraindicated** because its complex with iron is itself toxic.
- For **chronic iron overload**, as occurs in thalassemia patients, oral chelating agent like **deferiprone** is preferred.

The antidote of acute iron poisoning is desferrioxamine (i.m.) whereas for chronic iron overload, deferiprone (oral) is preferred.

Folic Acid

It consists of pteridine, paraaminobenzoic acid (PABA) and glutamic acid. Dietary folic acid is in the form of polyglutamates and these are cleaved off in the intestine before absorption. Maximum **absorption** occurs in **jejunum**. It is *reduced to first* dihydrofolic acid (**DHFA**) and *then to* tetrahydrofolic acid (**THFA**), which is methylated to form **methyl tetrahydrofolate**. Latter compound is the main form in which it is transported in blood. **THFA** participates in many **one carbon transfer** reactions. Important among these are conversion of **homocysteine to methionine** (which releases THFA from its methylated form) with vitamin B₁₂ as the intermediary carrier **and generation of thymidylate**.



- **Deficiency** of folic acid results in **megaloblastic anemia** that is indistinguishable from that due to vitamin B₁₂ deficiency.
- Main uses of folic acid are in the treatment of megaloblastic anemia due to folic acid deficiency (dietary, due to malabsorption, phenytoin therapy, chronic alcoholism etc.). It is also indicated in **pregnancy to prevent neural tube defects** in the fetus. It should be started as soon as the pregnancy is diagnosed.
- **Leucovorin** (folinic acid, formyl THFA or citrovorum factor) can be used to **prevent the toxicity of methotrexate**.

Vitamin B₁₂

- This vitamin *contains cobalt and cyanocobalamin and hydroxocobalamin* are the two forms that are present in diet.
- It is present in animal foods (liver, kidney, meat, cheese, egg yolk etc.) and the **only vegetable source is legumes** (microorganisms in the nodules synthesize it).
- Vitamin B₁₂ is released from the foods with the help of gastric acid and then it combines with intrinsic factor (secreted by stomach), and the combination is **absorbed in terminal ileum**. After absorption, it is transported in the blood in combination with transcobalamin II. **Active forms** of this vitamin are **deoxyadenosyl-cobalamin** and **methyl-cobalamin**.
- It serves several functions like **conversion of homocysteine to methionine** (folic acid is also required) which is essential for one carbon transfer reactions, **conversion of methylmalonyl Co A to succinyl Co A** (this reaction is required for myelin formation and methylcobalamin is utilized, folic acid is not required for this reaction) and also conversion of **methionine to S-adenosyl methionine**.
- **Deficiency** of vitamin B₁₂ leads to **megaloblastic anemia** which is indistinguishable from folic acid deficiency. **Deficiency** also have manifestations related to loss of myelin like **sub acute combined degeneration of spinal cord** (symptoms of *lesions of posterior column* like loss of vibration and proprioception, paraesthesia, depressed stretch reflexes and mental changes like poor memory and hallucinations etc.)
- Vitamin B₁₂ is used for **treatment** of megaloblastic anemia (**i.m. or s.c. for pernicious anemia** due to deficiency of intrinsic factor and **orally for other causes**), **for correcting neurological abnormalities in diabetics** etc. (methylcobalamin is used) and also for treatment of **tobacco amblyopia** (*hydroxocobalamin is used, it combines with cyanide to form cyanocobalamin*).

Vitamin B₁₂ is absorbed in terminal ileum whereas iron is absorbed in duodenum.

- If the cause of megaloblastic anemia is not known, **folic acid alone should not be given** because it will correct the blood picture of anemia but neurological deficits due to vitamin B₁₂ deficiency may be aggravated (due to diversion of small amount of B₁₂ left, in correcting anemia instead of utilization in myelin formation).
- If the cause of megaloblastic anemia is not known, **folic acid alone should not be given** because it will correct the blood picture of anemia but neurological deficits due to vitamin B₁₂ deficiency may be aggravated (due to diversion of small amount of B₁₂ left, in correcting anemia instead of utilization in myelin formation).

HEMATOPOIETIC GROWTH FACTORS

- Apart from nutritional agents, certain endogenous substances are required for proper hematopoiesis; these substances are known as growth factors. **Growth factor for RBCs is erythropoietin**, for WBCs, it is granulocyte colony stimulating factor (G-CSF) and granulocyte monocyte colony stimulating factor (GM-CSF) and for **platelets** these are **thrombopoietin and IL-11**.
- Erythropoietin is secreted from kidney and helps in the formation of red blood cells. Recombinant human erythropoietin (**Epoetin**) is mainly useful for anemia due to **chronic renal failure** and also due to bone marrow suppressing drugs like

If the cause of megaloblastic anemia is not known, folic acid alone should not be given.

N

Peginesatide is a new drug called erythropoiesis stimulating agent (ESA). It acts by stimulating erythropoietin receptors. It is indicated for treatment of anemia due to CRF in patients on dialysis.

M

CAUSES OF MEGALOBLASTIC ANEMIA

Prime – Phenytoin
Primidone
B – B₁₂ and folic acid deficiency
A – Alcohol
T – Trimethoprim
S – Sulfasalazine
M – Metformin
A – Antifolates (Methotrexate, Pyrimethamine, Proguanil)
N – N₂O

M

TREATMENT OF ITP

Corticosteroids
±
IV IG or anti-D
↓ Not responding
Corticosteroids
+
Rituximab
or
Romipostim (S.C.)
or
Eltrombopag (oral)

zidovudine and anticancer drugs. Response is manifested as elevated hematocrit and reticulocyte count. Major *adverse effect* is *polycythemia* and *hypertension*. **Darbopoietin alpha** is long acting derivative having similar indications.

- **Recombinant G-CSF** is **filgrastim** and recombinant **GM-CSF** is **sargramostim**. These are **used for leucopenia** induced by cancer chemotherapy and are also useful **for harvesting peripheral blood stem cells** (these substances result in mobilization of stem cells from bone marrow to peripheral blood, which can be utilized for transplantation). Filgrastim is better tolerated although both can cause bone pain. **GM-CSF** is associated with *capillary leak syndrome*.
- **Oprelvekin** is the drug, which is **recombinant IL-11** and is used for the prevention and treatment of **thrombocytopenia induced by cancer chemotherapy**.
- **Romiplostim** is a new class of drugs called “**PEPTIBODIES**”. These are peptides (containing biological activity) linked to antibody fragments (increase the half-life of peptide). It acts as an **agonist of thrombopoietin** receptor and is **indicated for chronic idiopathic thrombocytopenic purpura (ITP)** by *subcutaneous route*. Its half-life is inversely proportional to serum platelet count (Longer in patients with thrombocytopenia and shorter in patients whose platelet count has recovered to normal).
- **Eltrombopag** is a new **orally active thrombopoietin agonist approved for ITP**.

	Blood cell	Growth factor	Drug	Indications
1.	RBC	Erythropoietin	Epoetin Darbopoietin Peginesatide	Anemia in CRF, myelosuppressive drug use [zidovudine and cancer chemotherapy]
2.	WBC	G-CSF GM-CSF	Filgrastin Peg-filgrastim Lenograstim Sargramostim Molgramostim	Neutropenia due to anti-cancer drugs Severe chronic neutropenia, Stem cell transplantation, Mobilization of peripheral blood stem cells.
3.	Platelets	IL-11 Thrombopoietin	Oprelvekin Romiplostim Eltrombopag	Thrombocytopenia due to anti-cancer drugs ITP ITP

Mnemonics:

```

1. FIL  GRA  STIM
   |      |      |
   |      |      |
Granulocyte  Stimulator i.e. G-CSF

2. SAR  GRA  MO  STIM
   |      |      |      |
   |      |      |      |
Granulocyte  Monocyte  Stimulator i.e. GM-CSF

3. ROMI PLO  STIM
   |      |      |
   |      |      |
Platelet  Stimulator

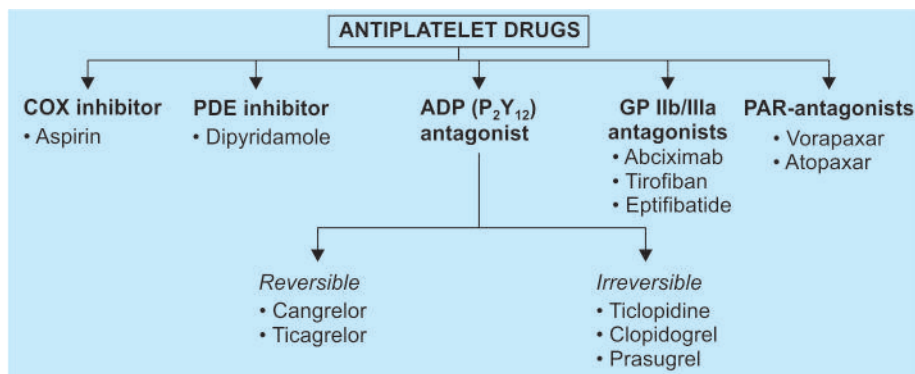
4. EL  TROMBOP  AG
   |      |      |
   |      |      |
Thrombopoietin  Agonist

5. PEGIN ESA  TIDE
   |      |      |
   |      |      |
Erythropoiesis Stimulating Agent
  
```

ANTIPLATELET DRUGS

- In arterial thrombi, platelets are the main constituents. Platelets first stick to damaged blood vessel wall and aggregation occurs which lead to release of ADP, TXA₂, serotonin and other substances that promote further aggregation by activating Gp IIb/IIIa receptors on the platelet surface. PGI₂ (prostacyclins) synthesized in vascular endothelium is a **potent inhibitor of aggregation of platelets**.

- Main drugs acting as **antiplatelet agents** are TXA₂ synthesis inhibitor (**aspirin**), ADP antagonists (**clopidogrel and ticlopidine**) and Gp IIb/IIIa antagonists (**abciximab, tirofiban, eptifibatide**).



- Aspirin inhibits COX enzyme irreversibly** and thus results in decreased synthesis of TXA₂ as well as PGI₂. TXA₂ is produced by platelets and as platelets do not contain nuclei, TXA₂ is not synthesized till there is production of fresh platelets, whereas vessel wall contains nucleus and thus can resume the synthesis of enzymes required for the formation of prostacyclins. The net effect is inhibition of TXA₂ synthesis leading to anti-aggregatory effects.
- Aspirin inhibits thromboxane synthesis but does not inhibit the enzyme thromboxane synthetase** (*dazoxiben is inhibitor of this enzyme*). **For antiplatelet action lowest doses of aspirin are required** (40-325 mg). It has no effect on platelet survival time and their adhesion to vessel wall.
- Dipyridamole** is another drug that acts by **inhibiting phosphodiesterase** (which breaks down cAMP) resulting in increased cAMP that potentiates prostacyclins and thus **anti-aggregation**.
- Ticlopidine, clopidogrel and prasugrel** act as **irreversible antagonists of P₂Y₁₂ receptor of ADP**. These drugs interfere with the activation of platelets by ADP and fibrinogen. Like dipyridamole, these drugs also increase platelet survival time. *Ticlopidine and clopidogrel are prodrugs and are converted to active metabolites in the liver by CYP₂C₁₉. Genetic polymorphisms in this enzyme can affect the antiplatelet action of these drugs. Further, proton pump inhibitors (like omeprazole) inhibit CYP₂C₁₉ and thus prevent activation of these drugs resulting in decreased antiplatelet effect.*
- Ticlopidine causes severe neutropenia** (Absolute neutrophil count < 500/μL) and **thrombocytopenia** and thus less commonly used, whereas clopidogrel is better tolerated. **Most common side effects** of these drugs are **gastrointestinal**.
- Prasugrel** is **strong antiplatelet drug** as compared to ticlopidine or clopidogrel. It is **faster acting than clopidogrel**. However, it also has higher risk of fatal bleeding and thus should be avoided in elderly patients (> 75 years old) and those with history of stroke.
- Gp IIb/IIIa antagonists are strongest antiplatelet drugs** as they block aggregation induced by all agonists. **Abciximab** is a monoclonal antibody against this receptor and is not antigenic. **Eptifibatide** and **tirofiban** are other drugs in this category.
- In addition to inhibiting Gp IIb/IIIa receptor, abciximab also inhibits α_vβ₃ receptor [which binds vitronectin] and α_Mβ₂ [a leucocyte integrin]. These actions are responsible for anti-inflammatory and/or anti-proliferative properties of abciximab. *Eptifibatide and tirofiban are specific for GpIIb/IIIa. Platelet bound abciximab has long half-life (days). In addition to bleeding, thrombocytopenia is the most serious complication of these agents.*

Aspirin inhibits thromboxane synthesis but does not inhibit the enzyme thromboxane synthetase



Ticlopidine, clopidogrel and prasugrel act as **irreversible** antagonists of P_2Y_{12} receptor of ADP whereas **Ticagrelor and cangrelor** are direct-acting **reversible** P_2Y_{12} receptor antagonists..

Feature	Abciximab	Eptifibatide	Tirofiban
Specificity for Gp IIb/IIIa	No	Yes	Yes
Plasma $t_{1/2}$	Short (min)	Long (2.5 hr)	Long (2 hr)
Platelet bound $t_{1/2}$	Long (days)	Short (s)	Short (s)
Renal clearance	No	Yes	Yes

- Cilastazole is a *phosphodiesterase-3 inhibitors* and results in elevated cAMP levels. It reduces platelet aggregation and also possess peripheral vasodilatory action. It can be used for the *treatment of intermittent claudication*.
- **Bleeding** is the main problem with all antiplatelet drugs.
- Antiplatelet drugs are used for **prophylaxis of MI (aspirin is used most commonly), cerebrovascular disease and in artificial heart valves (dipyridamole + warfarin is preferred)**.

New Antiplatelet Agents

- Two groups of newer antiplatelet agents are in advanced stages of development.
- **Ticagrelor** and **cangrelor** are direct-acting **reversible** P_2Y_{12} receptor antagonists. *Ticagrelor is orally effective*. As compared to clopidogrel, it produces *greater and more predictable antiplatelet action*. It also has *more rapid onset and offset of action* as compared to clopidogrel. It is the first new antiplatelet drug to demonstrate a greater reduction in cardiovascular death than clopidogrel in patients with acute coronary syndromes. It has recently been approved by FDA. **Cangrelor** is *intravenous reversible* P_2Y_{12} receptor antagonist in late stages of development.
- **Vorapaxar** is an *orally active inhibitor of thrombin receptors* on platelets called *protease-activated receptor 1 (PAR-1)*. It has recently been approved as antiplatelet drug in patients with history of MI or peripheral artery disease.

COAGULANTS

Main coagulant in the body is vitamin K. It is of three types; K_1 (**phytonadione**), K_2 (**menaquinone**) and K_3 (**menadione**). *Vitamin K is involved in the activation of various clotting factors (like II, VII, IX and X) as well as anti-clotting proteins (like protein C and S)*. It carries out the final step in activation of these factors, i.e. **gamma carboxylation of glutamate residues**.

Main indications of using vitamin K are

- Deficiency states like dietary deficiency, prolonged antimicrobial therapy, liver disease etc.
- Newborns (because usually they have deficiency of this vitamin).
- Overdose of oral anticoagulants like warfarin.

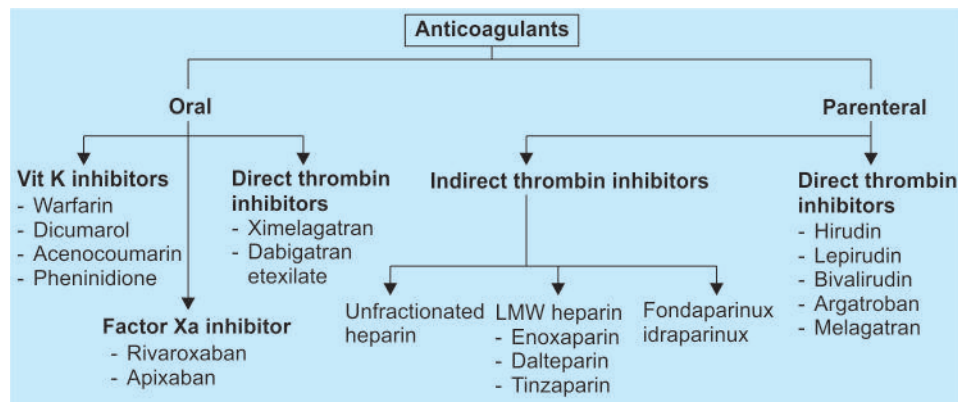
For most of these indications, vitamin K_1 is used. **Menadione** (K_3) is **contra-indicated in patient with G-6-PD deficiency** (causes hemolysis) and in **newborn** (more chances of **kernicterus** due to competitive inhibition of glucuronidation of bilirubin and its displacement from plasma protein binding sites).

ANTICOAGULANTS

Three major groups of anticoagulants are used; warfarin group, indirect thrombin inhibitors (heparin group) and direct thrombin inhibitors. Heparin can be used both in vivo as well as in vitro.



Vitamin K is involved in the activation of various clotting factors (like II, VII, IX and X) as well as anti-clotting proteins (like protein C and S)



1. Oral Anticoagulants

- Drugs in this group include **warfarin**, bishydroxycoumarin (**dicumarol**), **acenocoumarin**, **phenindione** etc. **Phenindione** causes **orange coloured urine** as well as liver and kidney damage.
- These drugs act by inhibiting the activation of vitamin K dependent clotting factors. These factors are synthesized by liver and activated by *gamma-carboxylation of glutamate residues* with the help of vitamin K. Hydroquinone form of vitamin K is converted to epoxide form in this reaction and regeneration of hydroquinone form by enzyme vitamin K epoxide reductase (VKOR) is required for this activity. Oral anticoagulants prevents this regeneration by inhibiting VKOR, thus **vitamin K dependent factors are not activated**. These factors include clotting factors **II, VII, IX and X** as well as **anti-clotting proteins, protein C and protein S**. As already activated factors are not affected, the effects of these drugs depend on disappearance of already activated factors from the blood.
- Warfarin is a racemic mixture of R and S isomers. S-warfarin is more active and is metabolized by CYP2C9. Polymorphisms in CYP2C9 may affect the activity of warfarin among different persons.
- Protein C** has **shorter half life** than most clotting factors (8 hours) so it is the first factor to decline and its deficiency may lead to **dermal vascular necrosis and hypercoagulation** (protein C is anti-clotting) as early appearing (3-10 days after initiation of therapy) adverse effects of warfarin and other drugs of this group. Among **clotting factors, first to disappear is factor VII** ($t_{1/2} = 6$ hours) and last to disappear is factor II ($t_{1/2} = 60$ hours). Therefore, the effect of oral anticoagulants is always delayed (develops gradually over 1-3 days) and these are thus **used for maintenance** of anticoagulation rather than initiation of treatment.
- Bleeding** is the most common **adverse effect** of all anticoagulants. If a patient develops **bleeding due to overdose** of warfarin, **fresh frozen plasma** (to supply clotting factors) is the **treatment of choice** but *specific antidote is vitamin K₁* (but the action will be delayed).
- Warfarin is absorbed well from GIT and it is highly plasma protein bound (99%). Its kinetics changes from first order to zero order within therapeutic concentrations.
- It crosses the placenta and can cause fetal warfarin syndrome; also known as Contradi syndrome (growth retardation, stippled epiphyses, hypoplasia of nose and hand bones etc.) if used during pregnancy (therefore contra-indicated). However, it is not secreted in the breast milk and can be safely given to nursing mothers.
- Prothrombin time is used to adjust the dose of warfarin (*because it mainly affects the extrinsic pathway*). Better test for monitoring the effect of oral anticoagulants is INR (international normalized ratio). It has been developed by WHO and is based on human brain thromboplastin.

Warfarin may lead to dermal vascular necrosis and hypercoagulation as early appearing (3-10 days after initiation of therapy) adverse effects.

If a patient develops bleeding due to overdose of warfarin, fresh frozen plasma (to supply clotting factors) is the treatment of choice but specific antidote is vitamin K₁.

$$\text{INR} = (\text{PT of patient} / \text{PT of reference})^{\text{ISI}}$$

Where ISI is international sensitivity index that depends on the sensitivity of reference thromboplastin to WHO standard thromboplastin.

- **Management of warfarin overdose** is done as follows:

*INR < 5 but above therapeutic range –	Discontinue warfarin temporarily and restart at low dose.
*INR 5-9 –	Vitamin K ₁ (1 mg oral)
*INR > 9 but no bleeding –	Vitamin K ₁ (2 – 3 mg oral)
*INR ≥ 20 or bleeding –	Fresh frozen plasma.

- Warfarin shows a number of **drug interactions**, therefore requires dose adjustment with several medications.
- Drugs **increasing the effect of warfarin**, thus requiring dose reduction include **broad spectrum antibiotics**, **cephalosporins** like cefamandole, cefoperazone and moxalactam (cause hypoprothrombinemia), **aspirin**, **phenylbutazone** and various microsomal enzyme inhibitors (**erythromycin**, **cimetidine** etc.).
- On the other hand, **enzyme inducers** (like **rifampicin**, **griseofulvin** etc) and **oral contraceptives** (increase clotting factors) **decrease the effect** and thus require increase in dose of warfarin.
- New **oral** anticoagulants include **dabigatran etexilate**, **rivaroxaban** and **apixaban**. These *do not require monitoring*. **Dabigatran etexilate** is a *prodrug* and its active metabolite is a *direct thrombin inhibitor* whereas **rivaroxaban** and **apixaban** are *factor Xa inhibitors*. Rivaroxaban has maximum (80%) whereas dabigatran etexilate has minimum (6%) oral bioavailability.

2. Indirect Thrombin Inhibitors

- This group includes **unfractionated heparin**, **low molecular weight heparin** (enoxaparin, dalteparin, tinzaparin, ardeparin, nadroparin and raviparin) and **fondaparinux** and **idraparinux**.
- **Heparin** is the **strongest organic acid** present in the body (in mast cells).
- Heparin is not physiologically active anticoagulant. Commercially it is produced from **ox lung** and **pig intestine**.
- This group of drugs act by **activating antithrombin III** (AT III) in plasma. Normally AT III inactivates several clotting factors, most importantly factor Xa and IIa (thrombin) but the reaction is very slow. Heparin accelerates this inactivation process by binding to ATIII and inducing the conformational change in it to expose the binding sites. Only conformational change is required for inactivation of factor Xa whereas inactivation of thrombin is also dependent on formation of scaffolding by heparin (that binds both ATIII and IIa). **Unfractionated heparin** provides this scaffolding and thus **inhibits both factor IIa and Xa** whereas **LMW heparins** and **fondaparinux** only cause conformational change in ATIII and thus **inhibit only factor Xa**.
- Heparin also increases the release of tissue factor pathway inhibitor (TFPI) from the endothelium that may contribute to its anticoagulant activity.
- As heparin is inhibiting already activated factors, so there is no time lag between the administration and action of this drug, therefore it can be used for initiation of anticoagulant therapy.
- Heparin is not absorbed by oral route, therefore should be given either by s.c. or i.v. routes (i.m. route is contra-indicated due to more chances of hematoma formation).
- **Unfractionated heparin** is metabolized by *non-renal routes* whereas **LMW heparin** and **fondaparinux** are excreted *by kidney* and are contra-indicated in renal failure.
- It does not cross the placenta and is thus **anticoagulant of choice during pregnancy**.
- At higher doses, heparin also exerts antiplatelet action.

Unfractionated heparin provides this scaffolding and thus inhibits both factor IIa and Xa whereas LMW heparins and fondaparinux only cause conformational change in ATIII and thus inhibit only factor Xa.

- Bioavailability of unfractionated heparin is inconsistent after s.c. route and its effect is **monitored by testing aPTT** (at low doses it selectively affects the intrinsic pathway).
- LMW heparin and fondaparinux** have long half lives and consistent s.c. absorption; therefore **do not require monitoring** and once daily s.c. doses are sufficient. Patients with **end stage renal failure and morbid obesity** may *require monitoring* with **anti-factor Xa assay**.

Feature	Heparin	LMWH
Bioavailability after S.C administration.	90%	100%
Plasma $t_{1/2}$	4 hr	17 hr
Release of TFPI	Yes	No
Antidote	Protamine	No

Effect of unfractionated heparin is monitored by testing aPTT whereas effect of warfarin is monitored by PT or INR

- LMW heparins are preferred as initial parenteral anticoagulants over unfractionated heparin for most of the indications. Unfractionated heparin is preferred over LMW heparin in:

- Patients with severe chronic kidney disease (creatinine clearance <30 mL/min.)
- Concomitant thrombolysis is being considered (LMW heparins are contra-indicated because of long $t_{1/2}$ and absence of antidote)
- Patients with venous thromboembolism and a perceived higher risk of bleeding (e.g. post-surgery).
- Patients with epidural catheters.

- The major **adverse effect** of these drugs also is **bleeding** which is **treated with fresh frozen plasma**. *Specific antidote of heparin is protamine* (highly basic drug that can cause release of histamine). It act as **chemical antidote** and neutralizes heparin weight by weight. *Protamine sulfate partially neutralizes the effects of LMW heparins whereas it has no effect on fondaparinux's anticoagulant activity.* Other adverse effects include **thrombocytopenia, alopecia, osteoporosis, hyperkalemia, elevation in hepatic transaminases and hypersensitivity reactions**.

ADVANTAGES OF LMWH OVER HEPARIN	
Advantage	Consequence
– Better bioavailability and longer $t_{1/2}$ after S.C. injection	Can be given S.C. once or twice daily
– Dose independent clearance	Simplified clearance
– Predictable response	No need of monitoring
– Lower risk of HIT-syndrome	Safer for long-term use
– Lower risk of osteoporosis	Safer for long term use

LMW heparin and fondaparinux have long half lives and consistent s.c. absorption; therefore do not require monitoring

- Pregnant females** receiving heparin therapy should be *supplemented with calcium* (to prevent osteoporosis).
- Thrombocytopenia (**HIT syndrome**; Heparin Induced Thrombocytopenia Syndrome) may occur due to formation of antibodies against complexes of heparin with platelet factor 4, that can result in *paradoxical thrombosis*. Most specific **diagnostic test** for HIT is *serotonin release assay*. Warfarin is contraindicated in such a case and LMW heparin should not be used. **Anticoagulant of choice for HIT syndrome is direct thrombin inhibitors** like **lepirudin** and **bivalirudin**. *Fondaparinux can be also used for this condition.*

Features of Heparin Induced Thrombocytopenia

- Platelet count $< 100,000/\mu\text{L}$ or decreased by $> 50\%$.
- Starts 5-10 days after starting heparin.
- More common with unfractionated heparin (than LMW heparin), Surgical patients (than medical patients) and females (than males)
- Venous thrombosis is more common than arterial.

Pulmonary embolism (PE) is treated by anticoagulants. Indications of thrombolytics in PE are:

- Massive PE i.e. with hemodynamic instability
- PE without hemodynamic instability but right ventricular compromise

Direct thrombin inhibitors (Lepirudin and Argatroban) are anticoagulants of choice for heparin induced thrombocytopenia.

Rivaroxaban and Apixaban are new oral anticoagulants that act by direct inhibition of factor Xa

RIVARoxaban
 RIVARsible
 Oral
 Xa
 Blocker
RIVAROXABAN

MANAGEMENT OF HIT

- Stop all forms of heparins and LMW Heparins.
- Do not give platelet transfusions.
- Direct thrombin inhibitors (Lepirudin and Argatroban) are anticoagulants of choice.
- Lepirudin is safe in liver failure whereas argatroban can be safely administered in anuria (renal failure).
- Initially, warfarin causes hypercoagulability, therefore should be avoided.
- Lepirudin is continued till platelet count reaches 1,00,000/ μ L.
- Now, warfarin should be started and direct thrombin inhibitors discontinued. Warfarin should be given for at least 30 days.
- Fondaparinux can also be used for HIT.

		Heparin	Oral Anticoagulants
1.	Route of administration	Parenteral (i.v, s.c.)	Oral
2.	Onset of action	Rapid	Delayed (1-3 days)
3.	Activity	In vitro and in vivo	In vivo only
4.	MOA	Activates Antithrombin III	↓ Activation of II, VII, IX, X
5.	Monitoring by	aPTT	PT
6.	Antagonist	Protamine sulphate	Vit. K ₁ (Phytonadione)
7.	Placental barrier	Does not cross placenta	Fetal warfarin syndrome
8.	Use	To initiate therapy	For maintenance

3. Direct Thrombin Inhibitors

This group includes **hirudin, lepirudin, bivalirudin, argatroban, dabigatran, melagatran** and **ximelagatran**. *Dabigatran and Ximelagatran (a prodrug of melagatran) can be given orally.* All other drugs are used parenterally. These drugs **directly inactivate factor IIa** (thrombin). These are the **anticoagulant of choice for heparin induced thrombocytopenia**. Bleeding is the major adverse effect of this group of drugs also. All of these drugs (*except argatroban*) are *excreted by kidney*, therefore, should be avoided in renal failure. *Argatroban* is secreted in bile and thus is *safe in renal failure*. *Lepirudin can be used in liver disease*.

Note:

- All can prolong aPTT whereas argatroban can prolong INR also.
- Bivalirudin has shortest $t_{1/2}$ (25 min)

4. Target Specific Oral Anticoagulants

Target specific (or direct) oral anticoagulants include dabigatran, rivaroxaban, edoxaban and apixaban. Dabigatran is a direct thrombin inhibitor. **Rivaroxaban, edoxaban and apixaban** are **new oral anticoagulants** that act by inhibiting factor Xa. These are **preferred over warfarin** in atrial fibrillation by European guidelines.

Warfarin is preferred in patients with:

- Mechanical prosthetic valves
- Advanced kidney disease [CrCL < 30 mL/min]
- Moderate or severe mitral stenosis
- Cannot afford new drugs

5. Other Anticoagulants

- **Danaparoid** (mixture of 84% heparan sulfate, 12% dermatan sulfate and 4% chondroitin sulfate) is approved for **prophylaxis of DVT**. It is also effective for **HIT syndrome**. It mainly promotes inhibition of factor Xa by antithrombin.

- **Rodenticides** contain long acting anticoagulants like bromadiolone, brodifacoum, diphénadione, chlorphenacinone and pindone. **Treatment is Vit. K.**
- **Drotrecogin alfa** is a recombinant form of **human activated protein C** that inhibits coagulation by proteolytic inactivation of factor Va and VIIIa. It also has anti-inflammatory activity. It *decreases mortality in patients with severe sepsis.*

USE OF ANTICOAGULANTS

- These drugs are mainly used for **venous thrombosis** and are highly effective in the **treatment and prophylaxis of deep vein thrombosis.**
- **Warfarin** is the most commonly used drug in a patient with **chronic atrial fibrillation** (to prevent the thromboembolism).
- Aspirin and heparin in combination are recommended for unstable angina.
- **Heparin** can also be used in disseminated intravascular coagulation (**defibrination syndrome**).
- Anticoagulants are of little value in cerebral thrombosis once neurological deficit has occurred but these can be used to decrease the occurrence of **stroke (antiplatelet drugs are preferred for this indication).**

CONTRAINDICATIONS OF ANTICOAGULANTS

All anticoagulants are contra-indicated in the conditions having increased risk of bleeding like *bleeding disorders, peptic ulcers, hemorrhoids, severe hypertension, sub acute bacterial endocarditis, tuberculosis* and along with *aspirin and other antiplatelet drugs.*

FIBRINOLYTICS/THROMBOLYTICS

Insoluble fibrin molecules are broken down to soluble fragments with the help of plasmin, which is generated from plasminogen with the help of tissue plasminogen activator (tPA). tPA selectively activates plasminogen that is bound to fibrin (in the thrombus), whereas the excess plasmin generated is inactivated by circulating antiplasmins. **Fibrinolytics** are the drugs which **activate plasminogen to form plasmin** and thus help in lysis of thrombus. These drugs can cause bleeding as the major adverse effect due to lysis of physiological thrombi as well as due to excessive amount of plasmin generated in the circulation. Important fibrinolytic drugs are **streptokinase, anistreplase urokinase, alteplase, reteplase and tenecteplase.**

Reteplase and tenecteplase are known as bolus fibrinolytics

- **Streptokinase** is obtained from β **hemolytic streptococci.**
- Unlike other plasminogen activators, streptokinase does not directly convert plasminogen to plasmin. Instead, it forms a complex with plasminogen and exposes its active site. This altered plasminogen starts acting like tPA and activates other plasminogen molecules to plasmin.
- It **activates fibrin bound as well as circulating plasminogen.** This is **antigenic** and can lead to allergic reactions. It can also lead to formation of **neutralizing antibodies**, thus it is less effective if given repeatedly, however it is **least expensive.**
- **Anistreplase** is formed by *combining streptokinase with Lys-plasminogen.* The active site of plasminogen thus exposed is masked with anisoyl group. After i.v. infusion, the anisoyl group is slowly removed by deacylation, giving the complex a $t_{1/2}$ of approximately 100 minutes. This allows drug administration via a single bolus infusion. However, like streptokinase, anistreplase is *antigenic* and is *not specific for fibrin-bound plasminogen.*
- **Urokinase** is isolated from human **urine** and is not antigenic.
- It directly converts plasminogen to plasmin. Like streptokinase and anistreplase, it also does not discriminate between fibrin-bound and circulating plasminogen and can induce a systemic lytic state. It is often *used for catheter-directed lysis of thrombi in deep veins or peripheral arteries.* Its *availability is limited* due to production problems.

Epsilon amino caproic acid (EACA) and tranexaemic acid are specific antidotes for overdose of fibrinolytic agents.

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- **Alteplase, reteplase and tenecteplase are recombinant tPA.** These are not antigenic and are more efficacious than streptokinase but incidence of hemorrhage is similar to streptokinase and urokinase. *Reteplase and tenecteplase (longest acting) are known as bolus fibrinolytics* since administration do not require prolonged intravenous infusion.

Main indication of these drugs is treatment of **acute myocardial infarction (STEMI)**, for which these should be administered i.v. **within 12 hours** preferably within first 3-6 hours. These are **also indicated in severe, life threatening pulmonary embolism**. These drugs are also contra-indicated in the conditions where risk of bleeding is more. Epsilon amino caproic acid (EACA) and tranexamic acid are specific antidotes for overdose of fibrinolytic agents.

CONTRAINDICATIONS OF FIBRINOLYTICS

	Absolute		Relative
1.	Absolute of hemorrhagic stroke at any time	1.	Current use of anticoagulants (INR $\geq$ 2)
2.	History of non-hemorrhagic stroke within the past year	2.	Recent (> 2 weeks) invasive or surgical procedure.
3.	Marked hypertension (systolic > 180 and/or diastolic > 110 mm Hg).	3.	Prolonged (> 10 min.) cardiopulmonary resuscitation.
4.	Suspicion of aortic dissection.	4.	Known bleeding diathesis
5.	Active internal bleeding (excluding menses)	5.	Pregnancy.
		6.	Hemorrhagic ophthalmic condition (e.g. hemorrhagic diabetic retinopathy.)
		7.	Active peptic ulcer disease.
		8.	History of severe hypertension that is currently adequately controlled.

Streptokinase, anistreplase and urokinase can activate fibrin bound as well as circulating plasminogen (can cause systemic lytic state) whereas reteplase, alteplase and tenecteplase are fibrin-specific.

PLASMA EXPANDERS

- These are high molecular weight substances that exert osmotic effect and retain fluid in blood vessels when infused I.V. These are used to correct hypovolemia due to blood loss as in trauma. The agents used are: Albumin, Dextran, Polygeline and Hetastarch.
- **Albumin:** It **does not interfere with blood grouping or coagulation** and is free of risk of transmission of hepatitis (as it is heat treated). Apart from hypovolemia, burns and shock, it can be used for hypoalbuminemia also. It is highly expensive.
- **Dextran:** These are most commonly used plasma expanders. These can **interfere with blood grouping, coagulation and platelet function**. These can reduce blood viscosity, *decrease rouleaux formation* and improve microcirculation. Dextran-70 is longer acting (24 hours) whereas dextran-40 is rapid but short acting.
- Plasma expanders are *contraindicated in severe anemia, heart failure, pulmonary edema, liver and kidney failure.*

DRUG OF CHOICE	
Condition	Drug of choice
• Anemia	
– Iron deficiency anemia	Ferrous sulphate
– Megaloblastic anemia	
* Folate deficiency	Folic acid
* B ₁₂ deficiency	Vitamin B ₁₂
* Pernicious anemia	Vitamin B ₁₂
* Chemotherapy induced anemia	Erythropoietin
– Anemia due to chronic kidney disease	Erythropoietin
• Iron poisoning	
– Acute	Desferrioxamine
– Chronic	Deferipirone
• Cyanide poisoning	Hydroxocobalamin/Amyl nitrite
• Deep vein thrombosis	
– Prophylaxis	Warfarin
– Initiation of therapy	LMW heparin + warfarin
– With severe chronic kidney disease	Unfractionated heparin
• Pulmonary embolism	
– Stable patient	LMW heparin
– Unstable patient	Thrombolytics (Reteplase)
• Chronic Atrial fibrillation	
– Prophylaxis	Dabigatran or Rivaroxaban or Apixaban
– In mechanical prosthetic valves	Warfarin
– Advanced kidney disease	Warfarin
– Mitral stenosis	Warfarin
• Myocardial Infarction	
– Acute STEMI	Thrombolytics (Reteplase)
– Prophylaxis	Aspirin
• Heparin overdose	Protamine
• Warfarin overdose	Vitamin K
• Bleeding due to overdose of anticoagulants (heparins or warfarin)	Fresh frozen plasma
• Fibrinolytic overdose	Tranexamic acid or Epsilon Amino Caproic Acid
• Chemotherapy induced leukopenia	Sargramostim
• Chemotherapy induced thrombocytopenia	Oprelvekin
Immune thrombocytopenic purpura	Corticosteroids
Heparin induced thrombocytopenia	Argatroban

MULTIPLE CHOICE QUESTIONS

HEMATINICS AND GROWTH FACTORS

1. A patient has subclinical folate deficiency. All of the following drugs can precipitate megaloblastic anemia in this patient except: (AIIMS May 2011)
 - (a) Alcohol
 - (b) Phenytoin
 - (c) Chloroquine
 - (d) Sulfasalazine
2. Which of the following is given to treat thrombocytopenia secondary to anti-cancer therapy and is known to stimulate progenitor megakaryocytes? (AI 2011)
 - (a) Filgrastim
 - (b) Oprelvekin
 - (c) Erythropoietin
 - (d) Iron dextran
3. All of the following are characteristic features of treatment of iron deficiency anemia with oral iron supplements, except: (DPG 2011)
 - (a) If 200-300 mg elemental iron is consumed, about 50 mg is absorbed
 - (b) The proportion of iron absorbed reduces as hemoglobin improves
 - (c) The reticulocyte count should begin to increase in two weeks and peak in 4 weeks—this suggests good response to treatment
 - (d) The treatment should be discontinued immediately once hemoglobin normalizes to prevent side effects of iron.
4. Posterior column sensations in lower limbs are lost in: (DPG 2011)
 - (a) Vitamin A deficiency
 - (b) Vitamin B₁₂ deficiency
 - (c) Vitamin C deficiency
 - (d) Vitamin D deficiency
5. Iron requirement is determined from the equation: (DPG 2011)
 - (a) $3 \times \text{wt. (kg)} \times \text{Hb deficit (g/dl)}$
 - (b) $3.3 \times \text{wt. (kg)} \times \text{Hb deficit (g/dl)}$
 - (c) $4 \times \text{wt. (kg)} \times \text{Hb deficit (g/dl)}$
 - (d) $4.3 \times \text{wt. (kg)} \times \text{Hb deficit (g/dl)}$
6. Pre-conceptional intake of which of the following results in decrease in incidence of neural tube defects? (AIIMS May 2008)
 - (a) Vitamin A
 - (b) Folate
 - (c) Vitamin E
 - (d) Vitamin C
7. For oral iron supplements used for iron deficiency anemia: (DPG 2009)
 - (a) Tolerable dose will deliver 40 to 60 mg of iron per day
 - (b) Mass of total salt is important in determining daily dose
 - (c) Treatment should be stopped as soon as normal hemoglobin level is reached
 - (d) Desired rate of hemoglobin improvement is 0.5 mg per day
8. Which of the following statements about erythropoietin is FALSE? (AI-2008)
 - (a) It is used for the treatment of anemia due to chronic renal failure
 - (b) It results in decrease in reticulocyte count
 - (c) It decrease the requirement of blood transfusions
 - (d) It can cause hypertension
9. In the treatment of undiagnosed megaloblastic anemia, vitamin B₁₂ and folic acid should be given together because: (AI-2008)
 - (a) Vitamin B₁₂ acts as a cofactor for dihydrofolate reductase
 - (b) Folic acid alone causes improvement of anemic symptoms but neurological dysfunction continues.
 - (c) Vitamin B₁₂ deficiency may result in methylfolate trap
 - (d) Folic acid is required for conversion of methylmalonyl-CoA to succinyl Co-A.
10. Filgrastim is used for the treatment of: (AI 2007)
 - (a) Neutropenia
 - (b) Anemia
 - (c) Polycythemia
 - (d) Neutrophilia
11. The most appropriate drug used for chelation therapy in beta thalassemia major is: (AI 2003)
 - (a) Oral desferrioxamine
 - (b) Oral deferiprone
 - (c) Intramuscular EDTA
 - (d) Oral succimer
12. Iron is most commonly absorbed from: (DPG 2010, AIIMS May, 2007)
 - (a) Duodenum and upper jejunum
 - (b) Lower jejunum
 - (c) Stomach
 - (d) Ileum
13. Which of the following is most likely to be used in a young child with chronic renal insufficiency?
 - (a) Cyanocobalamin
 - (b) Desferrioxamine

- (c) Erythropoietin
(d) Filgrastim (G-CSF)
14. The difference between iron sorbitol-citric acid and iron dextran is that the former
(a) Cannot be injected i.v.
(b) Is not bound to transferrin in plasma
(c) Is not excreted in urine
(d) Produces fewer side effects
15. Which of the following metabolic reactions require vitamin B₁₂ but not folate?
(a) Conversion of malonic acid to succinic acid
(b) Conversion of homocysteine to methionine
(c) Conversion of serine to glycine
(d) Thymidylate synthesis
16. Which of the following is an indication for the use of folinic acid?
(a) Prophylaxis of neural tube defects in the offspring of women receiving anticonvulsant medications
(b) Counteracting toxicity of high dose methotrexate therapy
(c) Pernicious anemia
(d) Anemia associated with renal failure
17. An old woman is required to receive 4 cycles of cancer chemotherapy. After her first cycle, she developed chemotherapy induced thrombo-cytopenia. Then in the next cycle, it would be appropriate to give this patient:
(a) Darbopoietin alpha
(b) Filgrastim (G-CSF)
(c) Iron dextran
(d) Oprelvekin (IL-11)
18. A 40 year old man has megaloblastic anemia and early signs of neurological abnormality. The drug most probably required is:
(a) Folic acid
(b) Iron sulphate
(c) Erythropoietin
(d) Vitamin B₁₂
19. A patient Seeta is diagnosed to be having iron deficiency anemia. The agent that can be used to improve the absorption of iron is:
(a) Antacids
(b) Tetracyclines
(c) Phosphates
(d) Ascorbic acid
20. Dr Nitin decided to give oral iron therapy to a patient of iron deficiency anemia. Which of the following adverse effects leads to poor compliance of medicine by the patient?
(a) Epigastric pain and bowel upset
(b) Black stools
(c) Staining of teeth
(d) Metallic taste
21. An old man, Om prakash presented with anorexia, weakness and paraesthesia. On further investigation his hemoglobin came out to be 5.8 g% and the peripheral smear showed the presence of macrocytes and neutrophils having hypersegmented nuclei. His tendon reflexes also were sluggish. Endoscopy revealed atrophic gastritis. Deficiency of which of the following factors can lead to such a clinical situation?
(a) Folic acid
(b) Vitamin B₁₂
(c) Pyridoxine
(d) Riboflavin
22. Megaloblastic anaemia may be caused by all of the following, except: (MPPG 2007)
(a) Dilantin toxicity
(b) Vitamin B₁₂ deficiency
(c) Folic acid deficiency
(d) Long term aspirin intake
23. Megaloblastic anemia is caused by all EXCEPT: (MPPG 2004)
(a) Aspirin
(b) Primidone
(c) Methotrexate
(d) N₂O
24. Folic acid: (TN 2006)
(a) Is also called as pteroyl glutamic acid
(b) Is useful in carriage of one carbon atom moiety
(c) Tetrahydrofolate is the active form
(d) All of the above
25. Filgrastim is a: (TN 2008)
(a) T-cell stimulating factor
(b) GnRH analogue
(c) G-CSF
(d) GM-CSF
26. Erythropoietin is mainly produced in: (RJ 2006)
(a) Liver
(b) Kidney
(c) Intestine
(d) Bone
27. Indication for intramuscular iron therapy is: (MH 2000)
(a) Pregnancy
(b) Postpartum period
(c) Emergency surgery
(d) Oral iron intolerance
28. Methotrexate should be given with which of the following to decrease its side effects? (MH 2002)
(a) Folic acid
(b) Cyanocobalamin
(c) Thiamine
(d) Folinic acid
29. Macrocytic anemia is noted with all of the following except: (Jharkhand 2006)
(a) Phenytoin
(b) Methotrexate
(c) Pyrimethamine
(d) Ciprofloxacin

30. Deficiency of this haemophilic factor during early pregnancy will result in neural tube defect:

- (a) Folic acid (Karnataka 2008)
- (b) Iron
- (c) Cyanocobalamine
- (d) Antioxidants

ANTIPLATELETS

31. Which of the following drugs does not act by blocking Gp IIb/IIIa receptors? (AI 2007)

- (a) Abciximab
- (b) Eptifibatide
- (c) Tirofiban
- (d) Clopidogrel

32. In low dose aspirin acts on: (AI 2001)

- (a) Cyclooxygenase
- (b) Thromboxane A_2 synthase
- (c) PGI_2 synthase
- (d) Lipoxigenase

33. All of the following statements about clopidogrel are correct EXCEPT: (AI 2001)

- (a) Directly interact with platelet membrane Gp IIb/IIIa receptor
- (b) Onset of action is slow
- (c) Duration of action is long
- (d) It is used as an alternative to aspirin in patients with cerebrovascular disease

34. With respect to ticlopidine, clopidogrel:

- (a) Is more likely to cause formation of antiplatelet antibodies
- (b) Is less likely to cause neutropenia
- (c) Is more likely to cause severe bleeding
- (d) Has a greater antiplatelet effect

35. A drug that binds to and inhibits Gp IIb/IIIa glycoprotein and is responsible for platelet antiaggregatory effects is:

- (a) Clopidogrel
- (b) Enoxaparin
- (c) Fondaparinux
- (d) Tirofiban

36. Drugs used in acute myocardial infarction are all EXCEPT:

- (a) Plasminogen activator inhibitors
- (b) Thrombolytics
- (c) Antiplatelet drugs
- (d) Alteplase

37. Which of the following statements regarding ticlopidine is TRUE?

- (a) It blocks GpIIb/IIIa receptors on platelet membrane
- (b) It prevents ADP mediated platelet adenylyl cyclase inhibition

- (c) It inhibits thromboxane A_2 synthesis in platelets
- (d) It does not prolong bleeding time

38. An old woman, Nanda suffered stroke for which she was given alteplase. She improved considerably. To prevent the recurrence of stroke, this patient is most likely to be treated indefinitely with:

- (a) Aspirin
- (b) Warfarin
- (c) Urokinase
- (d) Enoxaparin

39. A patient Amit Kumar is suffering from atherosclerosis. Which of the following is the most beneficial drug for prevention of stroke in this patient?

- (a) Aspirin
- (b) Warfarin
- (c) Low dose subcutaneous heparin
- (d) Digoxin

40. Aspirin prolongs bleeding by inhibiting the synthesis of which of the following? (Karnataka 2009)

- (a) Adenosine receptors
- (b) Cyclic AMP
- (c) Prostacyclin
- (d) Thromboxane A_2

41. Glycoprotein IIb/IIIa receptor antagonist is:

- (a) Clopidogrel (IIP 2005)
- (b) Abciximab
- (c) Tranexamic acid
- (d) Ticlopidine

42. All are antiplatelet drugs Except: (IIP 2006)

- (a) Aspirin
- (b) Clopidogrel
- (c) Dipyridamole
- (d) Warfarin

43. Clopidogrel is an antiplatelet agent that acts by:

- (a) Reducing myocardial oxygen requirements during exertion and stress (NIMHANS 1991) (TN 2004)
- (b) Reducing myocardial oxygen requirements and by inducing coronary artery vasodilatation
- (c) Inhibiting ADP-induced platelet aggregation
- (d) None of the above

44. Mechanism of action of aspirin is inhibition of:

- (a) Thromboxane A_2 synthesis (TN 2006)
- (b) Phosphodiesterase
- (c) HMG-CoA reductase
- (d) Pancreatic lipase

45. Abciximab is:

- (a) Antibody against IIb/IIIa receptors (RJ 2006, 2005)
- (b) Antibody against Ib/IX receptors
- (c) Topoisomerase inhibitor
- (d) Adenosine inhibitor

46. **Tirofiban is a:** (RJ 2008)
 (a) Monoclonal antibody
 (b) Antiplatelet drug
 (c) Anti-inflammatory drug
 (d) Antianginal drug
47. **All are antiplatelet drugs except:** (Jharkhand 2006)
 (a) Clopidogrel
 (b) Abciximab
 (c) Ticlopidine
 (d) Aprotinin
48. **Aspirin is not given in a patient who is already on heparin because aspirin causes:** (Kolkata 2007)
 (a) Platelet dysfunction
 (b) Aspirin inhibits the action of heparin
 (c) Enhanced hypersensitivity of heparin
 (d) Therapy of heparin cannot be monitored
- ANTICOAGULANTS**
49. **LMW heparin is preferred over unfractionated heparin because:** (AIIMS Nov 2013)
 (a) LMW heparin directly inhibit thrombin whereas unfractionated heparin acts via activation of antithrombin
 (b) LMW heparins have lesser risk of causing bleeding
 (c) LMW heparin can be given subcutaneously as well as orally
 (d) LMW heparin has consistent bioavailability.
50. **Apixaban is a new drug that acts by:** (AI 2012)
 (a) Inhibiting TNF alpha
 (b) Inhibiting coagulation factor Xa
 (c) Inhibiting platelet aggregation
 (d) Activating plasminogen
51. **Recent oral direct thrombin inhibitor which can be used for prevention of stroke is:** (AIIMS Nov 2011)
 (a) Dabigatrin
 (b) Ximelagatran
 (c) Lepirudin
 (d) Saxagliptin
52. **Vitamin K is involved in the post-translational modification of?** (AI 2010)
 (a) Glutamate
 (b) Aspartate
 (c) Glycine
 (d) GABA
53. **Which of the following is vitamin K-dependent clotting factor?** (AIIMS Nov 2010)
 (a) Factor VII
 (b) Factor I
 (c) Factor XI
 (d) Factor XII
54. **Anti-coagulant of choice for heparin induced thrombocytopenia is?** (AI 2010)
 (a) Lepirudin
 (b) Aprotinin
 (c) Abciximab
 (d) Plasminogen
55. **Vitamin K dependent clotting factors are:** (DPG 2011)
 (a) Factor IX and X
 (b) Factor IV
 (c) Factor XII
 (d) Factor I
56. **All are true about warfarin, except:**
 (a) It inhibits the activation of vitamin K dependent clotting factors (AIIMS May 2009)
 (b) Its half life is 36 hours
 (c) It can cross placenta
 (d) Its dose is increased in liver disease
57. **Drug used in heparin overdose is:**
 (a) Protamine sulfate (AIIMS May 2009, TN 2008, 2003, 2002, DPG 2004, DNB 2000, RJ 2000)
 (b) Phylloquinone
 (c) Ticlopidine
 (d) Clopidogrel
58. **As compared to unfractionated heparin, low molecular weight heparins:** (DPG 2009)
 (a) Are absorbed more uniformly when given subcutaneously
 (b) Require more frequent laboratory monitoring
 (c) Can be given to patients with heparin induced thrombocytopenia
 (d) Predispose to a higher risk of osteopenia
59. **True statements about heparin are all EXCEPT:** (AI 2007)
 (a) It prolongs aPTT
 (b) Hyperkalemia is not seen
 (c) It can result in alopecia
 (d) It can cause thrombocytopenia
60. **Hemorrhage secondary to heparin administration can be corrected by the administration of:** (AI 2003)
 (a) Vitamin K
 (b) Whole blood
 (c) Protamine
 (d) Ascorbic acid
61. **A diabetic female on INH and rifampicin for TB developed DVT. She was started on warfarin, PT is not raised, and next step should be:** (AI 2001)
 (a) Increase the dose of warfarin
 (b) Replace warfarin with acenocoumarin
 (c) Switch ethambutol for rifampicin
 (d) Use LMW heparin
62. **Which of the following is not used for thromboprophylaxis:** (AIIMS Nov., 2007)
 (a) Heparin
 (b) Warfarin
 (c) Antithrombin III
 (d) Aspirin

63. Vitamin K is a cofactor in: (AIIMS Nov., 2007)
 (a) Carboxylation
 (b) Hydroxylation
 (c) Deamination
 (d) Hydrolysis
64. Anticoagulant effect of warfarin is increased by all of the following EXCEPT: (AIIMS May, 2006)
 (a) Cimetidine
 (b) Phytonadione
 (c) Amiodarone
 (d) Phenylbutazone
65. A patient of thrombosis of veins has been receiving coumarin therapy for three years. Recently she developed bleeding tendency. How will you reverse the effect of coumarin therapy? (AIIMS MAY 2006)
 (a) Protamine injection
 (b) Vit K injection
 (c) Infusion of fibrinogen
 (d) Whole blood transfusion
66. Heparin is the commonly used anticoagulant in cardiac surgery. All of the following are true about heparin EXCEPT: (AIIMS Nov, 2005)
 (a) Weakest acid found in living beings
 (b) Most commercial preparations of heparin are derived from pig intestine
 (c) Acts via antithrombin activation
 (d) Produce thrombocytopenia
67. Urgent reversal of warfarin induced bleeding can be done by the administration of: (AIIMS Nov, 2004)
 (a) Cryoprecipitate
 (b) Platelet concentrates
 (c) Fresh frozen plasma
 (d) Packed red blood cells
68. In a warfarin treated patient skin necrosis is found in: (PGI June, 2006, 2003)
 (a) Protein C deficiency
 (b) Protein S deficiency
 (c) AT III deficiency
 (d) Factor VII deficiency
 (e) Factor X deficiency
69. True statements about vitamin K are: (PGI June, 2003)
 (a) Increases the synthesis of factor II, VII, IX and X
 (b) Require exposure to sunlight
 (c) Causes hemolytic anemia in patients with G-6-PD deficiency
 (d) $t_{1/2}$ is < 6 hour
70. In contrast to heparin, enoxaparin:
 (a) Can be used without monitoring the patient's aPTT
 (b) Is less likely to have a teratogenic effect
 (c) Is more likely to be given intravenously
 (d) Is more likely to cause thrombosis and thrombocytopenia
71. Hypercoagulability and dermal vascular necrosis are early appearing adverse effects of:
 (a) Clopidogrel
 (b) Heparin
 (c) Warfarin
 (d) Vitamin K
72. Which of the following is an anticoagulant drug?
 (a) Heparin
 (b) Ximelagatran
 (c) Fondaparinux
 (d) All of these
73. Which of the following is NOT an advantage of low molecular weight heparin over unfractionated heparin?
 (a) Higher efficacy in arterial thrombosis
 (b) Less frequent dosing
 (c) Higher and more consistent subcutaneous bioavailability
 (d) Laboratory monitoring of response not required
74. Which of the following statements about oral anticoagulants is FALSE?
 (a) They interfere with an early step in the synthesis of clotting factors
 (b) Irrespective of the dose administered, their anticoagulant effect has a latency of onset of 1-3 days
 (c) Their dose is adjusted by repeated measurement of prothrombin time
 (d) They are contraindicated during pregnancy
75. Which of the following drugs should not be administered concomitantly with warfarin as it decreases the effect of oral anticoagulants?
 (a) Broad spectrum antibiotic
 (b) Cimetidine
 (c) Aspirin
 (d) Oral contraceptive
76. In which of the following clinical conditions, use of anticoagulants provide maximum benefit?
 (a) Prevention of recurrences of myocardial infarction
 (b) Prevention of venous thrombosis and pulmonary embolism
 (c) Cerebrovascular accident
 (d) Retinal artery thrombosis
77. You started a patient on oral warfarin. Which of the following factors show the most rapid decline in the blood levels after the initiation of warfarin therapy?
 (a) Factor VII
 (b) Protein C
 (c) Factor X
 (d) Prothrombin
78. Heparin therapy should be monitored with intermittent estimation of: (RJ 2006, 2005, 2000, DPG 2000, Karnataka 20002)
 (a) Bleeding time
 (b) Prothrombin time
 (c) PTTK
 (d) All of the above
79. Heparin acts via activation of:
 (a) Antithrombin III (MH 2005, 2002, DPG 1999)
 (b) Factor VIII
 (c) Factor II and X
 (d) Factor V

80. The anticoagulant of choice in pregnancy is:
 (a) Heparin (UP 2007, UP 2006, RJ 2006, Karnataka 2005)
 (b) Warfarin
 (c) Dicumarol
 (d) Phenindione
81. Which of the following drugs does not cross placenta?
 (a) Heparin (UP 2008)
 (b) Warfarin
 (c) Dicumarol
 (d) Nicoumalone
82. All of the following are anticoagulants, except:
 (a) Phytonadione (TN 2007)
 (b) Warfarin
 (c) LMW heparin
 (d) Lepirudin
83. Orally acting direct thrombin inhibitor is?
 (a) Bivalirudin (MH 2008)
 (b) Ximelgatran
 (c) Melagatran
 (d) Argatroban
84. Heparin does not cause:
 (a) Osteoporosis (Jharkhand 2005)
 (b) Factor V inhibition
 (c) Thrombocytopenia
 (d) Prolongation of aPTT
85. All of the following are seen with heparin therapy except:
 (a) Skin necrosis (AP 2002)
 (b) Thrombosis and thrombocytopenia
 (c) Osteoporosis
 (d) Alopecia
86. Which of the following is NOT an adverse effect of heparin?
 (a) Bleeding (MP 2008)
 (b) Thrombocytopenia
 (c) Hypokalemia
 (d) Osteoporosis
87. All of the following statements are true regarding warfarin toxicity (skin necrosis) except: (Kolkata 2008)
 (a) Skin necrosis occurs during initiation of therapy
 (b) Most common sites are toes and tips of fingers
 (c) Decreased quantity of protein C
 (d) Decreased incidence of adverse effects if therapy with LMWH is started.
88. Oral anticoagulants are monitored by:
 (a) Bleeding time (BT) (Karnataka 2002)
 (b) Coagulation time (CT)
 (c) Prothrombin time (PT)
 (d) Partial thromboplastin time (PTT)
89. Structurally, heparin is: (Karnataka 2001)
 (a) Homopolysaccharide
 (b) Heteropolysaccharide
 (c) Glycoprotein
 (d) Mucoprotein
90. Low molecular weight heparin inhibits clotting factor:
 (a) IIa (Karnataka 2001)
 (b) IXa
 (c) Xa
 (d) Both (a) and (c)

FIBRINOLYTIC AND MISCELLANEOUS

91. Thrombolytics can provide relative mortality reduction in the treatment of acute myocardial infarction, if patient comes within:
 (a) 6 hours (AIIMS May 2012)
 (b) 12 hours
 (c) 18 hours
 (d) 24 hours
92. Which of the following drugs is *not* recommended in septic shock:
 (a) Normal saline (DPG 2009)
 (b) Activated protein C
 (c) Steroids
 (d) Rituximab
93. Treatment of choice in a patient of acute pulmonary embolism with right ventricular hypokinesia and a compromised cardiac output but normal blood pressure is:
 (a) Thrombolytic agent (DPG 2007, AIIMS Nov, 2001)
 (b) Low molecular weight heparin
 (c) IV filters
 (d) Warfarin
94. Dextran is a good plasma expanders, but it has disadvantage of:
 (a) Interference with blood group matching (PGI Dec. 2006)
 (b) Causes thrombocytopenia
 (c) Decreases microcirculation
 (d) Promote rouleaux formation
95. If a fibrinolytic drug is used for the treatment of acute myocardial infarction, the adverse effect most likely to occur is:
 (a) Acute renal failure
 (b) Development of antiplatelet antibodies
 (c) Encephalitis secondary to liver dysfunction
 (d) Hemorrhagic stroke
96. Which of the following medications would be prescribed most frequently to patients suffering from chronic atrial fibrillation?
 (a) Lidocaine
 (b) Bretylium
 (c) Warfarin
 (d) Adenosine
97. Streptokinase was infused in a patient for the management of deep vein thrombosis, following which the patient developed hematemesis. Which of the given agents can be chosen to manage this episode of hematemesis?
 (a) Vitamin K
 (b) Noradrenaline
 (c) Epsilon amino caproic acid
 (d) Rutin

98. Shaswat, A 67-year-old male comes to the physician's office complaining of severe pain in the right foot with paleness of right toe. The patient had a history of receiving unfractionated heparin 7 days back. The hemogram of the patient is as shown below:
- | | |
|----------|-----------------------|
| Hb | 13.2 g/dL |
| WBC | 10000/mm ³ |
| Platelet | 50000/mm ³ |
- Which of the following should be used to treat this condition?
- High dose of Heparin
 - Platelet infusions
 - Argatroban
 - Warfarin
99. Alteplase differs from streptokinase as it:
- Is longer acting (Karnataka 2009)
 - Is derived from human kidney
 - Is cheap
 - Activates plasminogen bound to fibrin
100. Which of the following has proved antithrombotic property:
- Gelatin (MPG 2007, MPG 2004, DPG 2004)
 - Dextran 40
 - Dextran 100
 - Hexastarch
101. Plasma expanders are used in:
- Severe anemia (UP 2007)
 - Severe trauma
 - Pulmonary oedema
 - Cardiac failure
102. Thrombolytic therapy with streptokinase is contraindicated in all of the following except:
- Supraventricular tachycardia (TN 2006)
 - Recent trauma
 - Recent cerebral bleeding
 - Recent surgery
103. Activated protein C is used therapeutically in:
- Abnormal PT/PTT (RJ 2008)
 - MI
 - Fungal infection
 - Sepsis
104. Absolute contraindication to thrombolytic therapy is:
- Pregnancy (MH 2003)
 - History of hemorrhagic stroke in past one year
 - Patients on nitrates
 - Hypertension
105. Which of the following plasminogen activator (fibrinolytic) can be given as bolus dose in patients with acute myocardial infarction:
- Urokinase (MH 2007)
 - Alteplase
 - Reteplase
 - None
106. A useful thrombolytic agent that leads to plasmin activation is:
- Vitamin K (Karnataka 2008)
 - Heparin
 - Streptokinase
 - Aspirin
107. Relative contraindication to thrombolytic therapy includes all the following except:
- Hypotension (Karnataka 2001)
 - Recent surgery
 - Active peptic ulcer
 - Pregnancy
108. Epsilon amino caproic acid is used to reduce bleeding due to:
- Heparin (Karnataka 2000)
 - Warfarin
 - Thrombocytopenia
 - Hyperplasminemia
109. Epsilon aminocaproic acid (EACA) can be used in the treatment of adverse effects caused by:
- Streptokinase
 - Heparin
 - Warfarin
 - Any of the above

RECENT QUESTIONS ASKED BY NATIONAL BOARD

- Does of vitamin K in case of serious bleeding is:
 - 2.5 mg
 - 5 mg
 - 10 mg
 - 20 mg
- Which of the following is an antiplatelet drug ?
 - Clopidogrel
 - Tranexamic acid
 - Streptokinase
 - Hirudin
- Low molecular weight heparin acts on factor-
 - XIa
 - Xa
 - IXa
 - IIa
- All are true about romiplostim except:
 - It is recombinant erythropoietin
 - It has a protein component in its structure
 - Its half life is variable
 - It is given subcutaneously
- All of the following have interaction with warfarin except:
 - Barbiturates
 - Oral contraceptives
 - Cephalosporins
 - Benzodiazepines

6. **Mechanism of action of clopidogrel is**
 - (a) Thromboxane A_2 inhibition
 - (b) Inhibit ADP mediated cAMP activation
 - (c) GP IIb/IIIa inhibition
 - (d) Phosphodiesterase inhibition
7. **Ticlopidine act by:**
 - (a) Decreasing ADP mediated cAMP activation
 - (b) Inhibiting COX enzyme irreversibly
 - (c) GP IIb/IIIa antagonist
 - (d) Phosphodiesterase inhibition
8. **Action of aspirin is due to:**
 - (a) Decrease in thromboxane A_2
 - (b) Inhibition of adenyl cyclase
 - (c) GP IIb/IIIa inhibition
 - (d) ADP antagonism
9. **Aspirin is contraindicated in a patient who is on treatment with:**
 - (a) Prednisolone
 - (b) Warfarin
 - (c) Theophylline
 - (d) Oral contraceptives
10. **What is the formula for parenteral iron therapy:**
 - (a) $4.4 \times \text{body weight (kg)} \times \text{Hb deficit (g/dl)}$
 - (b) $3.3 \times \text{body weight (kg)} \times \text{Hb deficit (g/dl)}$
 - (c) $2.2 \times \text{body weight (kg)} \times \text{Hb deficit (g/dl)}$
 - (d) $1.1 \times \text{body weight (kg)} \times \text{Hb deficit (g/dl)}$
11. **Cyanide poisoning can be treated by:**
 - (a) Pyridoxine
 - (b) Vitamin B_{12}
 - (c) Hyperbaric oxygen
 - (d) Flumazenil
12. **Mechanism of action of aspirin is:**
 - (a) Inhibits COX-2 preferentially
 - (b) Inhibits COX-1 preferentially
 - (c) Inhibits COX 1 and COX 2 reversibly
 - (d) Inhibits COX 1 and COX 2 irreversibly
13. **True about heparin induced thrombocytopenia are all except:**
 - (a) Low molecular weight heparins should not be used for treatment
 - (b) It causes both arterial and venous thrombosis
 - (c) More common with fractionated heparin
 - (d) Occurs after about a week of heparin therapy
14. **Clopidogrel inhibit platelet aggregation by:**
 - (a) Inhibit GpIIb/IIIa
 - (b) Inhibits phosphodiesterase
 - (c) Inhibits ADP
 - (d) Inhibits cyclooxygenase
15. **Protamine antagonism for heparin is:**
 - (a) Competitive
 - (b) Chemical
 - (c) Toxic
 - (d) Noncompetitive
16. **Low molecular weight heparin inhibits:**
 - (a) Factor Xa
 - (b) Factor Xa and IIa
 - (c) Factor IIa
 - (d) Factors II, VII, IX and X
17. **Warfarin anticoagulants inhibits following coagulation factors:**
 - (a) II, V, VII, IX
 - (b) II, VII, IX, X
 - (c) II, V, IX, X
 - (d) II, IX, X, XIII
18. **Which one of the following statement is incorrect regarding Heparin induced thrombocytopenia:**
 - (a) Heparin should be discontinued immediately
 - (b) Alternative anticoagulant such as lepirudin should be administered
 - (c) Low molecular weight heparins should be avoided
 - (d) Heparin should be replaced with Warfarin
19. **Decreased effect of warfarin is seen in case of:**
 - (a) Nephrotic syndrome
 - (b) Acute intake of alcohol
 - (c) Concurrent treatment with phenylbutazone
 - (d) Congestive heart failure
20. **All of the following are true regarding LMWH (Low Molecular Weight Heparin) except:**
 - (a) It has higher and predictable bioavailability
 - (b) It inhibits both factor IIa and Xa
 - (c) PT; aPTT monitoring is not required
 - (d) It has more favorable pharmacokinetics
21. **Drug of choice for deep vein thrombosis prophylaxis in surgical patients is:**
 - (a) Intravenous unfractionated heparin
 - (b) Subcutaneous unfractionated heparin
 - (c) Subcutaneous low molecular weight heparin
 - (d) Warfarin
22. **Initial treatment for pulmonary embolism is:**
 - (a) Fibrinolysis
 - (b) Anticoagulation
 - (c) Surgical embolectomy
 - (d) Venacaval filter
23. **A patient diagnosed to have deep vein thrombosis is being treated with heparin. Which of the following test will you order to adjust its dosage:**
 - (a) Platelet count
 - (b) Prothrombin time
 - (c) Bleeding time
 - (d) Activated partial thromboplastin time
24. **Malonyl aciduria is seen in deficiency of:**
 - (a) Vitamin B_{12}
 - (b) Vitamin B_2
 - (c) Pyridoxine
 - (d) Folic acid

25. All of the following changes seen in megaloblastic anemia can be corrected by administration of folic acid except:
- Megaloblastic hyperplasia of bone marrow
 - Macrocytic normochromic changes in RBC
 - Neurological changes
 - Loss of appetite and easy fatigue
26. Which of the following statements is not true for heparin:
- Acts by activating anti-thrombin III
 - Protamine sulphate antagonizes its action
 - Requires aPTT monitoring in patient
 - Has only in vivo anticoagulant action
27. All of the following are vitamin K dependent coagulation factors except:
- Factor X
 - Factor VII
 - Factor II
 - Factor VIII
28. Which of the following drugs may cause thrombocytopenia:
- Ticlopidine
 - Clopidogrel
 - Abciximab
 - Aspirin
29. Activity of extrinsic pathway of blood coagulation is measured by:
- Bleeding time
 - Prothrombin time/INR
 - aPTT
 - Thrombin time
30. Which one of the following preferentially activates plasminogen bound to fibrin and avoids the systemic lytic state:
- Streptokinase
 - Aminocaproic acid
 - Tranexamic acid
 - Alteplase
31. Rate of iron uptake is regulated by which one of the following:
- Mucosal cell iron stores
 - Route of administration
 - Preparation administered
 - Age of the patient
32. The most common adverse effect with ticlopidine is:
- Neutropenia
 - Diarrhea
 - Hemorrhage
 - Thrombocytopenic purpura
33. Which one of the following is ineffective in acute iron toxicity:
- Desferrioxamine
 - BAL
 - Whole bowel irrigation
 - Deferasirox
34. The biochemical role of vitamin K in the post translational modification of clotting factors is by:
- Glycosylation
 - Carboxylation
 - Acetylation
 - Phosphorylation
35. Platelet aggregation is inhibited by all except:
- Aspirin
 - Clopidogrel
 - Thromboxane A2
 - Eptifibatide
36. Warfarin act by
- Inhibiting the activation of vitamin K dependent factors
 - Inhibiting thrombin indirectly through antithrombin III
 - Directly inhibiting thrombin
 - Inhibiting Gp IIb/IIIa
37. Anticoagulant not used in vitro is:
- Heparin
 - Warfarin
 - Oxalate
 - Citrate
38. Antagonist of heparin is:
- Protamine
 - Vitamin K
 - Warfarin
 - Fresh frozen plasma
39. Ticlopidine is an:
- Antiplatelet drug
 - Antiarrhythmic drug
 - Anticoagulant drug
 - Antifibrinolytic drug
40. All are true about heparin except:
- Antidote is protamine sulphate
 - Can be administered only in vivo
 - Cannot be given orally
 - Increases a PTT

EXPLANATIONS

1. Ans. (c) Chloroquine (Ref: Harrison 17/e p649)

Megaloblastic anemia can be caused by deficiency of folic acid or vitamin B12. The drugs that can result in deficiency of folic acid include

Causes of megaloblastic anemia

Prime –
 Phenytoin
 Primidone
 B – B₁₂ and folic acid deficiency
 A – Alcohol
 T – Trimethoprim
 S – Sulfasalazine
 M – Metformin
 A – Antifolates (Methotrexate pyrimethamine, proguanil)
 N – N₂O

2. Ans (b) Oprelvekin (Ref: Katzung's 11/e p580-581)

Oprelvekin (IL-11) is used to prevent and treat thrombocytopenia.

3. Ans. (d) The treatment should be discontinued immediately once hemoglobin normalizes to prevent side effects of iron. (Ref: Katzung 11/e p571-572)

- A normal individual without iron deficiency absorbs 5–10% of iron, or about 0.5–1 mg daily. Iron absorption increases in response to low iron stores or increased iron requirements
- In an iron deficient individual, about 50–100 mg of iron can be incorporated into hemoglobin daily, and about 25% of oral iron given as ferrous salt can be absorbed. Therefore, 200–400 mg of elemental iron should be given daily to correct iron deficiency most rapidly.
- The reticulocyte count should begin to increase in two weeks and peak in 4 weeks. This suggests good response to treatment
- Treatment with oral iron should be continued for 3–6 months. This will correct the anemia and replenish iron stores.

4. Ans. (b) Vitamin B₁₂ deficiency (Ref: KDT 6/e p589)

- Deficiency of vitamin B12 leads to megaloblastic anemia which is indistinguishable from folic acid deficiency.
- Deficiency also have manifestations related to loss of myelin like sub acute combined degeneration of spinal cord (symptoms of lesions of posterior column like loss of vibration and proprioception, paraesthesia, depressed stretch reflexes and mental changes like poor memory and hallucinations etc.)

5. Ans (d) $4.3 \times \text{wt. (kg)} \times \text{Hb deficit (g/dl)}$ (Ref: KDT 6/e p585)

Total iron requirement can be calculated by the formula:

- $4.3 \times \text{Body weight (kg)} \times \text{Hemoglobin deficit (g/dl)}$
- This formula includes iron required for replenishment of stores also.

6. Ans. (b) Folate (Ref: Dutta 6/e p104, 409; KDT 6/e p491)

- **Neural tube defect occurs due to deficiency of folic acid.**
- *The neural tube closure occurs approximately 2-3 days after conception, so it is quite obvious that folic acid supplementation should be given before conception.*

7. Ans. (a) Tolerable dose will deliver 40 to 60 mg of iron per day (Ref: Katzung 10/e p530; KDT 6/e p585-86)

- Tolerable dose of elemental iron is 200 mg per day in three divided doses i.e. app. 60 mg per dose.
- Mass of elemental iron is more important in determining daily dose rather than mass of total salt, because different salts provide different amount of elemental iron.
- Treatment with oral iron should be continued even after reaching the desired hemoglobin level to replenish the stores.
- Desired rate of hemoglobin improvement is 0.5 to 1 mg per week (not day).

8. Ans. (b) It results in decrease in reticulocyte count (Ref: Katzung 10/e p537-538; KDT 6/e p592)

- Erythropoietin is a hematopoietic growth factor that is normally produced by the kidneys.
- Normally, there is an inverse relationship between serum erythropoietin levels and hemoglobin levels. When Hb decreases and anemia becomes more severe, serum erythropoietin level increases exponentially. But, anemia due to chronic renal failure is an exception to this inverse relationship. In CRF, erythropoietin is not produced, that results in anemia. So, exogenous erythropoietin will markedly improve anemia in CRF patients whereas there is less likelihood of response in other anemias.
- Erythropoietin consistently improves the hematocrit and Hb levels and usually eliminates the need of blood transfusions in CRF patients.
- An increase in reticulocyte count is usually observed in 10 days and increase in hematocrit and Hb levels in about 2-6 weeks.

9. Ans. (b) Folic acid alone causes improvement of anemic symptoms but neurological dysfunction continues (Ref: Katzung 10/e p532; KDT 6/e p591)

- Vitamin B₁₂ is required for conversion of methionine to homocysteine and for formation of succinyl CoA from methylmalonyl CoA.
- Deficiency of vitamin B₁₂ results in megaloblastic anemia, GI manifestations and neurological abnormalities (due to demyelination).
- Folic acid alone will correct the symptoms of megaloblastic anemia but it does not prevent neurological abnormalities, which continue to proceed.
- Neurological abnormalities manifests initially in the form of loss of posterior column sensations (vibration, proprioception etc.), but later on can result in subacute combined degeneration of spinal cord.

10. Ans. (a) Neutropenia (Ref: Katzung's 11/e p580-581)

- Filgrastim (G-CSF) and sargramostim (GM-CSF) are used to prevent or treat chemotherapy induced neutropenia.
- Erythropoietin is used to treat anemia associated with chronic renal failure and cancer chemotherapy.
- Oprelvekin (IL-11) is used to prevent and treat thrombocytopenia.

11. Ans. (b) Oral Deferiprone (Ref: KDT 6/e p868)

- Drug of choice for acute iron poisoning is desferrioxamine, however it has to be administered parenterally. It is not effective by oral route.
- In beta thalassemia major, iron excess can result due to repeated blood transfusions and massive hemolysis. Chelating agent has to be administered for long time in this case. Therefore, oral Deferiprone is preferred in this case.

12. Ans. (a) Duodenum and upper jejunum (Ref: KK Sharma 2007/675, Katzung 11/e p571)

- Maximum iron absorption occurs in duodenum and proximal jejunum.
- Vitamin B₁₂ is absorbed in distal ileum whereas folic acid is absorbed in proximal jejunum.

13. Ans. (c) Erythropoietin (Ref: KDT 6/e p592)

Chronic renal failure may result in anemia due to deficient production of erythropoietin.

14. Ans. (a) Cannot be injected i.v. (Ref: KDT 6/e p586)

Iron sorbitol citrate should not be used i.v. because it may rapidly saturate the transferrin receptors and can result in high concentrations of free iron.

15. Ans. (a) Conversion of malonic acid to succinic acid (Ref: KDT 6/e p588)

Conversion of malonic acid to succinic acid requires vitamin B₁₂ but not folate. This reaction is required for myelin formation and deficiency of B₁₂ is responsible for demyelination.

16. Ans. (b) Counteracting toxicity of high dose methotrexate therapy (Ref: KDT 6/e p592)

- Prophylaxis of neural tube defects require treatment with folic acid.
- Methotrexate toxicity can be prevented by 5'-formyltetrahydrofolate (folinic acid).
- Pernicious anemia requires the therapy with vitamin B₁₂.
- Anemia associated with chronic renal failure is treated with erythropoietin.

17. **Ans. (d) Oprelvekin (IL-11)** (Ref: *Katzung 11/e p580*)

- Oprelvekin acts like megakaryocyte colony stimulating factor and can be used to treat and prevent chemotherapy induced thrombocytopenia.
- Filgrastim (G-CSF) and sargramostim (GM-CSF) are used to prevent leucopenia.

18. **Ans. (d) Vitamin B₁₂** (Ref: *KDT 6/e p591*)

Deficiency of vitamin B₁₂ results in megaloblastic anemia and demyelination. It can cause subacute combined degeneration of spinal cord and peripheral neuritis.

19. **Ans. (d) Ascorbic acid** (Ref: *KDT 6/e p582, 583*)

Substances improving the absorption of iron		Substances improving the absorption of iron	
1.	Acid	1.	Antacids
2.	Reducing substances like ascorbic acid	2.	Phosphates
3.	Meat	3.	Phytates
		4.	Tetracyclines
		5.	Food in the stomach

20. **Ans. (a) Epigastric pain and bowel upset** (Ref: *KDT 6/e p585*)

21. **Ans. (b) Vitamin B₁₂** (Ref: *KDT 6/e p589*)

Diagnosis of the patient is pernicious anemia. Factors favouring this diagnosis are:

- Megaloblastic anemia.
- Demyelination (decreased tendon reflexes)
- Atrophic gastritis

So, he would require B₁₂ supplementation.

22. **Ans. (d) Long term aspirin intake** (Ref: *KDT 6/e p591*)

Dilantin is phenytoin. It results in folic acid deficiency that can result in megaloblastic anemia.

23. **Ans. (a) Aspirin** (Ref: *Harrison's 17/e p647,649; KDT 6/e p591-592*)

24. **Ans. (d) All of the above** (Ref: *KDT 6/e p590*)

25. **Ans. (c) G-CSF** (Ref: *Katzung 11/e p581*)

26. **Ans. (b) Kidney** (Ref: *KDT 6/e p592*)

27. **Ans. (d) Oral iron intolerance** (Ref: *KDT 6/e p585*)

28. **Ans. (d) Folinic acid** (Ref: *KDT 6/e p823*)

29. **Ans. (d) Ciprofloxacin** (Ref: *KDT 6/e p591 790, 823*)

30. **Ans. (a) Folic acid** (Ref: *KDT 6/e p591*)

31. **Ans. (d) Clopidogrel** (Ref: *KDT 6/e p610*)

Clopidogrel inhibits ADP receptors whereas abciximab, tirofiban and eptifibatide are GP IIb/IIIa antagonists.

32. **Ans. (a) Cyclooxygenase** (Ref: *KDT 6/e p609*)

Aspirin acts by inhibiting the enzyme cyclooxygenase.

33. **Ans. (a) Directly interacts with platelet membrane Gp II b/IIIa receptor** (Ref: *KDT 6/e p609, 610*)

- Inhibitors of Gp IIb/IIIa receptors are abciximab, tirofiban and eptifibatide.
- Ticlopidine and clopidogrel acts as antagonists of P₂Y₁₂ type of ADP receptors.
- These drugs can be used in patients in whom aspirin is contra-indicated.
- Clopidogrel is preferred over ticlopidine because latter can cause thrombocytopenia.
- Both of these drugs are prodrugs, so slow acting.
- Both of these are irreversible and thus long acting.

34. **Ans. (b) Is less likely to cause neutropenia** (Ref: KDT 6/e p610)

- Ticlopidine and clopidogrel are ADP antagonists and are used as antiplatelet drugs.
- Antiplatelet action, chances of bleeding and formation of antibodies is similar with these two agents.
- Clopidogrel is better tolerated because it is less likely to cause severe neutropenia and thrombocytopenia as compared to ticlopidine.

35. **Ans. (d) Tirofiban** (Ref: KDT 6/e p610)

36. **Ans. (a) Plasminogen activator inhibitor** (Ref: KDT 6/e p537, 538, 606, 607)

- Tissue plasminogen activators are used in acute MI (not the inhibitors)
- Thrombolytic agents like streptokinase, urokinase, alteplase and reteplase are used to lyse the thrombus.
- Antiplatelet drugs like aspirin are started to prevent the re-infarction.

37. **Ans. (b) It prevents ADP mediated platelet adenylyl cyclase inhibition** (Ref: KDT 6/e p609, 610)

- Abciximab, eptifibatide and tirofiban inhibits GpIIb/IIIa receptors.
- Ticlopidine and clopidogrel inhibits ADP receptors.
- Aspirin inhibits TXA₂ synthesis in platelets.
- Bleeding time is prolonged by antiplatelet drugs whereas PT is prolonged by oral anticoagulants and aPTT by heparin.

38. **Ans. (a) Aspirin** (Ref: KDT 6/e p608, 609)

Antiplatelet drugs like aspirin or clopidogrel are used to prevent arterial thrombosis (in diseases like MI and stroke).

39. **Ans. (a) Aspirin** (Ref: KDT 6/e p610, 611)

- Antiplatelet drugs are used for the prophylaxis of arterial thrombotic conditions like stroke and MI.
- Atrial fibrillation increases the risk of thromboembolism and can result in stroke.

40. **Ans. (d) Thromboxane A₂** (Ref: KDT 6/e p189)

41. **Ans. (b) Abciximab** (Ref: Katzung 11/e p599)

42. **Ans. (d) Warfarin** (Ref: Katzung 11/e p598-599)

43. **Ans. (c) Inhibiting ADP-induced platelet aggregation** (Ref: KDT 6/e p610)

44. **Ans. (a) Thromboxane A₂ synthesis** (Ref: KDT 6/e p609)

45. **Ans. (a) IIb/IIIa glycoprotein antibodies** (Ref: KDT 6/e p610)

46. **Ans. (b) Antiplatelet drug** (Ref: KDT 6/e p610)

47. **Ans. (d) Aprotinin** (Ref: KDT 6/e p609)

Aprotinin is a natural proteinase inhibitor identical to pancreatic trypsin inhibitor. It inhibits mediators of inflammatory response, fibrinolysis and thrombin generation. Aprotinin decreases the requirement of blood transfusions in patients undergoing CABG. It has been withdrawn because of high mortality and renal morbidity.

48. **Ans. (a) Platelet dysfunction** (Ref: KDT, 6/e p603)

49. **Ans. (d) LMW heparin has consistent bioavailability.** (Ref: KDT 7/e p619)

- Major advantage of LMW heparins over unfractionated heparin is that it does not require monitoring as it has consistent subcutaneous bioavailability
- Both of these work by activating antithrombin. Unfractionated heparin act by inhibiting both factor X and factor II whereas low molecular weight heparin can inhibit only factor X
- Risk of bleeding is present with both LMW as well as unfractionated heparin
- None of these is effective orally. These are administered either by i.v. or by subcutaneous route.

50. **Ans. (b) Inhibiting coagulation factor Xa:** (Ref: Harrison 18/e p1000)

Rivaroxaban and Apixaban are newer oral anticoagulants that act by inhibiting factor Xa.

Newer oral anticoagulants that are currently being asked in the exams are:

- Dabigatran (Direct thrombin inhibitor)
- Rivaroxaban
- Apixaban

51. **Ans. (a) Dabigatran:** (Ref: *Katzung 11/e p594, CMDT 2012/537*)

Ximelagatran was the first oral direct thrombin inhibitor approved; however it was later withdrawn because of **hepatotoxicity**. Recently a new direct thrombin inhibitor dabigatran has been approved for the prophylaxis of stroke and systemic embolism in nonvalvular atrial fibrillation. It is administered as a prodrug; dabigatran etexilate. It is not metabolized by CYP enzymes however dose adjustment is required in renal failure.

52. **Ans. (a) Glutamate** (Ref: *Katzung 11/e p595*)

Vitamin K causes gamma carboxylation of glutamate residues in many clotting factors that result in their activation.

53. **Ans. (a) Factor VII** (Ref: *Ganong, 21/e p547*)

Vitamin K-dependent factors are clotting factor II (prothrombin), VII, IX, and X and anti-clotting factors protein C and protein S.

54. **Ans. (a) Lepirudin** (Ref: *CMDT- 2010/486*)

55. **Ans. (a) Factor IX and X** (Ref: *Katzung 11/e p595*)

56. **Ans. (d) Its dose is increased in liver disease** (Ref: *Katzung 11/e p595-596*)

- Warfarin is an oral anticoagulant that acts by inhibiting the γ -carboxylation of glutamate residues in vitamin-K dependent clotting factors (II, VII, IX and X).
- It has 99% binding to albumin that result in
 - Long half life ($t_{1/2}$ = 36 hours)
 - Small volume of distribution
 - Lack of urinary excretion of unchanged drug
- It readily crosses the placenta. If given during pregnancy, it can result in 'Contradi syndrome' in the fetus.
- Liver disease reduces the synthesis of clotting factors, thus increases the effect of warfarin. The dose of this drug therefore, needs to be reduced in liver disease.

57. **Ans. (a) Protamine sulfate** (Ref: *Katzung 11/e p593*)

Protamine sulfate is antidote of heparin overdose whereas vitamin K is used as antidote for warfarin toxicity.

58. **Ans. (a) Are absorbed more uniformly when given subcutaneously** (Ref: *Katzung 10/e p546; KDT 6/e p599*)

- Unlike unfractionated heparin, LMW heparins have more consistent s.c. bioavailability and thus do not require monitoring.
- Adverse effects of both type of heparins are similar.
- Both are contra-indicated in heparin induced thrombocytopenia where the agent of choice is direct thrombin inhibitors like lepirudin.

59. **Ans. (b) Hyperkalemia is not seen** (Ref: *KDT 6/e p599; CMDT 2010/798*)

- Monitoring of anticoagulant effect of heparin is done by measuring aPTT.
- Adverse effect of heparin include
 - Bleeding
 - Osteoporosis
 - Thrombocytopenia
 - Hypersensitivity Reactions
 - Alopecia
 - Hyperkalemia (because heparin inhibits aldosterone production in adrenal glands)

60. **Ans. (b) Whole blood** (Ref: *KDT 7th/620*)

Protamine is heparin antagonist but it is used infrequently because the action of heparin disappears by itself in a few hours, and whole blood transfusion is indicated to replenish the loss when bleeding occurs. It is indicated when heparin action needs to be terminated rapidly *e.g.*, after cardiac or vascular surgery.

61. **Ans. (d) Use LMW heparin** (See below)

- Anticoagulant effect of warfarin is assessed by the measurement of prothrombin time (PT). Failure of elevation of PT indicates the decreased effect of warfarin. Rifampicin is an enzyme inducer and can decrease the effect of warfarin.
- Rifampicin is the most effective drug for tuberculosis and should not be replaced.

- Acenocoumarin is also an oral anti-coagulant. Its metabolism is also subjected to induction by rifampicin.
- Effect of warfarin starts in 4-5 days. Therefore if we increase the dose of warfarin, it will take 5 days to prevent DVT. For immediate action, we should start heparin or LMW heparin
- However, heparin needs to be given by injection, thus not suitable for long-term use.
- Therefore, the next step will be to shift to heparin but long-term treatment will be by increasing the dose of warfarin.

62. Ans. (c) Antithrombin III (Ref: *Katzung 10/e p544; KDT 6/e p603-605*)

- Anticoagulants are mainly used for venous thrombosis and are highly effective in treatment and prophylaxis of deep vein thrombosis. Warfarin is the most commonly used drug in a patient with chronic atrial fibrillation (to prevent the thromboembolism).
- Aspirin and heparin in combination are recommended for unstable angina.
- Heparin can also be used in disseminated intravascular coagulation (defibrination syndrome).
- Anticoagulants are of little value in cerebral thrombosis once neurological deficit has occurred but these can be used to decrease the occurrence of stroke (antiplatelet drugs are preferred for this indication).

63. Ans. (a) Carboxylation (Ref: *Katzung 10/e p549, 550; KDT 6/e p600-601*)

Vitamin K is involved in activation of various clotting factors (like II, VII, IX and X) as well as anti-clotting proteins (like protein C and S). It carries out the final step in activation of these factors i.e. gamma carboxylation of glutamate residues in these factors.

64. Ans. (b) Phytonadione (Ref: *KDT 6/e p602*)

Vitamin K₁ (phytonadione) is the antidote of warfarin. It decreases the effect of oral anticoagulants.

65. Ans. (b) Vit. K injection (Ref: *KDT 6/e p602*)

Vitamin K is used to reverse bleeding tendency (raised INR) in warfarin overdose whereas fresh frozen plasma is treatment of choice for bleeding due to warfarin.

66. Ans. (a) Weakest acid found in living beings (Ref: *KDT 6/e p597*)

- Heparin is the strongest organic acid found in human beings.
- It acts by activating AT-III that inhibits factor Xa and IIa.
- Adverse effects of heparin are : Bleeding, Osteoporosis, Thrombocytopenia, Hypersensitivity, Alopecia
- Most commercial preparations of heparin are derived from ox lung and pig intestine.

67. Ans. (c) Fresh frozen plasma (Ref: *KDT 6/e p602*)

Treatment of choice for urgent reversal of bleeding due to oral anticoagulant overdose is fresh frozen plasma. It is administered to replenish the deficient factors.

68. Ans. (a) Protein C-deficiency (b) Protein S deficiency (Ref: *Goodman and Gilman 12/e 854*)

- Warfarin associated skin necrosis is seen in patients having **protein C deficiency**. Lesion is usually seen between **3rd and 10th day of therapy**.
- Development of the syndrome is unrelated to the dose. The favored sites are breast, thighs and buttocks.
- Warfarin induced skin lesion is treated with vitamin K and heparin.
- The course of lesion is not altered by discontinuation of the drug.

69. Ans. (b) Does not require exposure to sunlight (c) Cause hemolytic anemia in patients with G-6-PD deficiency (Ref: *KDT 6/e p595*)

- Vitamin K is used as a cofactor in the activation (not synthesis) of prothombin, factor VII, IX and X. Menadi-one overdose causes haemolytic anaemia in patient with G-6-PD deficiency and in neonates.
- It may precipitate kernicterus in newborn.
- Half life of Vit-K is 72 hours.
- Sunlight is required for formation of vitamin D (not vitamin K)

70. Ans. (a) Can be used without monitoring the patient's aPTT (Ref: *KDT 6/e p599*)

- Enoxaprin is a LMW heparin. It does not require monitoring.
- Both heparin as well as enoxaprin do not cross placenta and are not teratogenic.

71. **Ans. (c) Warfarin** (Ref: KDT 6/e p602)
Oral anticoagulants inhibit the activation of several clotting factors (II, VII, IX and X) as well as anti-clotting proteins (protein C and S). First to disappear is protein C that can result in hypercoagulation resulting in dermal vascular necrosis.
72. **Ans. (d) All of these** (Ref: KDT 6/e p597)
73. **Ans. (a) Higher efficacy in arterial thrombosis** (Ref: KDT 6/e p603)
Anticoagulants are mainly effective for venous thrombosis (like in DVT).
74. **Ans. (a) They interfere with an early step in the synthesis of clotting factors** (Ref: KDT 6/e p600, 601)
Oral anticoagulants inhibit the activation of factor II, VII, IX and X. These do not affect the synthesis of these factors.
75. **Ans. (d) Oral contraceptives** (Ref: KDT 6/e p603)
Estrogen increases the synthesis of various clotting factors and produce a hypercoagulable state. Thus OCP containing estrogen decrease the effectiveness of warfarin and other oral anticoagulants.
76. **Ans. (b) Prevention of venous thrombosis and pulmonary embolism** (Ref: KDT 6/e p603)
 - Anticoagulants are mainly used for prophylaxis of venous thrombosis (DVT and pulmonary embolism)
 - Antiplatelet drugs are used to prevent arterial thrombosis (MI and stroke).
77. **Ans. (b) Protein C** (Ref: KDT 6/e p602)
78. **Ans. (c) PTTK** (Ref: KDT 6/e p598, 599)
79. **Ans. (a) Antithrombin III** (Ref: KDT 6/e p597)
80. **Ans. (a) Heparin** (Ref: KDT 6/e p598)
81. **Ans. (a) Heparin** (Ref: KDT 6/e p598, 601)
82. **Ans. (a) Phytonadione** (Ref: KDT 6/e p593)
83. **Ans. (b) Ximelgatran** (Ref: Katzung 11/e p514)
84. **Ans. (b) Factor V inhibition** (Ref: KDT 6/e p599)
85. **Ans. (a) Skin necrosis** (Ref: KDT 6/e p599)
86. **Ans. (c) Hypokalemia** (Ref: KDT 6/e p599)
87. **Ans. (b) Most common sites are toes and tips of fingers** (Ref: Harrison 18/e p433)
Common sites of warfarin-induced skin necrosis are breasts, thighs and buttocks.
88. **Ans. (c) Prothrombin time (PT)** (Ref: K.D.T. 6/e p602)
89. **Ans. (b) Heteropolysaccharide** (Ref: Katzung 11/e p591)
90. **Ans. (c) Xa** (Ref: KDT 6/e p599)
91. **Ans. (b) 12 hours** (Ref: Harrison 18/e p2027)
- Fibrinolytic therapy can reduce the relative risk of in-hospital death by up to 50% when administered within the first hour of the onset of symptoms of STEMI, and much of this benefit is maintained for at least 10 years.
 - Since myocardium can be salvaged only before it has been irreversibly injured, the timing of reperfusion therapy, by fibrinolysis or a catheter-based approach, is of extreme importance in achieving maximum benefit.
 - The patients treated within 1–3 h of the onset of symptoms generally benefit most. Although reduction of the mortality rate is more modest, the therapy remains of benefit for many patients seen 3–6 h after the onset of infarction, and some benefit appears to be possible up to 12 h, especially if chest discomfort is still present and ST segments remain elevated.
 - Compared with PCI for STEMI (primary PCI), fibrinolysis is generally the preferred reperfusion strategy for patients presenting in the first hour of symptoms, if there are logistical concerns about transportation of the patient to a suitable PCI center (experienced operator and team with a track record for a “door-to-balloon” time of <2 h), or there is an anticipated delay of at least 1 h between the time that fibrinolysis could be started versus implementation of PCI.
92. **Ans. (d) Rituximab** (Ref: Harrison 17/e p1700-1701)
 - Septic shock is managed by maintaining the cardiovascular system with the help of i.v. fluids particularly normal saline along with antibiotics.

- Adrenal insufficiency has been noted in many cases of septic shock that can be treated by steroids.
- Activated protein C available as drotrecogin alpha is also approved for septic shock.
- Rituximab has no role in treatment of septic shock.

93. **Ans. (a) Thrombolytic agent** (Ref: KDT 6/e p606, 607)

- Anticoagulants are the mainstay for the treatment of pulmonary embolism.
- Thrombolytic therapy is indicated in massive pulmonary embolism with hemodynamic instability and in hemodynamically stable patients but with compromised right ventricular function.

94. **Ans. (a) Interference with blood group matching** (Ref: KDT 6/e p622)

Dextran is a polysaccharide obtained from sugar beet. It is a plasma expander and has all properties of an ideal plasma expander except :

- May interfere with **blood grouping** and **cross matching**.
- Some polysaccharide reacting antibodies if present in patients may cross-react with dextran and trigger an **anaphylactoid reaction**.
- They coat the platelets and coagulation factors and may interfere with **coagulation** and **platelet function**, thus prolong bleeding time. It is not used when hypofibrinogenemia, thrombocytopenia or bleeding is present.
- Dextran prevents rouleaux formation of RBCs and has anti-sludging effects, thereby increasing microcirculation. [Satoskar 18/e p453].

95. **Ans. (d) Hemorrhagic stroke** (Ref: KDT 6/e p607, 608)

Bleeding is the most common adverse effect of anticoagulants, antiplatelets and fibrinolytic agents. This bleeding can manifest as hemorrhagic stroke.

96. **Ans. (c) Warfarin** (Ref: KDT 6/e p604)

Patients of chronic atrial fibrillation are at high risk of developing thromboembolism. Oral anticoagulants are most frequently advised drugs in these patients to decrease the risk of this adverse effect.

97. **Ans. (c) Epsilon amino caproic acid** (Ref: KDT 6/e p608)

Tranexamic acid and EACA are antidotes for the management of fibrinolytic drug poisoning.

98. **Ans. (c) Argatroban** (Ref: Katzung 11/e p592)

It is a case of heparin induced thrombocytopenia (HIT). Four 'T' are used to suspect the diagnosis of HIT:

- Thrombocytopenia
- Timing of heparin administration (5-14 days) before developing thrombocytopenia
- Thrombosis
- Other causes of thrombocytopenia not evident.

DOC for HIT is direct thrombin inhibitors like argatroban.

99. **Ans. (d) Activates plasminogen bound to fibrin** (Ref: KDT 6/e p606)

Fibrinolytics are the drugs which activate plasminogen to form plasmin and thus help in lysis of thrombus. These drugs can cause bleeding as the major adverse effect due to lysis of physiological thrombi as well as due to excessive amount of plasmin generated in the circulation.

100. **Ans. (b) Dextran 40** (Ref: KDT 6/e p622)

Dextran 40 and 70 interferes with coagulation and platelet function and thus prolong bleeding time and so is not used in hypofibrinogenemia, thrombocytopenia or in presence of bleeding.

101. **Ans. (b) Severe trauma** (Ref: KDT 6/e p623)

102. **Ans. (a) Supraventricular tachycardia** (Ref: KDT 6/e p607-608)

103. **Ans. (d) Sepsis** (Ref: CMDT/2010, 437)

104. **Ans. (b) History of hemorrhagic stroke in past one year** (Ref: KDT 6/e p607)

105. **Ans. (c) Reteplase** (Ref: KDT 6/e p606)

106. Ans. (c) Streptokinase (Ref: KDT 6/e p606)
107. Ans. (a) Hypotension (Ref: KDT 6/e p607-608)
108. Ans. (d) Hyperplasminemia (Ref: KDT 6/e p508)
109. Ans. (a) Streptokinase (Ref: KDT 6/e p608)

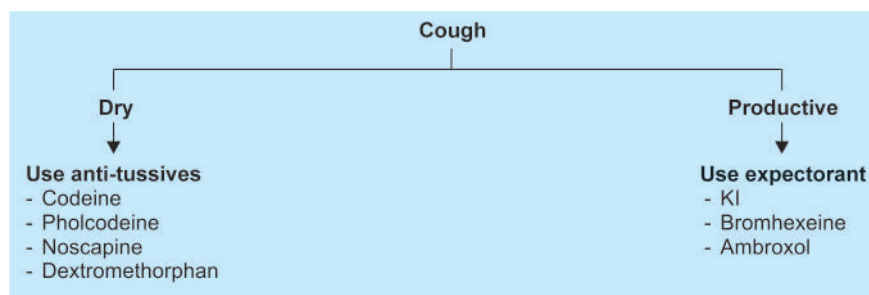
ANSWERS OF RECENT QUESTIONS ASKED BY NATIONAL BOARD

1. Ans (c) 10 mg (Ref: KDT 7th/615)
2. Ans (a) Clopidogrel (Ref: KDT 7th/629)
3. Ans (b) Xa (Ref: KDT 7th/619)
4. Ans (a) It is recombinant Erythropoietin (Ref: CMDT 2015/540)
5. Ans (d) Benzodiazepines (Ref: KDT 7th/623)
6. Ans (b) Inhibit ADP mediated cAMP activation (Ref: KDT 7th/629)
7. Ans (a) Decreasing ADP mediated cAMP activation (Ref: KDT 7th/630)
8. Ans (a) Decrease in thromboxane A₂ (Ref: KDT 7th/629)
9. Ans. (b) Warfarin (Ref: KDT 6/e p90)
10. Ans. (a) 4.4. X body weight (kg) X Hb deficit (g/dl) (Ref: KDT 6/e p858)
11. Ans. (b) Vitamin B₁₂ (Ref: KDT 7/e p609)
12. Ans. (d) Inhibits COX 1 and COX 2 irreversibly (Ref: KDT 7/e p193)
13. Ans. (c) More common with fractionated heparin (Ref: CMDT p526-527)
14. Ans. (c) Inhibits ADP (Ref: KDT 7/e p630)
15. Ans. (b) Chemical (Ref: KDT 7/e p620)
16. Ans. (a) Factor Xa (Ref: KDT 7/e p619)
17. Ans. (b) II, VII, IX, X (Ref: KDT 7/e p620-621)
18. Ans. (d) Heparin should be replaced with Warfarin (Ref: KDT 7/e p618)
19. Ans. (a) Nephrotic syndrome (Ref: KDT 7/e p622-623)
20. Ans. (b) It inhibits both factor IIa and Xa (Ref: KDT 7/e p619)
21. Ans. (d) Warfarin (Ref: KDT 7/e p624)
22. Ans. (b) Anticoagulation (Ref: CMDT 2014/ p291)
23. Ans. (d) Activated partial thromboplastin time (Ref: KDT 7/e p618)
24. Ans. (a) Vitamin B₁₂ (Ref: KDT 7/e p607)
25. Ans. (c) Neurological changes (Ref: KDT 7/e p610)
26. Ans. (d) Has only in vivo anticoagulant action (Ref: KDT 7/e p617)
27. Ans. (d) Factor VIII (Ref: KDT 7/e p621)
28. Ans. (a) Ticlopidine (Ref: KDT 7/e p630)
29. Ans. (b) Prothrombin time/INR (Ref: KDT 7/e p621)
30. Ans. (d) Alteplase (Ref: KDT 7/e p627)
31. Ans. (a) Mucosal cell iron stores (Ref: KDT 7/e p601)
32. Ans. (b) Diarrhea (Ref: KDT 7/e p630)
33. Ans. (b) BAL (Ref: KDT 7/e p906)
34. Ans. (b) Carboxylation (Ref: KDT 7/e p614)

35. Ans. (c) **Thromboxane A₂** (Ref: KDT 7/e p630-631)
36. Ans. (a) **Inhibiting the activation of vitamin K dependent factors** (Ref: KDT 7/e p620-621)
37. Ans. (b) **Warfarin** (Ref: KDT 7/e p621)
38. Ans. (a) **Protamine** (Ref: KDT 7/e p620)
39. Ans. (a) **Antiplatelet drug** (Ref: KDT 7/e p630)
40. Ans. (b) **Can be administered only in vivo** (Ref: KDT 7/e p617-618)

COUGH

It may be productive (with expectoration) or non productive (dry cough). Dry cough is useless and should be suppressed by using an anti-tussive agent. On the other hand, productive cough should be allowed but made easier by the use of expectorants.

**EXPECTORANTS**

These agents increase bronchial secretions or reduce its viscosity. **Potassium iodide** acts directly (by irritating bronchial glands) as well as indirectly (by gastric irritation) to increase bronchial secretions. However, it interferes with thyroid function tests and on prolonged use, can also lead to hypothyroidism. It **may also lead to flaring up of acne** in adolescents. It should not be used in pregnancy (risk of fetal hypothyroidism) and in patients sensitive to iodine. **Bromhexine** causes depolymerization of mucopolysaccharides and thus results in making the mucus less viscid (mucolytic). **Ambroxol** (metabolite of bromhexine) is also a mucolytic drug.

Potassium iodide acts directly (by irritating bronchial glands) as well as indirectly (by gastric irritation) to increase bronchial secretions..

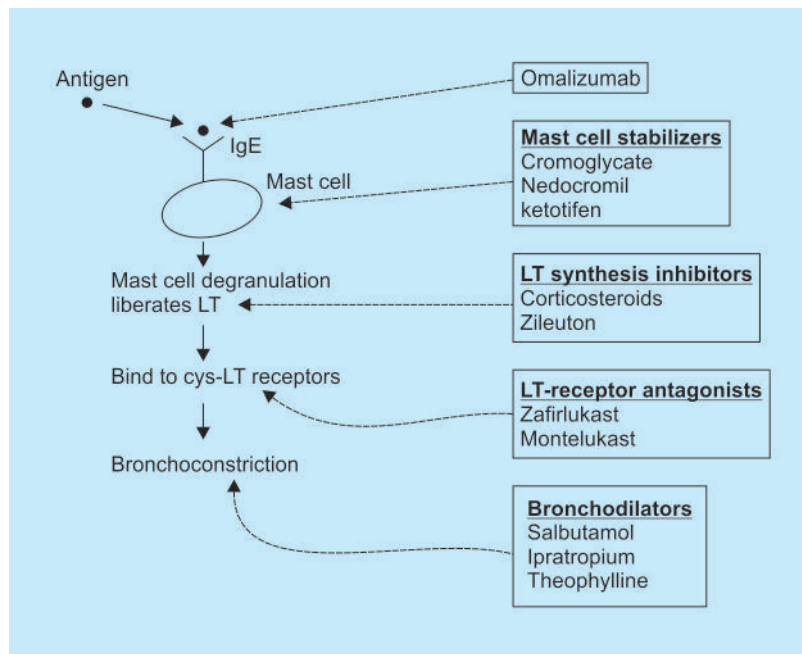
ANTI-TUSSIVES

These drugs suppress cough, either by acting directly in the CNS or by inhibiting cough impulses in the respiratory tract. These drugs should be used **only for dry** (non productive) cough. Anti-tussives include **codeine, pholcodeine, noscapine** and **dextromethorphan**.

BRONCHIAL ASTHMA

It is a condition of bronchial hyperreactivity associated with inflammation. IgE binds to mast cells on first exposure to antigen. On subsequent exposure, the antigen binds to this IgE (bound to mast cells) and its activation leads to degranulation of mast cells, resulting in the release of mediators. Important mediators include leukotrienes (LTs), prostaglandins (PGs), platelet activating factor (PAF), histamine and protease enzymes. These mediators can lead to bronchoconstriction (and thus acute attack of asthma) as well as inflammation leading to hyperreactivity. **The only drugs effective for the treatment of acute attack of bronchial asthma are bronchodilators** (sympathomimetics, parasympatholytics and methyl xanthines). Other drugs used in asthma include those inhibiting IgE (omalizumab), stabilizing mast cells (sodium cromoglycate), decreasing production of mediators (corticosteroids and zileuton) and those inhibiting the actions of mediators (zafirlukast, montelukast).

The only drugs effective for the treatment of acute attack of bronchial asthma are bronchodilators



M

Umeclidinium (anticholinergic) plus **vilanterol** (LABA) combination is recently approved for maintenance treatment of COPD.

1. Bronchodilators

These are the only drugs useful in terminating acute attack of bronchial asthma. Three groups of drugs may act as bronchodilators:

SYMPATHOMIMETICS

Adrenergic drugs (β_2 agonists) act by stimulating GPCRs that result in the activation of adenylyl cyclase and finally increase in cAMP, which cause smooth muscle relaxation (*bronchodilation*). cAMP also *decreases the mediator release from mast cells*. These drugs *also inhibit microvascular leakage and increase mucociliary transport* by increasing ciliary activity. By inhalational route, these are the **fastest acting drugs**. Adrenaline and isoprenaline produce bronchodilation quickly whereas ephedrine has slower onset of action. Above mentioned drugs are non selective and thus are not preferred (tachycardia and increase in the BP are their sideeffects). Selective β_2 agonists are preferred agents for bronchial asthma. *Salbutamol, Levalbuterol, pirbuterol, terbutaline, isoetharine, bitolterol, fenoterol and procaterol are short acting whereas salmeterol, formoterol, arformoterol, carmoterol, olodaterol and indacaterol are long acting β_2 agonists.*

Salbutamol (albuterol), metaproterenol, pirbuterol and terbutaline are fast acting drugs by inhalational route (optimal particle size: 2-5 μm , deposition can be increased by holding the breath in inspiration), so they are used for aborting an attack of acute asthma. These drugs are **not suitable for prophylaxis** because of shorter duration of action. Chronic use of these drugs may lead to tolerance due to down regulation of β_2 receptors. **Salmeterol, bambuterol (prodrug of terbutaline) and formoterol are long acting β_2 selective agonists.** **Salmeterol is delayed acting**, therefore useful only for prophylaxis whereas **formoterol** is

BETA-2 AGONISTS

Short acting

- Salbutamol
- Terbutaline
- Levalbuterol
- Pirbuterol
- Isoetharine
- Bitolterol
- Fenoterol
- Procaterol

Long acting

- Salmeterol
- Formoterol
- Arformoterol
- Carmoterol
- Olodaterol
- Indacaterol

M

SalMETEROL and **ForMOTEROL** contains metro in name. Metro runs long distances, so these are long acting.

Salmeterol contains S i.e. slow acting (not for acute attack) whereas Formoterol starts with F i.e. fast acting (so, can be used for acute attack).

fast acting also, so it is useful in aborting acute attack of bronchial asthma as well as for prophylaxis. *Bitolterol* is a prodrug and is activated to form *colterol* by esterases in lung. **Muscle tremor** and tachycardia are the major side effect of β_2 agonists. Long-term use of β_2 agonists may result in the development of tolerance.

ANTICHOLINERGICS

These drugs cause dilation of mainly **large airways** (β_2 agonists cause bronchiolar dilation). These are **less efficacious and slower acting** bronchodilators than sympathomimetics. These drugs are **more effective for COPD** than bronchial asthma. **Ipratropium, tiotropium and umclidinium** are anticholinergic drugs (M_3 antagonists) that can be used only by inhalational route. **Tiotropium and umclidinium are longer acting** than ipratropium. Tiotropium is used in long-term prophylaxis of bronchial asthma (only in combination with corticosteroids) whereas umclidinium is used for maintenance treatment of airflow obstruction in COPD. These drugs are **bronchodilators of choice in patients of bronchial asthma on β blocker therapy** (β_2 agonists will be ineffective).

Anticholinergics are more effective for COPD than bronchial asthma.

Anticholinergic drugs are bronchodilators of choice in patients of bronchial asthma on β blocker therapy.

METHYLXANTHINES

This group includes caffeine, theophylline and theobromine. Methylxanthines *act by blockade of adenosine receptors* (adenosine is a bronchoconstrictor) and by *inhibition of enzyme phosphodiesterase* (involved in the breakdown of cAMP). At high dose, these drugs can result in *release of Ca^{++}* from sarcoplasmic reticulum in skeletal and cardiac muscles. These drugs are *CNS stimulant drugs* and at toxic dose can result in tremors, delirium and convulsions. These can lead to vomiting due to gastric irritation and CTZ stimulation. **Theophylline** is a potent vasodilator (due to increase in cAMP) and can cause hypotension which leads to reflex tachycardia. *Positive chronotropic and inotropic effects* may be produced even at low doses due to inhibition of presynaptic adenosine receptors (heteroreceptors at sympathetic nerve endings). At toxic doses, arrhythmias can be produced. Caffeine can cause *vasoconstriction of cranial vessels* (so useful in migraine) whereas *dilation of other blood vessels* takes place with methylxanthines. Therapeutic effect of methylxanthines in bronchial asthma is due to *bronchodilation, which is slow but sustained*. Theophylline is given by oral route and **aminophylline** is administered by **slow i.v. infusion**. Kinetics of **theophylline** changes from first order to **zero order** within therapeutic dose range. It has **narrow therapeutic index**. Toxic symptoms are related to GIT, CNS and CVS as described above. *Smoking* and enzyme inducers (phenytoin, phenobarbitone, rifampicin etc.) decrease the plasma levels of theophylline, therefore *require increase in dose*. On the other hand, drugs like *ciprofloxacin, erythromycin and cimetidine* are powerful microsomal enzyme inhibitors, *predisposing to toxicity of theophylline*. **Children clear theophylline faster than adults** (require high dose) whereas clearance of theophylline is **slower in elderly, premature infants and neonates** (require less dose). Further, children are more liable to develop CNS toxicity.

Methylxanthines act by

- Blockade of adenosine receptors
- Inhibition of enzyme phosphodiesterase.
- Release of Ca^{++} from sarcoplasmic reticulum in skeletal and cardiac muscles.

Theophylline is a potent vasodilator and can cause hypotension which leads to reflex tachycardia.

Children clear theophylline faster than adults (require high dose) whereas clearance of theophylline is slower in elderly, premature infants and neonates (require less dose).

Interactions of Theophylline

Dose reduction is required in	Dose should be increased in
• Elderly	• Smokers
• Patients with CHF	• Children
• Patients of pneumonia	• Concomitant administration of enzyme inducers like rifampicin and inducers like rifampicin and phenobarbitone
• Hepatic insufficiency	
• With enzyme inhibitors like ciprofloxacin, cimetidine and erythromycin	

Apart from bronchial asthma, theophylline can also be used to **reduce** the frequency of **episodes of apnea in premature infants** because methylxanthines improve contractility and

Roflumilast, cilomilast and tofemilast are PDE-4 inhibitors being tried for bronchial asthma.

reverse fatigue of diaphragm. **Roflumilast, cilomilast and tofomilast** are *PDE-4 inhibitors* being tried for bronchial asthma.

Note: Recently, it has been found that theophylline at low doses exert anti-inflammatory action by activating a nuclear enzyme; histone deacetylase-2.

2. Drug Inhibiting IgE Action

Ketotifen has antihistaminic action apart from mast cell stabilizing property.

Omalizumab is a monoclonal antibody against IgE and is indicated to prevent the attack of bronchial asthma in patients not responding to combination of long acting β_2 agonist and a high dose of inhalational steroid. It is administered by s.c. route.

3. Mast Cell Stabilizers

Sodium cromoglycate and **nedocromil** prevent the degranulation of mast cells by trigger stimuli. These are indicated only for prophylaxis of bronchial asthma. These are given by inhalational route. **Ketotifen** has antihistaminic action apart from mast cell stabilizing property and is specially indicated for patients with multiple disorders (atopic dermatitis, perennial rhinitis, conjunctivitis etc.).

4. Drugs Decreasing the Action of LTs

This group includes the drugs that interfere with generation of LTs (corticosteroids and lipoxygenase inhibitors) and also that interfere with the action of LTs (leukotriene receptor antagonists).

CORTICOSTEROIDS

These are potent anti-inflammatory drugs and also decrease bronchial hyperreactivity and mucosal edema. Anti-inflammatory action is due to decreased recruitment of inflammatory cells as well as decreased production of PGs and LTs. Arachidonic acid (AA) is released from the membrane phospholipids with the help of enzyme phospholipase A_2 that is inhibited by corticosteroids. AA is converted to PG and TX by cyclooxygenase and to LT with the help of enzyme 5-lipoxygenase (5 LOX). Thus, these mediators are not generated when corticosteroid therapy is initiated. Systemic steroids have a lot of adverse effects, therefore are reserved for resistant severe chronic asthma and in status asthmaticus. These are not bronchodilators but increase the sensitivity to β_2 agonists. **Inhaled steroids** include **beclomethasone, budesonide, mometasone, fluticasone, flunisolide** and **triamcinolone**. These have very little oral absorption and thus little systemic activity after inhalation (>90% reaches GIT after inhalational route, only 4-5% is retained in lungs). **Hoarseness of voice** and **oropharyngeal candidiasis** are very common adverse effects. Candidiasis can be prevented by gargling after each dose and topical nystatin (can be used for treatment also). *Systemic corticosteroids should be avoided in pregnancy but inhaled steroids are safe.* **Ciclesonide** is an inhaled corticosteroid which is metabolized by enzymes in the lungs. Thus, it has least risk of toxicity from systemic absorption when given inhalationally. It is known as **soft steroid**.

Intramuscular triamcinolone acetonide is a depot preparation but proximal myopathy is a major problem with this therapy.

LIPOOXYGENASE INHIBITORS

Zileuton inhibits synthesis of LTB_4 (chemotactic) and LTC_4 and LTD_4 (bronchoconstrictor). Limiting features of this drug are short duration of action and **hepatotoxicity**.

Z I LEUT ON
| | |
Inhibits Leukotriene Number i.e. ↓ synthesis by inhibiting lipoxygenase

Inhaled steroids include:

- Beclomethasone
- Budesonide
- Mometasone
- Fluticasone
- Flunisolide
- Triamcinolone

Ciclesonide is an inhaled corticosteroid which is metabolized by enzymes in the lungs. Thus, it has least risk of toxicity from systemic absorption when given inhalationally. It is known as **soft steroid**.

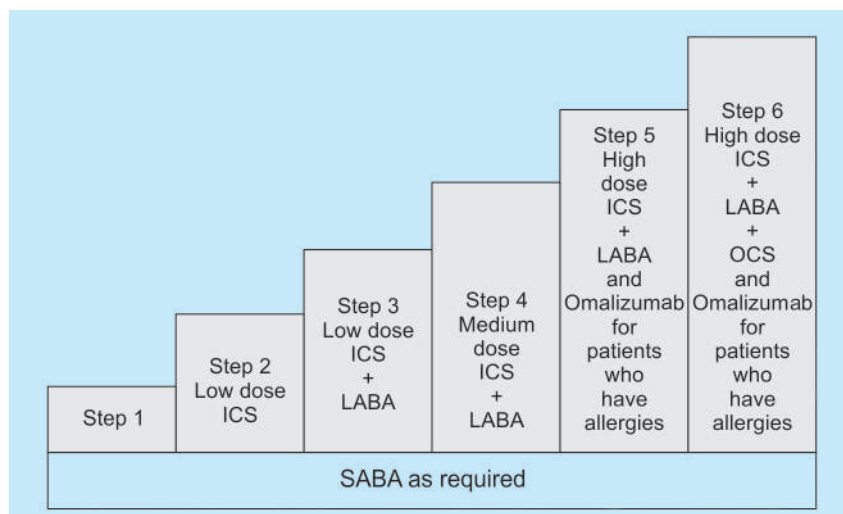
Recently $MgSO_4$ by i.v. and inhalational route has been tried for acute severe asthma.

LT RECEPTOR ANTAGONISTS

Montelukast and **zafirlukast** inhibit the bronchoconstrictor action of LTs at cys LT₁ receptor. These are used as prophylactic agents for bronchial asthma. These are very safe drugs but few cases of **Churg Strauss syndrome** (vasculitis with eosinophilia) have been associated with their use.



STEPWISE APPROACH FOR ASTHMA THERAPY



- **SABA:** Short acting β_2 agonist (e.g. salbutamol); LABA: Long acting β_2 agonist (e.g. salmeterol); ICS: Inhaled corticosteroids; OCS: Oral corticosteroids.
- **Exercise-Induced Asthma:** It typically begins after the end of exercise and recovers spontaneously within 30 minutes. Treatment is usually not required but can be done by SABA. Best method to prevent exercise-induced asthma is regular treatment with **inhaled corticosteroids** (Ref. Harrison 17th/1601) which reduces mast cells. Anti-leukotrienes, mast cell stabilizers and β_2 agonists can also be used for this function.
- **Aspirin Induced Asthma:** Recently, it has been found that aspirin acetylated COX-2 enzyme can convert arachidonic acid to 15-HETE (15-hydroxyeicosatetraenoic acid). In WBCs, 15-HETE is converted to epi-lipoxins (15-epi-LXA₄ or 15-epi LXB₄). These are called **aspirin-triggered lipoxins** and have powerful bronchoconstrictor action. This finding can explain induction of asthma with aspirin but not by other COX-inhibitors.

Note:

- LABA should not be given in the absence of ICS therapy as they do not control the underlying inflammation. Recently, FDA has issued a black box warning for this combination due to slightly increased risk of mortality from asthma attacks.
- In pregnancy; SABA, ICS and theophylline are considered safe. If oral corticosteroids are required prednisone should be used. Because, for action it needs to be converted to prednisolone and fetal liver cannot carry out this reaction. Fetus is thus protected from the systemic effects of corticosteroids.

AEROSOL DELIVERY OF DRUGS

Four classes of anti-asthma drugs (β_2 agonists, anticholinergics, sodium cromoglycate and steroids) can be administered by inhalational route. This route is aimed to decrease systemic side effects of these drugs. Two types of aerosols can be used.

- *Aerosols using drug in solution:* These include *metered dose inhaler* (MDI) and *nebulizer*.
 - **MDI** use chlorofluorocarbons (less preferred due to their effect on ozone layer) or hydrofluoroalkane propellants. These deliver the drug in spray form. Disadvantage of these devices is that they *require proper co-ordination* between deep inspiration and inhaler activation which many patients (especially children and elderly) are unable to do. Use of a spacer decrease the requirement of this co-ordination
 - **Nebulizers** produce a mist of drug solution generated by pressurized air. These *do not require hand-inspiration co-ordination* and are therefore preferred in children, elderly and very severe episodes of asthma.
- *Aerosols using drugs as dry powder:* These include **spinhaler and rotahaler**. Disadvantage of these devices is that they *require high velocity inspiration* (not suitable for children, elderly and very sick patients) and these can cause *irritation of the air passage* (leading to cough and bronchoconstriction).

DRUG OF CHOICE	
Condition	Drug of choice
• Bronchial Asthma	
– Acute attack	Salbutamol
– Acute attack in pregnancy	Salbutamol
– Acute attack during labour	Ipratropium
– Acute attack in patients on beta blocker therapy	Ipratropium
– Prophylaxis	Corticosteroids
• Exercise-induced asthma	
– Acute attack	Salbutamol
– Prophylaxis	Corticosteroids
• Aspirin-induced asthma	
– Acute attack	Salbutamol
– Prophylaxis	Corticosteroids

MULTIPLE CHOICE QUESTIONS

- Which of the following drugs can be administered by subcutaneous route? *(AIIMS May 2013)*
 - Albuterol
 - Terbutaline
 - Metaproterenol
 - Pirbuterol
- Mechanism of action of theophylline in bronchial asthma is: *(AI 2010)*
 - Phosphodiesterase 4 inhibition
 - Beta2 agonism
 - Anticholinergic action
 - Inhibition of mucociliary clearance
- To prevent exercise induced bronchial asthma drug used is: *(DPG 2009)*
 - Sodium cromoglycate
 - Ipratropium bromide
 - Terbutaline
 - Epinephrine
- Which of the following drugs has been found to be useful in acute severe asthma? *(DPG 2009)*
 - Magnesium Sulphate
 - Anti-leukotrine
 - Cromolyn Sodium
 - Cyclosporine
- Leukotriene receptor antagonist used for bronchial asthma is: *(RJ 2008, MH 2007, AI 2007)*
 - Zafirlukast
 - Zileuton
 - Cromolyn sodium
 - Aminophylline
- Which enzyme is inhibited by aminophylline? *(AI 2006)*
 - Monoamine oxidase
 - Alcohol dehydrogenase
 - Phosphodiesterase
 - Cytochrome P 450
- With which of the following receptors theophylline has an antagonistic interaction? *(AI 2005, UP 2005)*
 - Histamine receptors
 - Bradykinin receptors
 - Adenosine receptors
 - Imidazoline receptors
- All of the following statements about theophylline are correct EXCEPT: *(AI 2001)*
 - Increase in dose is required in cardiopulmonary disease
 - Increases cAMP
 - Increase in dose is required in smokers
 - Inhibits phosphodiesterase
- The loading dose of aminophylline is: *(AIIMS May, 2006)*
 - 50-75 mg/kg
 - 0.5-1 mg/kg
 - 2-3.5 mg/kg
 - 5-6 mg/kg
- Which of the following is NOT an adverse effect of salbutamol? *(AIIMS Nov, 2003)*
 - Tachycardia
 - Tolerance
 - Hypokalemia
 - Hypoglycemia
- Inhibition of 5-lipoxygenase is useful in: *(AIIMS Nov, 02)*
 - Cardiac failure
 - Bronchial asthma
 - Hepatic failure
 - Arthritis
- The drug not used in acute asthma is: *(AIIMS May, 02)*
 - Salbutamol
 - Ipratropium
 - Montelukast
 - Hydrocortisone
- Inflammation in the airways can be reduced by: *(PGI June, 2006)*
 - Fluticasone
 - Budesonide
 - Theophylline
 - Salbutamol
 - Ipratropium
- True about zafirlukast is: *(PGI Dec. 2005)*
 - It inhibits lipoxygenase pathway
 - It decreases the frequency of asthma attacks as compared to glucocorticoids
 - It blocks LT receptor
 - It is effective in acute bronchial asthma
 - It can be administered orally
- Drugs which increase level of theophylline include: *(PGI June, 2002)*
 - Ciprofloxacin
 - Barbiturates
 - Cimetidine
 - Allopurinol
 - Phenytoin
- Which of the following anti-asthma drugs is NOT a bronchodilator?
 - Ipratropium bromide
 - Theophylline
 - Formoterol
 - Sodium cromoglycate

17. The most prominent and dose related side effect of salbutamol is:
 - (a) Rise in blood pressure
 - (b) Muscle tremor
 - (c) Hyperglycemia
 - (d) Central nervous system stimulation
18. Which of the following drugs is the fastest acting inhaled bronchodilator?
 - (a) Ipratropium bromide
 - (b) Formoterol
 - (c) Salbutamol
 - (d) Salmeterol
19. Which of the following actions is NOT exhibited by methylxanthines?
 - (a) Intracellular release of Ca^{2+}
 - (b) Antagonism of adenosine
 - (c) Inhibition of phosphodiesterase
 - (d) None of the above
20. Which of the following statements about theophylline is TRUE?
 - (a) Its use in asthma has declined because of narrow safety margin
 - (b) Its dose needs to be reduced in the smokers
 - (c) It acts by increasing the formation of cAMP
 - (d) Its plasma half life is longer in children as compared to that in adults
21. Relatively higher dose of theophylline is required to attain therapeutic plasma concentration in:
 - (a) Smokers
 - (b) Congestive heart failure patients
 - (c) Those receiving erythromycin
 - (d) Those receiving cimetidine
22. Which of the following drugs CANNOT be administered by inhalation?
 - (a) Theophylline
 - (b) Ipratropium bromide
 - (c) Budesonide
 - (d) Terbutaline
23. In comparison to inhaled adrenergic agonists, the inhaled anticholinergics:
 - (a) Are more effective in bronchial asthma
 - (b) Are better suited for control of an acute attack of asthma
 - (c) Produce slower response in bronchial asthma
 - (d) Produce little benefit in chronic obstructive lung disease
24. One of the most common side effects of inhaled beclomethasone dipropionate is:
 - (a) Pneumonia
 - (b) Oropharyngeal candidiasis
 - (c) Atrophic rhinitis
 - (d) Pituitary adrenal suppression
25. Omalizumab is a monoclonal antibody used for the treatment of:
 - (a) Digitalis toxicity
 - (b) Bronchial asthma
 - (c) Rheumatoid arthritis
 - (d) Breast carcinoma
26. Which of the following drugs is effective in the treatment of acute asthmatic attack?
 - (a) Zafirlukast
 - (b) Nedocromil
 - (c) Prednisolone
 - (d) Albuterol
27. Which of the following β_2 agonists is given by inhalation, and is suitable for both terminating acute asthma attacks as well as for twice daily prophylaxis?
 - (a) Terbutaline
 - (b) Bambuterol
 - (c) Salmeterol
 - (d) Formoterol
28. A 55-year-old female who is taking propranolol for the management of a cardiovascular disease experiences an acute asthmatic attack. Which of the following drugs would you prescribe to attenuate this asthmatic attack?
 - (a) Cromolyn sodium
 - (b) Salbutamol
 - (c) Beclomethasone
 - (d) Ipratropium bromide
29. The following drug is NOT useful during acute attack of bronchial asthma: *(Karnataka 2009)*
 - (a) Salbutamol
 - (b) Hydrocortisone
 - (c) Cromolyn sodium
 - (d) Theophylline
30. All of the following drugs useful in bronchial asthma are bronchodilators EXCEPT: *(DPG 2001, 1997)*
 - (a) Theophylline
 - (b) Salmeterol
 - (c) Beclomethasone
 - (d) Ipratropium
31. All of the following are the adverse effects seen with the use of salbutamol EXCEPT: *(MP 2008, DPG 2000)*
 - (a) Tremors
 - (b) Palpitation
 - (c) Hypotension
 - (d) Hypokalemia
32. Which of the following is a bronchodilator? *(DPG 2000)*
 - (a) Corticosteroids
 - (b) Salmeterol
 - (c) Ketotifen
 - (d) Sodium cromoglycate
33. The drug that DOES NOT result in theophylline toxicity is: *(DPG 1999)*
 - (a) Ciprofloxacin
 - (b) Amoxicillin
 - (c) Erythromycin
 - (d) Cimetidine

34. All of the following drugs can precipitate acute attack of asthma EXCEPT: (DPG 1998)
 (a) Phenylbutazone
 (b) Naproxen
 (c) Glucocorticoids
 (d) Aspirin
35. Ipratropium bromide used in bronchial asthma, is: (UP 2008)
 (a) β -Sympathomimetics
 (b) Methylxanthines
 (c) Anticholinergics
 (d) Mast cell stabilizers
36. Which of the following is long acting sympathomimetics used in bronchial asthma? (UP 2008)
 (a) Salbutamol
 (b) Terbutaline
 (c) Bambuterol
 (d) Salmeterol
37. Dextromethorphan is an: (TN 2008)
 (a) Antihistaminic
 (b) Antitussive
 (c) Expectorant
 (d) Antiallergic
38. Disodium cromoglycate is used by which of the following routes? (RJ 2001)
 (a) Inhalation
 (b) Oral
 (c) IV
 (d) IM
39. Which is a "Soft steroid" used in bronchial asthma? (RJ 2008)
 (a) Budesonide
 (b) Dexamethasone
 (c) Ciclesonide
 (d) Flunisolide
40. Omalizumab is administered in bronchial asthma by which route? (RJ 2008)
 (a) Oral
 (b) Intravenous
 (c) Subcutaneous
 (d) Aerosol
41. Directly acting cough suppressant is: (MH 2000)
 (a) Dextromethorphan
 (b) Bromhexine
 (c) Acetyl cysteine
 (d) Carbapentate
42. In a patient of chronic asthma on treatment with theophylline, which of the following should not be used to treat his upper respiratory tract infection? (MH 2003)
 (a) Ampicillin
 (b) Cephalixin
 (c) Erythromycin
 (d) All
43. Which of the following inhibits theophylline metabolism? (MH-PGM-CET 2007) (MH 2008)
 (a) INH
 (b) Griseofulvin
 (c) Prednisolone
 (d) Ciprofloxacin
44. Longest acting β -agonist is: (AP 2000)
 (a) Salbutamol
 (b) Terbutaline
 (c) Salmeterol
 (d) Theophylline
45. Complications of aerosol steroids use include: (AP 2000)
 (a) Oral candidiasis
 (b) Cushing's syndrome
 (c) Decreased ACTH
 (d) Systemic complications
46. The following drug is contraindicated in bronchial asthma: (AP 2002)
 (a) Propranolol
 (b) Ipratropium bromide
 (c) Theophylline
 (d) Ketotifen
47. Release of histamine and leukotrienes from mast cells is prevented by: (Kolkata 2008, Bihar 2006)
 (a) Zileuton
 (b) Nedocromil sodium
 (c) Zafirlukast
 (d) Fexofenadine
48. Advantage of salmeterol over salbutamol is its: (Karnataka 2001)
 (a) Shorter duration of action
 (b) More potency
 (c) Longer duration of action
 (d) Lesser cardiac effects
49. Interaction of theophylline with ciprofloxacin is: (UP 2008)
 (a) Ciprofloxacin increases theophylline metabolism
 (b) Ciprofloxacin decreases theophylline metabolism
 (c) Theophylline increases ciprofloxacin metabolism
 (d) Theophylline decreases ciprofloxacin metabolism
50. Theophylline overdose causes: (UP 2008)
 (a) Bradycardia
 (b) Seizures
 (c) Drowsiness
 (d) Bronchospasm
51. Therapeutic blood range of theophylline in microgram per millilitre is: (UP 2008)
 (a) 0-5
 (b) 5-10
 (c) 5-15
 (d) 5-20

52. In theophylline metabolism, drug interactions occurs with all Except: (UP 2008)

- (a) Cimetidine
- (b) Phenobarbitone
- (c) Rifampine
- (d) Tetracyclines

RECENT QUESTIONS ASKED BY NATIONAL BOARD

1. Mechanism of action of theophylline in bronchial asthma include all of the following except:

- (a) Phosphodiesterase inhibition
- (b) Adenosine receptor antagonism
- (c) Increased histone deacetylation
- (d) Beta -2 receptor stimulation

2. Which of the following is a long acting beta 2 agonist?

- (a) Salmeterol
- (b) Orciprenaline
- (c) Penoterol
- (d) Pexbaterol

3. Omalizumab is used for:

- (a) Rheumatoid arthritis
- (b) Asthma
- (b) Prostate cancer
- (d) CLL

4. Efficacy of salmeterol is increased if it is given along with:

- (a) Theophylline
- (b) Corticosteroid
- (c) Ipratropium
- (d) Sodium cromoglycate

5. Omalizumab is indicated for which of the following conditions:

- (a) Multiple myeloma
- (b) Psoriasis
- (c) Bronchial asthma
- (d) Rheumatoid arthritis

6. Most common dose related side effects of salbutamol is:

- (a) Nervousness
- (b) Palpitations
- (c) Restlessness
- (d) Tremors

7. Which of the following is a long acting beta 2 agonist:

- (a) Salbutamol
- (b) Salmeterol
- (c) Terbutaline
- (d) Levalbuterol

8. Mechanism of actions of montelukast is:

- (a) Competitive antagonist of leukotriene receptors
- (b) Inhibits alpha receptor
- (c) Beta receptor agonist
- (d) Non-competitive inhibitor of leukotriene synthesis

9. Mechanism of action of zileuton is:

- (a) Inhibits production of IgE
- (b) Inhibits Lipoxygenase
- (c) Inhibits Cyclooxygenase
- (d) Inhibits activity of mast cells

10. Which of the following does not have a role in acute attack of asthma?

- (a) Cromolyn sodium
- (b) Ipratropium
- (c) Steroids
- (d) Salbutamol

11. Which of the following is not a bronchodilator?

- (a) Beta 2 agonists
- (b) Methylxanthines
- (c) Steroids
- (d) Anticholinergic

12. Drug of choice for treatment of acute asthmatic attacks is:

- (a) Leukotriene antagonists
- (b) Lipoxygenase inhibitors
- (c) Beta 2 agonists
- (d) Anticholinergics

13. Which of the following class of drugs is a precipitant of acute asthma?

- (a) Beta-adrenergic receptor agonists
- (b) NSAIDs
- (c) Calcium channel blockers
- (d) H₁ blockers

14. Adverse effects of salmeterol include:

- (a) Hyperkalemia
- (b) Seizures
- (c) Tremors
- (d) Interstitial nephritis

15. A 34 years old man with a long history of asthma is referred to pulmonologist. The physician decides to prescribe zileuton. The mechanism of action of this drug is to:

- (a) Antagonize leukotriene D4 receptor
- (b) Inhibits 5-lipoxygenase
- (c) Inhibit phosphodiesterases
- (d) Stimulate beta2 receptors

16. Select the CORRECT statement regarding use of inhaled glucocorticoids in bronchial asthma:

- (a) They are used for acute attacks of asthma
- (b) They have high systemic activity
- (c) They are superior to β_2 agonists in symptom control
- (d) Oral candidiasis can occur as a side effect

- 17. Which of the following drug is not used in the treatment of bronchial asthma:**
- β_2 agonists
 - Corticosteroids
 - Cholinesterase inhibitors
 - Phosphodiesterase inhibitors
- 18. All of the following are useful in the management of acute asthma except:**
- Hydrocortisone intravenously
 - Salbutamol inhalation
 - Salmeterol inhalation
 - Terbutaline inhalation
- 19. Which of the following drugs prevents the release of leukotrienes and histamine from mast cells?**
- Zileuton
 - Fexofenadine
 - Nedocromil
 - Tiotropium
- 20. Which of the following is a long acting β_2 selective agonist?**
- Formoterol
 - Isoprenaline
 - Salbutamol
 - Ephedrine
- 21. In bronchial asthma the mechanism of action of corticosteroids is:**
- Relax airway smooth muscle directly
 - Inhibits mast cell deregulation
 - Inhibits adenosine receptors
 - Inhibits lymphocytic eosinophilic mucosal inflammation
- 22. Leukotrienes inhibitors are very effective in which one of the following conditions:**
- Exercise induced asthma
 - Antigen induced asthma
 - Aspirin induced asthma
 - Occupational asthma
- 23. Inhaled sodium cromoglycate:**
- Prevents the antigen antibody combination
 - May cause cardiac arrhythmias
 - Is of benefit in preventing exercise induced bronchial spasm
 - Is effective in alleviating an acute episode of allergic asthma
- 24. Most common side effect of inhalational beclomethasone is:**
- Adrenal suppression
 - Oropharyngeal candidiasis
 - Bronchoconstriction
 - Hepatitis
- 25. Efficacy of inhaled steroids is maximum when particle size is:**
- 1-5 μm
 - 5-10 μm
 - 10-15 μm
 - 15-20 μm
- 26. Zileuton is:**
- 5 lipooxygenase inhibitor
 - TX A_2 inhibitor
 - Leukotriene receptor antagonist
 - Prostaglandin synthesis inhibitor

EXPLANATIONS

1. Ans. (b) Terbutaline (Ref: *Katzung 12/e p344*)

All four drugs i.e. albuterol (salbutamol), terbutaline, metaproterenol and pirbuterol are available as metered dose inhaler. Salbutamol and terbutaline are also available in tablet forms.

Only terbutaline is available as subcutaneous injection. This route is indicated only for severe asthma requiring emergency treatment when aerosolized therapy is not available or has been ineffective.

2. Ans. (a) Phosphodiesterase 4 inhibition (Ref: *Katzung 11/e p345*)

Theophylline is used in bronchial asthma. Its mechanism of action is:

- Inhibition of phosphodiesterases particularly PDE-4.
- Antagonism of adenosine receptors.
- Enhancement of histone deacetylation. Acetylation of histone is required for activation of inflammatory gene transcription. By inhibiting this process, low-dose theophylline may restore responsiveness to corticosteroids.

3. Ans. (a) Sodium cromoglycate (Ref: *Katzung 10/e p325; KDT 6/e p223*)

Mast cell stabilizers like cromoglycate and nedocromil are used to prevent exercise induced asthma. However, corticosteroids are preferred for this indication.

4. Ans. (a) Magnesium sulphate (Ref: *Harrison 17/e p1605*)

Magnesium sulphate by i.v. or inhalational route has been used for the treatment of acute severe asthma. All other drugs mentioned in the options are used for prophylaxis of asthma.

5. Ans. (a) Zafirlukast (Ref: *KDT 6/e p222-223*)

- Montelukast, zafirlukast and idalukast are Cys-LT₁ receptor antagonists.
- Zileuton inhibits the production of leukotrienes by inhibiting the enzyme 5-lipoxygenase.

6. Ans. (c) Phosphodiesterase (Ref: *KDT 6/e p220*)

7. Ans. (c) Adenosine receptors (Ref: *KDT 6/e p220*)

8. Ans. (a) Increase in dose is required in cardiopulmonary disease (Ref: *KDT 6/e p220, 221*)

- Theophylline is a methylxanthine derivative. It acts by inhibiting the metabolism of cAMP through inhibition of the enzymes, phosphodiesterase-III and IV. Resulting increase in cAMP is responsible for bronchodilation.

Dose reduction is required in	Dose should be increased in
• Elderly	• Smokers
• Patients with CHF	• Children
• Patients of pneumonia	• Concomitant administration of enzyme inducers like rifampicin and phenobarbitone
• Hepatic insufficiency	
• With enzyme inhibitors like ciprofloxacin, cimetidine and erythromycin	

9. Ans. (d) 5-6 mg/kg (Ref: *KDT 6/e p221*)

Aminophylline is administered in a dose of 5-7 mg/kg slow intravenous infusion. In children, dose required is 7.5 mg/kg.

10. Ans. (d) Hypoglycemia (Ref: *KDT 6/e p127*)

β_2 agonists like salbutamol and terbutaline can cause several adverse effects like:

- Tachycardia due to stimulation of chronotropic β_2 receptors and at high dose due to stimulation of β_1 receptors also.
- Tremors may result due to stimulation of muscle spindles.
- Tolerance may develop due to desensitization of receptors.
- Transient hyperkalemia followed by prolonged hypokalemia is seen on continued use.
- Hyperglycemia may develop due to release of glucagon and stimulation of glycogenolysis and gluconeogenesis.

11. Ans. (b) Bronchial asthma (Ref: KDT 6/e p223)

Leukotrienes are potent bronchoconstricting agents. These agents play a major role in the pathogenesis of bronchial asthma. The drugs acting by inhibiting their synthesis (i.e. lipoxygenase inhibitors) or action (Cys-LT receptor antagonists), are useful in the prophylaxis of bronchial asthma.

12. Ans. (c) Montelukast (Ref: KDT 6/e p222, 223)

- Only bronchodilator drugs are useful for the treatment of acute attack of asthma. Main drugs are:
 - Beta 2 agonists e.g. salbutamol, terbutaline
 - Anticholinergics e.g. ipratropium, tiotropium
 - Methylxanthines e.g. theophylline
- In addition, steroids like hydrocortisone are used for the treatment of status asthmaticus.
- Other drugs used for asthma (like mast cell stabilizers, leukotriene receptor antagonists and lipoxygenase inhibitors) are indicated only for prophylaxis.

13. Ans. (a) Fluticasone; (b) Budesonide (Ref: KDT 6/e p224-225)

Steroids are anti-inflammatory drugs used in asthma.

14. Ans. (a) It inhibit Lipoxygenase pathway; (c) It blocks LT receptor; (e) Given orally (Ref: KDT 6/e p222-223)

- Zafirlukast and montelukast are cysteinyl leukotriene receptor antagonists. They cause modest improvement in lung function and reduction in asthma symptoms and lessen the need for beta-agonist rescue therapy. These drugs can be considered as alternatives to low-dose inhaled corticosteroids in patients with persistent asthma.
- Zafirlukast is long acting and can be given twice to once daily orally. It is a modest bronchodilator that reduces asthma morbidity, provides protection against exercise induced asthma and diminishes nocturnal symptoms.
- These are less effective than corticosteroids.

15. Ans. (a) Ciprofloxacin; (c) Cimetidine; (d) Allopurinol (Ref: KDT 6/e p221)

- **Drugs which inhibit theophylline metabolism and increase its plasma level are:**
 - Erythromycin
 - Ciprofloxacin
 - Cimetidine
 - OCP
 - Allopurinol
- **Agents which induce theophylline metabolism and decrease its plasma level are :**
 - Smoking
 - Phenytoin
 - Rifampicin
 - Phenobarbitone

16. Ans. (d) Sodium cromoglycate (Ref: KDT 6/e p217)**17. Ans. (b) Muscle tremor** (Ref: KDT 6/e p217)**18. Ans. (c) Salbutamol** (Ref: KDT 6/e p217)**19. Ans. (d) None of the above** (Ref: KDT 6/e p220)**20. Ans. (a) Its use in asthma has declined because of narrow safety margin** (Ref: KDT 6/e p221)

- Theophylline has a narrow therapeutic index. Its use has been declined due to narrow safety margin.
- It inhibits the enzyme phosphodiesterase and thus decreases the metabolism of cAMP. It does not increase the formation of cAMP.
- Smoking is a powerful enzyme inducer. Dose of theophylline should be increased in smokers.
- Children metabolize theophylline faster than adults whereas elderly metabolize it slowly. Therefore, half life of theophylline is shorter in children as compared to adults.

21. Ans. (a) Smokers (Ref: KDT 6/e p221)**22. Ans. (a) Theophylline** (Ref: KDT 6/e p220)

- β_2 agonists like salbutamol and terbutaline can be administered by inhalational route.
- Ipratropium and tiotropium are inhalational anticholinergic agents.

- Inhalational steroids include budesonide, fluticasone, beclomethasone and flunisolide.
 - Theophylline is given by oral route and is not used by inhalational route.
23. **Ans. (c) Produce slower response in bronchial asthma** (Ref: KDT 6/e p222)
- Anticholinergic drugs like ipratropium and tiotropium produce slower response in bronchial asthma.
 - Anticholinergic drugs are more effective in COPD than bronchial asthma.
24. **Ans. (b) Oropharyngeal candidiasis** (Ref: KDT 6/e p225)
- Most common adverse effect of inhaled corticosteroids is oropharyngeal candidiasis. Pituitary adrenal suppression is less likely with inhalational route of corticosteroids than with oral route.
25. **Ans. (b) Bronchial asthma** (Ref: KDT 6/e p226)
- Omalizumab is a monoclonal antibody against IgE. It is useful for the management of bronchial asthma.
26. **Ans. (d) Albuterol** (Ref: KDT 6/e p217)
27. **Ans. (d) Formoterol** (Ref: KDT 6/e p218)
- Terbutaline is a fast acting bronchodilator useful for terminating the acute attack of bronchial asthma. Due to short duration of action, it is not suitable for chronic prophylaxis.
 - Bambuterol, salmeterol and formoterol are long acting β_2 agonists useful for chronic prophylaxis.
 - Bambuterol and salmeterol are delayed acting, therefore are not suitable for acute attacks.
 - Formoterol is fast acting also, therefore can be used for the treatment of acute attack of asthma.
28. **Ans. (d) Ipratropium bromide** (Ref: KDT 6/e p222)
- Inhaled β_2 agonists are the agents of choice for termination of acute attack of bronchial asthma. However, as the patient is receiving β -blockers, treatment with β_2 agonists will be ineffective (receptors are already blocked). Therefore, other bronchodilators like anticholinergic agents (ipratropium) or methylxanthines (theophylline) will be useful in such a case.
29. **Ans. (c) Cromolyn sodium** (Ref: KDT 6/e p223)
30. **Ans. (c) Beclomethasone** (Ref: KDT 6/e p217)
31. **Ans. (c) Hypotension** (Ref: KDT 6/e p217)
32. **Ans. (b) Salmeterol** (Ref: KDT 6/e p217)
33. **Ans. (b) Amoxycillin** (Ref: KDT 6/e p221)
34. **Ans. (c) Glucocorticoids** (Ref: KDT 6/e p217)
- COX inhibitors like aspirin, indomethacin, naproxen and phenylbutazone etc. inhibit the formation of PGs from arachidonic acid. This results in diversion of metabolism of arachidonic acid to produce LTs. Large excess of LTs are therefore produced with the use of NSAIDs. These drugs therefore, can result in precipitation of acute attack of asthma (because LTs are bronchoconstrictors).
 - Glucocorticoids are useful in the treatment and prophylaxis of bronchial asthma.
35. **Ans. (c) Anticholinergics** (Ref: KDT 6/e p217)
36. **Ans. (d) Salmeterol** (Ref: KDT 6/e p218)
37. **Ans. (b) Antitussive** (Ref: KDT 6/e p213)
38. **Ans. (a) Inhalation** (Ref: KDT 6/e p223)
39. **Ans. (c) Ciclesonide** (Ref: Katzung 11/e p348)
- Ciclesonide has got high topical: systemic activity ratio.
40. **Ans. (c) Subcutaneous** (Ref: Katzung 11/e p355)
41. **Ans. (a) Dextromethorphan** (Ref: KDT 6/e p215)
42. **Ans. (c) Erythromycin** (Ref: KDT 6/e p221)
43. **Ans. (d) Ciprofloxacin** (Ref: KDT 6/e p221)
44. **Ans. (c) Salmeterol** (Ref: KDT 6/e p218)

45. Ans. (a) Oral candidiasis (Ref: KDT 6/e p225)
46. Ans. (a) Propranolol (Ref: KDT 6/e p217)
47. Ans. (b) Nedocromil sodium (Ref: KDT 6/e p223)
48. Ans. (c) Longer duration of action (Ref: KDT 6/e p218)
49. Ans. (b) Ciprofloxacin decreases theophylline metabolism (Ref: KDT 6/e p221)
50. Ans. (b) Seizures (Ref: KDT 6/e p221)
51. Ans. (d) 5-20 (Ref: KDT 6/e p221)
52. Ans. (d) Tetracyclines (Ref: KDT 6/e p221)

ANSWERS OF RECENT QUESTIONS ASKED BY NATIONAL BOARD

1. Ans (a) Phosphodiesterase inhibition (Ref: KDT 7/e p225, 226)
2. Ans (a) Salmeterol (Ref: KDT 7/e p223)
3. Ans (b) Asthma (Ref: KDT 7/e p231)
4. Ans (b) Corticosteroid (Ref: KDT 7/e p223)
5. Ans. (c) Bronchial asthma (Ref: KDT 7/e p222)
6. Ans. (d) Tremors (Ref: KDT 7/e p223)
7. Ans. (b) Salmeterol (Ref: KDT 7/e p223)
8. Ans. (a) Competitive antagonist of leukotriene receptors (Ref: KDT 7/e p228)
9. Ans. (b) Inhibits Lipoyxygenase (Ref: KDT 7/e p229)
10. Ans. (a) Cromolyn sodium (Ref: KDT 7/e p229)
11. Ans. (c) Steroids (Ref: KDT 7/e p222)
12. Ans. (c) Beta 2 agonists (Ref: KDT 7/e p223)
13. Ans. (b) NSAIDs (Ref: KDT 7/e p195)
14. Ans. (c) Tremors (Ref: KDT 7/e p223)
15. Ans. (b) Inhibits 5-lipoxygenase (Ref: KDT 7/e p229)
16. Ans. (d) Oral candidiasis can occur as a side effect (Ref: KDT 7/e p230)
17. Ans. (c) Cholinesterase inhibitors (Ref: KDT 7/e p222)
18. Ans. (c) Salmeterol inhalation (Ref: KDT 7/e p223)
19. Ans. (c) Nedocromil (Ref: KDT 7/e p229)
20. Ans. (a) Formoterol (Ref: KDT 7/e p223)
21. Ans. (d) Inhibits lymphocytic eosinophilic mucosal inflammation (Ref: KDT 7/e p229-230)
22. Ans. (c) Aspirin induced asthma (Ref: KDT 7/e p228)
23. Ans. (c) Is of benefit in preventing exercise induced bronchial spasm (Ref: KDT 7/e p229)
24. Ans. (b) Oropharyngeal candidiasis (Ref: KDT 7/e p230)
25. Ans. (a) 1-5 μm (Ref: KDT 7/e p232)
26. Ans. (a) 5 lipoxygenase inhibitor (Ref: KDT 7/e p229)

CHAPTER 12

Gastrointestinal Tract

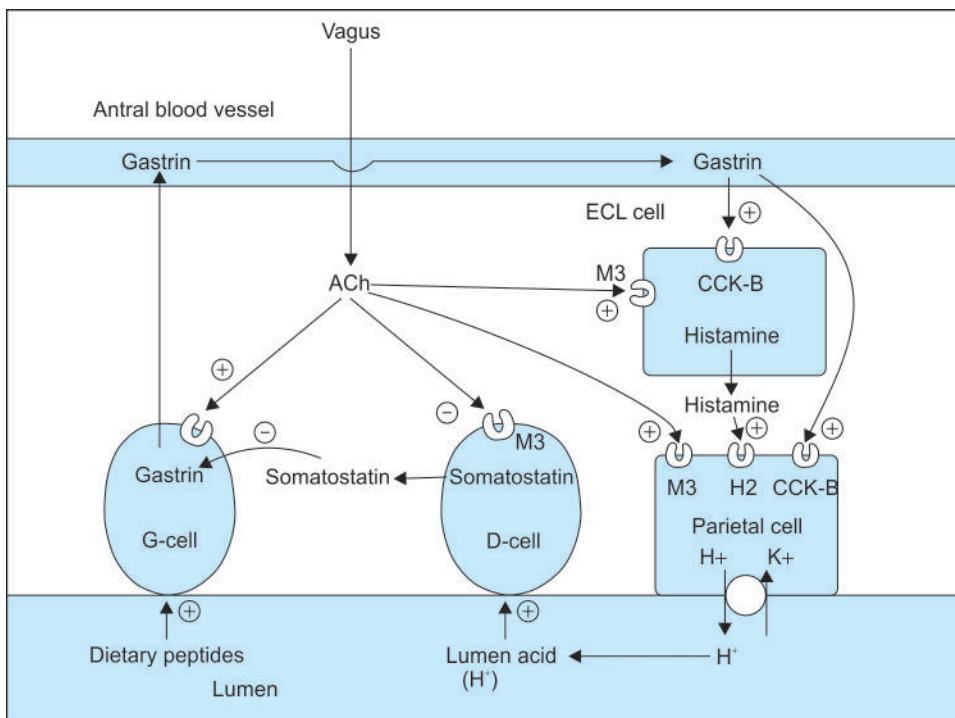
PEPTIC ULCER DISEASE

Peptic ulcer disease arises from the *imbalance between defensive factors* (mucus, bicarbonate and mucosal blood flow) and *aggressive factors* (acid, pepsin, NSAIDs and *Helicobacter pylori*).

Hydrochloric acid is secreted by gastric parietal cells due to stimulation of $H^+ K^+$ ATPase (proton pump). Histamine (through H_2 receptors), acetylcholine (through M_1 and M_3 receptors) and gastrin (through CCK receptors) are important stimulators of proton pump. ACh and gastrin exert their action directly as well as through release of histamine.

Proton pump is stimulated by

- Histamine (H_1 receptors)
- Acetylcholine (M_1 and M_3 receptors)
- Gastrin (CCK receptors)



Antral G-cells produce gastrin on stimulation by dietary peptides. Gastrin mainly stimulates release of histamine from entero-chromaffin like (ECL) cell and weakly stimulates proton pump itself. Parietal cells secrete H^+ in the lumen through $H^+ - K^+ - ATPase$ (proton pump). Vagus nerve (via ACh) help in increasing acid by three mechanisms:

- Direct stimulation of proton pump
- Stimulation of ECL-cells to release histamine
- Direct release of gastrin (by action of G-cells) and inhibition of somatostatin by action on D-cells (later inhibits release of gastrin).

The main strategies employed for the treatment of peptic ulcer disease and gastritis are to:

1. Neutralize gastric acid by *antacids*.
2. Decrease secretion of acid in stomach.
3. Increase protective factors like mucus and bicarbonate.
4. Protect the ulcer by forming a layer over it.
5. Stimulate the healing of ulcer.
6. Kill *H. pylori* associated with peptic ulcer disease.

Major role of antacids in peptic ulcer is to provide prompt relief from ulcer pain.

Al (OH)₃ causes constipation whereas magnesium salts are responsible for diarrhea.

Proton pump inhibitors have short $t_{1/2}$ but can inhibit acid secretion for more than 24 hours due to irreversible inhibition of proton pump.

PPIs are drugs of choice for

- Peptic ulcer disease (PUD) due to any etiology (even NSAID induced).
- Gastroesophageal reflux disease (GERD)
- Zollinger Ellison Syndrome (ZES).

Recent studies have suggested an increase in risk of hip fracture in patients taking PPI on long term.

Antacids

These drugs are weak bases that neutralize gastric acid (do not decrease the volume of acid secreted). Their **major role** in peptic ulcer is to provide **prompt relief from ulcer pain**. Antacids may be systemic (absorbed from the GIT) or local (poorly absorbed). **Sodium bicarbonate** is rapidly acting **systemic antacid**. It is not indicated for long term use because:

- It releases CO₂ that can cause belching and gastric distension (ulcer perforation can occur).
- Sodium chloride formed in the neutralization reaction can be absorbed that can exacerbate fluid retention in patients of CHF and hypertension.
- Systemic and urinary alkalosis may occur.
- Rebound hyperacidity can occur.

- **Aluminium hydroxide** [Al(OH)₃], **magnesium trisilicate**, **megaldrate** and **magnesium hydroxide** [Mg(OH)₂] are **non systemic antacids**. These are slower but longer acting drugs. Rebound acidity does not occur. **Al (OH)₃ causes constipation** whereas **magnesium** salts are responsible for **diarrhea**. Most of the market preparations contain these agents in combination to minimize the impact on bowel movements.
- **Simethicone** is a water repellent, pharmacologically inert **anti-foaming agent**. It reduces flatulence and can also be used to prevent bed sores.
- Antacids decrease the absorption of acidic drugs (acidic drugs are ionized in alkaline medium) and tetracyclines (by forming complexes).
- **Milk alkali syndrome** (*hypercalcemia, renal insufficiency and metabolic alkalosis*) may be caused by excessive doses of Na₂CO₃ or CaCO₃ with calcium containing foods (like milk).

Drugs Decreasing Acid Secretion

PROTON PUMP INHIBITORS (PPIs)

- These are **prodrugs** (active moiety is sulfenamide) and act by **irreversibly inhibiting H⁺ K⁺ ATPase** in gastric parietal cells. The drugs in this group include **omeprazole, pantoprazole, esomeprazole, lansoprazole and rabeprazole**. These drugs are weak bases and can be destroyed by gastric acid. To protect them from gastric acid, these are given as enteric coated tablets. This coating dissolves in alkaline medium (intestinal juice) and prodrugs are absorbed. On reaching parietal cells, active moiety (sulfenamide) is formed and gets trapped. These can *inhibit both basal acid output* (nocturnal acid secretion) as well as *meal stimulated acid output* (maximal acid output).
- PPIs are given orally in early morning empty stomach (just before breakfast). **Pantoprazole, esomeprazole and lansoprazole can be given i.v.** These drugs have short $t_{1/2}$ but can inhibit acid secretion for more than 24 hours (**hit and run drugs**, inhibit proton pump irreversibly).
- **PPIs are the drugs of choice for peptic ulcer disease (PUD) due to any etiology (even NSAID induced).** These are **also** the agents of choice for gastroesophageal reflux disease (**GERD**) and Zollinger Ellison Syndrome (**ZES**). *For prevention of stress induced gastric bleeding, H₂ blockers (i.v. infusion) are preferred over PPIs.* In patients with nasogastric tube, immediate release omeprazole (by nasogastric tube) is currently preferred.
- PPIs are quite safe drugs and have diarrhea, headache and abdominal pain as adverse effects. These have been shown to be **carcinogenic in rodents** but no such case has been reported in humans.

- **Long-term use of PPI is associated with:**
 - Subnormal vitamin B₁₂ levels (reduced absorption)
 - Increase in risk of hip fractures (reduced Ca²⁺ absorption)

Contd...

Contd...

- Increased risk of enteric bacterial infections
 - *C. difficile* infections
 - Bacterial gastroenteritis
- Pneumonia

Note:

- **Lansoprazole is most potent PPI**
- Lansoprazole is safest PPI in **pregnancy**.
- Esomeprazole, lansoprazole and pantoprazole can be given by i.v. route.
- Omeprazole and esomeprazole are microsomal enzyme inhibitors. These may decrease the metabolism of diazepam.
- Lansoprazole enhances the metabolism of theophylline

H₂ RECEPTOR ANTAGONISTS

- These drugs competitively inhibit H₂ receptors in parietal cells, thus inhibiting the acid secretion. ACh and gastrin act partly by causing the release of histamine, therefore acid secreting capacity of these agents also is decreased by H₂ blockers. Drugs in this group are **cimetidine, ranitidine, famotidine, roxatidine, nizatidine and loxatidine**.
- These drugs are *more effective for reducing basal (nocturnal) acid secretion (histamine mediated) than stimulated acid secretion* (stimulated by gastrin, ACh, as well as histamine). These drugs can be used for GERD, PUD, ZES and prevention of stress induced ulcers. **Cimetidine is not used routinely** because:
 - It can cross blood brain barrier and result in **mental state changes**.
 - It inhibits binding of dihydrotestosterone to androgen receptors that can manifest as **impotence** in males.
 - It inhibits metabolism of estradiol and increases serum prolactin levels on long term use, thus can cause gynaecomastia (in males) and galactorrhoea (in females).
 - **It is a potent inhibitor of CYP enzymes** and can increase plasma concentration of warfarin, theophylline and many other drugs.
 - It is the **least potent H₂ blocker**.



Anti-histaminics (H₂ blockers) are more effective for reducing basal (nocturnal) acid secretion (histamine mediated) than stimulated acid secretion (stimulated by gastrin, ACh, as well as histamine).

Note:

- **Famotidine is most potent H₂ blocker.**
- All H₂ blockers except famotidine inhibits the gastric first pass metabolism of ethanol
- **Loxatidine is a non-competitive blocker** of H₂ receptors.
- **Nizatidine also possess anti-AChE activity** and can cause bradycardia and enhanced gastric emptying
- **Nizatidine is having negligible first pass metabolism (~100% bioavailability)**

ANTICHOLINERGICS

- Non-selective anti-muscarinic drugs like propantheline and oxyphenonium can be used for decreasing gastric acid secretion. However, by increasing gastric emptying time, these drugs prolong the exposure of ulcer bed to gastric acid. Further anticholinergic adverse effects like dry mouth, blurred vision, constipation and urinary retention are commonly seen with these drugs. **Pirenzepine and telenzepine are selective M₁ blockers** that are preferred antimuscarinic agents for peptic ulcer disease as these are devoid of anticholinergic adverse effects.

Note:

- Acid suppressing agents (like PPIs, H₂ blockers etc.) can result in tolerance and rebound hyperacidity due to secondary hypergastrinemia.

Drugs Increasing Protective Factors

PGE₁, PGE₂ and PGI₂ act as anti-ulcer drugs by increasing the release of mucus and bicarbonate

Misoprostol (PGE₁ analogue) is the **MOST SPECIFIC** drug for treatment and prevention of NSAID induced peptic ulcer whereas drug of choice is proton pump inhibitor.

Sucralfate should not be given with antacids as it polymerises only in acidic medium.

Bismuth subcitrate is used for peptic ulcer whereas another salt, bismuth subsalicylate is used in Traveller's diarrhea. It reduces stool frequency by inhibiting PG synthesis and chloride secretion apart from having antimicrobial and gastroprotective effects.

7

Triple drug therapy for *H. Pylori*

C–Clarithromycin
A–Amoxicillin
P–Proton pump inhibitor

and by increasing the mucosal blood flow. PGs also inhibit H⁺ K⁺ ATPase and decrease the acid production. **Misoprostol** (PGE₁ analogue) is the **MOST SPECIFIC drug** for treatment and prevention of **NSAID induced peptic ulcer** (*DOC is PPI*). **Enprostil** and **rioprostil** (PGE₂ analogue) are other drugs in this group. Commonest side effect of PG analogues is diarrhea and colicky abdominal pain.

Ulcer Protective Agents

These drugs form a covering over the ulcer bed that prevents its exposure to gastric acid. **Sucralfate** and **colloidal bismuth subcitrate** are two important ulcer protective drugs.

- **Sucralfate:** It is aluminium salt of sulfated sucrose. At pH below 4, its molecules polymerize to form a sticky layer that covers the ulcer base and acts as a physical barrier to prevent acid exposure. It can bind phosphates also and **can result in hypophosphatemia**. It **should not be given with antacids** because it acts only in acidic medium (antacids raise the pH by neutralizing the gastric acid). *Most common side effect of sucralfate is constipation.*
- **Colloidal bismuth subcitrate:** It also forms an acid resistant coating over the ulcer. It **also dislodges *H. pylori*** from the surface of gastric mucosa and kills it. Adverse effects include blackening of tongue and bismuth toxicity (osteodystrophy and encephalopathy).
- **Rebamipide** and **Ecabet** are *cytoprotective drugs* acting by increase in PG generation and by scavenging reactive oxygen species.

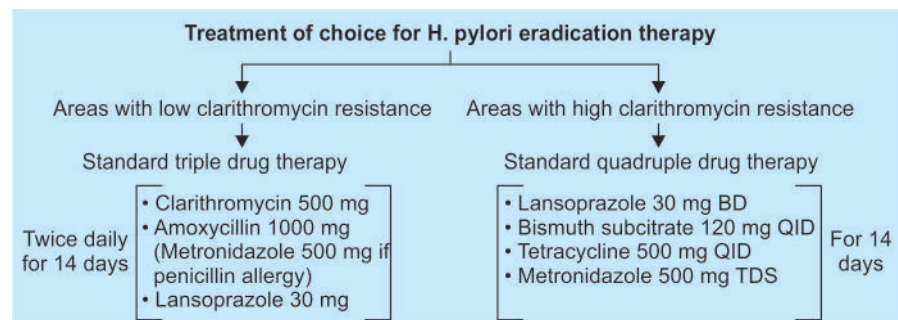
Ulcer Healing Drugs

Carbenoloxone is obtained from the roots of licorice. It causes epithelisation of ulcer without decreasing acid production. It can displace aldosterone from plasma protein binding sites and result in hypertension, sodium and water retention and hypokalemia.

Anti *Helicobacter Pylori* Drugs

H. pylori infection can be detected by “urea breath test”. It is responsible for relapse of PUD. Drugs used for the treatment of *H. pylori* include:

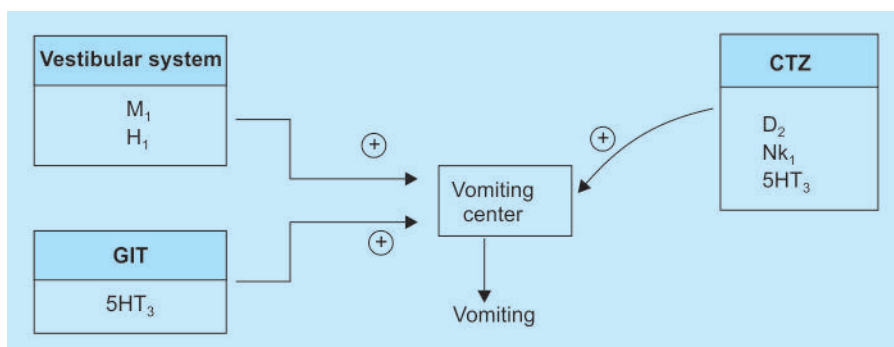
- Metronidazole/tinidazole
- Amoxicillin
- Clarithromycin
- Tetracycline
- Colloidal bismuth subcitrate
- Omeprazole/lansoprazole



ANTI EMETIC DRUGS

Vomiting (emesis) occurs due to stimulation of vomiting centre (VC) in lateral medullary reticular formation. It receives input from GI mucosa, chemoreceptor trigger zone (CTZ) and vestibular apparatus.

- Irritation of GI mucosa by drugs or irritants leads to release of serotonin that stimulates VC via $5HT_3$ receptors.
- CTZ is rich in dopamine (D_2) and serotonin ($5HT_3$) and neurokinin (NK_1) receptor.
- Motion sickness occurs due to stimulation of vestibular apparatus and cerebellum. These structures result in stimulation of VC by activating M_1 and H_1 receptors.
- By stimulation of H_1 receptors, histamine plays a permissive role in all types of vomiting.



Drugs For Motion Sickness

- **Hyoscine** is used as i.m. injection or transdermal patch (applied behind pinna) for **prophylaxis of motion sickness**. It has **no role in treatment**, once the vomiting starts.
- **Antihistaminics** like promethazine, diphenhydramine, cyclizine or meclizine can also be used for prophylaxis.
- **Cinnarizine** (antihistaminic with anticholinergic and antiserotonergic properties) is used for treatment of **vertigo**.

Drugs for Morning Sickness

- Combination of **doxylamine** (antihistaminic) with **pyridoxine** (Vit B₆) in high dose is **safest anti-emetic drug in pregnancy**
- **D₂ blockers** although effective should not be used due to their **teratogenic** potential

Drugs for Chemotherapy and Radiation therapy Induced Vomiting

- **5 HT₃ blockers** like **ondansetron, granisetron, dolasetron, palonosetron and ramosetron** are **DOC** for this condition.
- **Palonosetron** is **most potent** 5 HT₃ blocker. **Dolasetron** may **prolong QT interval**.
- **Palonosetron** has **longest t_{1/2}** whereas **ondansetron** has **shortest t_{1/2}**.
- Efficacy of these drugs increases if used along with antihistaminics, D₂ blockers or dexamethasone.
- These drugs are also effective in *hyperemesis of pregnancy and post operative nausea*.
- D₂ blockers like metoclopramide and domperidone can also be used
- Vomiting due to **cisplatin (most emetogenic anti cancer drug)** can occur *within 24 hours* or it may be **delayed (after 2 days)**. **DOC** for the former condition is **5HT₃ blocker** whereas for the latter condition, **DOC** is **aprepitant** (substance P antagonist). *Palonosetron may also be effective in delayed emesis.*
- **Aprepitant** is a **highly selective NK1 receptor antagonist, orally active**, and enter the

Combination of doxylamine (antihistaminic) with pyridoxine (Vit B₆) in high dose is safest anti-emetic drug in pregnancy

5 HT₃ blockers like ondansetron, granisetron, dolasetron, palonosetron and ramosetron are **DOC** for chemotherapy induced vomiting.

brain. It is *metabolized by CYP3A4 enzymes* and can also inhibit the metabolism of drugs metabolized by this enzyme e.g. warfarin.

- **Fosaprepitant** is an *intravenous prodrug of aprepitant*.
- **Netupitant** is a newer NK1 antagonist approved for chemotherapy induced vomiting (both acute and delayed in combination with palonosetron)

Drugs for Post Operative Vomiting

5 HT₃ antagonists are preferred over other drugs.

Other Drugs for Vomiting

- **Steroids** like dexamethasone can be used as anti-emetic agents in chemotherapy induced vomiting.
- **Benzodiazepines** like lorazepam and alprazolam may be useful for anticipatory component of nausea and vomiting before surgery.
- **Dronabinol (a cannabinoid)** possesses anti-emetic properties and acts by stimulating CB₁ receptors. It can also **stimulate appetite** (*used for AIDS with anorexia*). Central sympathomimetic (tachycardia, palpitations etc.) effects, paranoid reactions and thinking abnormalities may appear as adverse effects.

EMETIC DRUGS

Apomorphine and ipecacuanha can be used to produce vomiting for treatment of poisonings. *Emetics should not be used for kerosene and corrosive (acid and alkali) poisonings.*

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

It is a condition in which acid in the stomach reaches the esophagus and causes mucosal inflammation. *Two strategies for the management of this condition are either to decrease the acid production (by PPIs) or to increase the forward movement of GIT (so that the contents do not reflux upwards).* The drugs used for increasing the GI motility are known as prokinetic drugs. These drugs can also be used for the treatment of gastroparesis, post operative paralytic ileus and constipation.

Prokinetic Drugs

- ACh is the main excitatory neurotransmitter in the GIT. Cholinergic neurons contain excitatory (5-HT₄) as well as inhibitory (5HT₃, D₂) presynaptic receptors.
- Thus D₂ and 5HT₃ antagonists and 5 HT₄ agonists will increase the release of ACh and stimulate the GI motility.

METOCLOPRAMIDE

It possesses *central as well as peripheral D₂ blocking action*. Central D₂ blocking action is responsible for its antiemetic effects.

- It is also a prokinetic drug due to **agonistic action at 5HT₄ receptors** (main mechanism) and **antagonistic action at 5HT₃ receptors**.
- **Prokinetic action** is due to release of ACh and thus *can be antagonized by atropine*. It increases gastric peristalsis (enhances gastric emptying) and LES tone but has no effect on colonic motility.
- Metoclopramide is mainly used as an **antiemetic** agent. It can also be used in **GERD** and for the treatment of **gastroparesis** (in diabetic patients). Another indication of this drug is to **enhance gastric emptying** for emergency general anaesthesia (if the patient has taken food within 4 hrs.)
- D₂ blocking action can result in **extrapyramidal side effects** (muscle dystonia, Parkinsonism etc.) and **hyperprolactinemia** (leading to **galactorrhoea**).

DOMPERIDONE

It is a D_2 receptor antagonist and **cannot cross blood brain barrier**. It is mainly used as an antiemetic (less efficacious than metoclopramide) drug and is devoid of extrapyramidal and hyperprolactinemic adverse effects. *It decreases l-dopa induced vomiting without interfering with its efficacy.*

Domperidone decreases l-dopa induced vomiting without interfering with its efficacy.

5HT₄ AGONISTS

Cisapride, mosapride, renzapride, prucalopride and tegaserod are 5-HT₄ agonistic drugs with no action on D_2 receptors (no antiemetic property). These drugs *increase whole GI motility including colon*.

- **Cisapride** was previously used for the treatment of GERD but it has been withdrawn in some countries due to its **QT prolonging action**. It is metabolized by CYP 3A4 and therefore **should not be administered with** microsomal enzyme inhibitors like **ketoconazole and erythromycin** (increased chances of torsades de pointes, an arrhythmia with QT prolongation). *Mosapride and renzapride do not prolong QT interval. Tegaserod* can be used for constipation dominant irritable bowel syndrome. However, recently it has also been **withdrawn** from India due to increased incidence of myocardial infarction and stroke.

Cisapride has been withdrawn in some countries due to its QT prolonging action whereas Tegaserod has been withdrawn from India due to increased incidence of myocardial infarction and stroke.

OTHER PROKINETIC DRUGS

- *Levosulpiride (l-isomer of sulpiride; an antipsychotic drug) is a newer D_2 blocker having prokinetic activity.*
- *Loxiglumide is a CCK₁ receptor antagonist indicated for constipation dominant IBS.*
- *Macrolides (like erythromycin) are motilin agonists. Erythromycin is indicated in diabetic gastroparesis. Rapid development of tolerance limits this use.*

IRRITABLE BOWEL SYNDROME (IBS)

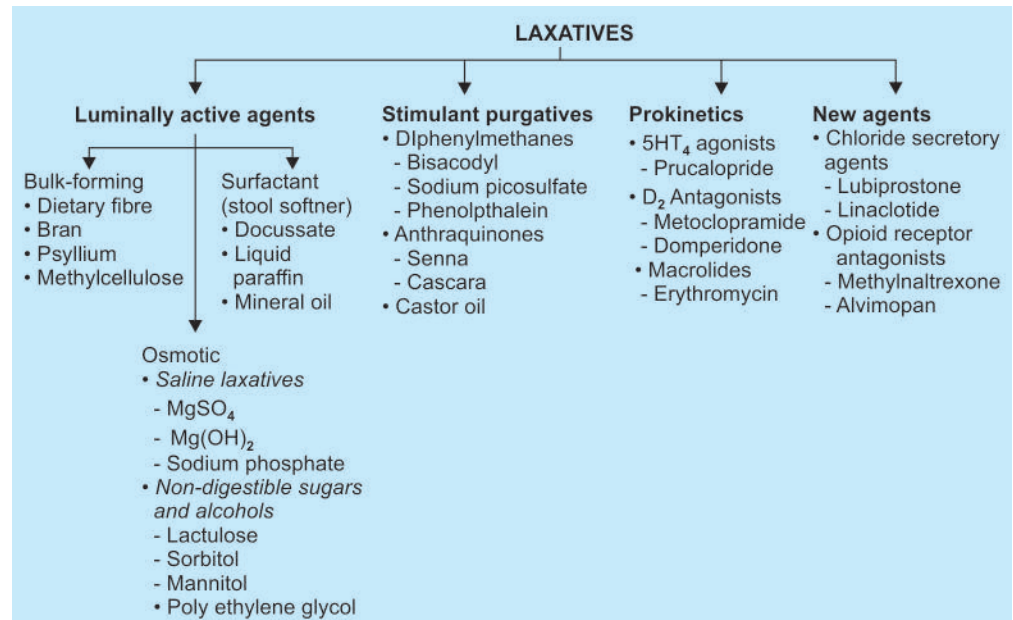
- It is a condition characterized by abdominal pain, bloating and altered bowel habits (diarrhea or constipation)
- **For relieving pain**, the drugs used are **TCAs** (fluoxetine is less effective) and **anticholinergics** like dicyclomine and hyoscine.

Treatment of IBS		
For pain relief	Diarrhea dominant	Constipation dominant
• Tricyclic antidepressants - Imipramine - Desipramine - Nortriptyline	• Opioids - Loperamide - Diphenoxylate	• 5-HT₄ agonist - Tegaserod - Prucalopride
• Anticholinergics - Dicyclomine - Hyoscine	• Kappa agonist - Fedotozine	• Loxiglumide
	• Reserpine analog - Mebeverine	• Chloride channel stimulant - Lubipristone
	• 5HT₃ antagonist - Alosetron	• Guanylate cyclase agonist-Linaclotide
	• Clonidine	

Linaclotide is a guanylate cyclase agonist indicated for oral treatment of idiopathic constipation and IBS with constipation.

CONSTIPATION

High fibre diet, adequate fluid intake and regular exercise are best measures to prevent constipation. Patients not responding to these measures may require laxatives. These can be classified as



Lubiprostone is used for chronic constipation. It acts by

- Stimulating Cl^- channel opening in the intestine,
- Increasing liquid secretion in gut
- Decreasing transit time.

- Bulk-forming agents are contraindicated in presence of megacolon
- Saline purgatives should not be given in chronic renal failure
- Stimulant purgatives are contra-indicated in presence of intestinal obstruction.
- *Chronic use of anthraquinone derivatives (like senna and cascara) may lead to melanosis coli (brown pigmentation of colon)*
- *Phenolphthalein* is not used now due to risk of *potential carcinogenicity*
- *Lubiprostone and Linaclotide*: These stimulate Cl^- channel opening in the intestine, increase liquid secretion in gut and decrease transit time, therefore used for chronic constipation.
- Methylnaltrexone and alvimopan are used for opioid induced constipation.

DIARRHEA

Diarrhea can be treated by antibiotics effective against the causative organism. In non-infective diarrhea, drugs useful are

OPIOIDS

Loperamide is a non-addictive over the counter anti-diarrheal drug. **Diphenoxylate** is another opioid but has addictive potential if used for prolonged periods. It is always given in combination **with atropine to prevent the abuse** (atropine will produce dry mouth and other anticholinergic side effects). These drugs are **contraindicated in infective diarrhea**.

OCTREOTIDE

This long acting **somatostatin analog** can be used to decrease **secretory diarrhea** and other symptoms of carcinoid syndrome and VIPoma. *In low doses (50 µg, s.c.), it stimulates motility, whereas at high doses (100-250 µg, s.c.), it inhibits motility.* In higher doses, it is also useful for the treatment of diarrhea due to vagotomy, short bowel syndrome and AIDS. It can also be used for treatment and prophylaxis of **acute pancreatitis**.

OTHER DRUGS

- **Racecadrotil** is *enkephalinase inhibitor* (inhibits breakdown of enkephalins; endogenous opioids) having antidiarrheal effect.
- **Clonidine** is indicated for diabetics with chronic diarrhea.

Atropine is added to loperamide to decrease its addictive potential.

Crofelemer is a new drug approved for relieving symptoms of diarrhea in AIDS patients taking anti-retroviral therapy. It acts by blocking two chloride channels; CFTR and anoctamin-1.

Oral Rehydration Solution (ORS)

- Hydration must be maintained in all cases of diarrhea to prevent fluid depletion and shock. It is mostly accomplished by the institution of oral rehydration solution.
- It contains sodium and potassium chloride, trisodium citrate and glucose. Glucose helps in the absorption of sodium because *glucose facilitated sodium reabsorption remains intact even in severe diarrhea*. Trisodium citrate is added to prevent acidosis. Previously sodium bicarbonate was used for this function but now sodium citrate is preferred because it imparts a longer shelf life to ORS. Composition of ORS used previously and now is as follows:

	Standard formula ORS	New Formula WHO-ORS
NaCl	3.5 g	2.6 g
KCl	1.5 g	1.5 g
Trisodium citrate	2.9 g	2.9 g
Glucose	20 g	13.5 g
Water	1 L	1 L
Na ⁺	90 mmol/L	75 mmol/L
K ⁺	20 mmol/L	20 mmol/L
Cl ⁻	80 mmol/L	65 mmol/L
Citrate	10 mmol/L	10 mmol/L
Glucose	111 mmol/L	75 mmol/L
Total osmolality	311 mosm/L	245 mosm/L

In new formula WHO-ORS, concentration of NaCl and glucose as well as total osmolality is decreased because

- WHO standard formula was based on cholera stools in which loss of Na⁺ was more. There is a significant decrease in cholera cases and major cause of diarrhea now-a-days is rota virus. New composition ORS is based on stool composition of rota virus patients.
- Use of standard formula ORS has lead to development of edema (excess of sodium) and increased stool frequency (unabsorbed glucose acts as laxative) in some patients.

In new formula WHO-ORS, concentration of NaCl and glucose as well as total osmolality is decreased.

INFLAMMATORY BOWEL DISEASE

Ulcerative colitis and Crohn's disease are two distinct disorders classified under inflammatory bowel disease (IBD).

AMINOSALICYLATES

- 5-aminosalicylic acid (5-ASA)** is the main anti-inflammatory compound that acts locally in the colon. When given alone by oral route, more than 80% is absorbed in proximal intestine and very little reaches the diseased site i.e. colon. To decrease the absorption it may be associated with some inert compound. **Sulfasalazine** (5-ASA + sulfapyridine), **olsalazine** (5-ASA + 5-ASA) and **balsalazide** (5-ASA + amino benzoyl alanine) are effective for the treatment of ulcerative colitis. The inert compound prevents the absorption in proximal GIT and the combination reaches the colon where the bacteria cleaves the azo bond to free 5-ASA for action. Approximately 85% sulfapyridine is absorbed from colon leading to adverse effects.
- Different formulations** (like **time release tablets** and **coating in pH sensitive resins** that dissolve at pH 7) of 5-ASA have been developed to deliver it to colon. These formulations are known as **mesalamine**.
- 5-ASA is the first line treatment for mild to moderate ulcerative colitis.** Efficacy in Crohn's disease has not been established. Absorption of sulfapyridine (in sulfasalazine) lead to nausea, vomiting, GI upset, bone marrow suppression, hypersensitivity and oligospermia. Olsalazine may result in secretory diarrhea.

5-ASA is the first line treatment for mild to moderate ulcerative colitis.

GLUCOCORTICOIDS

- **Prednisone, prednisolone, hydrocortisone and budesonide** are used in the treatment of moderate to severe ulcerative colitis and Crohn's disease.
- Purine analogs
- **Azathioprine and 6-MP** are important agents for the induction and maintenance of remission of ulcerative colitis and Crohn's disease.

METHOTREXATE

- It is used for the induction and maintenance of remission of Crohn's disease but not ulcerative colitis.

ANTI-TNF- α THERAPY

- **Infliximab, adalimumab and certolizumab** are useful in Crohn's disease. Efficacy in ulcerative colitis is doubtful. **Infliximab** is given by **i.v.** route whereas other two are administered s.c. **Certolizumab** is a pegylated anti-TNF- α indicated for Crohn's disease.

**Monoclonal Antibodies for Crohn's Disease**

- Infliximab
- Adalimumab
- Certolizumab
- Natalizumab
- Vedolizumab

ANTI-INTEGRIN THERAPY

- **Natalizumab** is recently approved for moderate to severe Crohn's disease not responding to other therapies. It is targeted against α_4 **subunit of integrins**. The patient on natalizumab therapy should not be on other immunosuppressants due to risk of **progressive multifocal leukoencephalopathy (PML)**.
- **Vedolizumab** is a new anti-integrin that blocks $\alpha_4 \beta_7$ in GIT but not in brain. It is, thus, less likely to cause PML.

DRUG OF CHOICE	
Condition	Drug of choice
• Peptic ulcer	
- Gastric ulcer	Proton pump inhibitors (PPI)
- Duodenal ulcer	PPI
- Stress ulcer	PPI
- NSAID-induced	PPI
- H. pylori associated	Lansoprazole + Amoxicillin + Clarithromycin
- Zollinger Ellison syndrome	PPI
- Gastro Esophageal Reflux Disease	PPI
• Vomiting	
- Chemotherapy induced	5-HT ₃ antagonists like palonosetron
- Levo-dopa induced	Domperidone
- Migraine associated	Metoclopramide
- Drug or disease associated	Metoclopramide
- Post-operative	Ondansetron
- Radiation induced	Ondansetron
- Cisplatin - induced	
* Early	5-HT ₃ antagonists
* Delayed	Aprepitant
- Prophylaxis of motion sickness	Hyoscine
- Pregnancy (Morning sickness)	Doxylamine + Pyridoxine
• Opioid induced constipation	Methyl naltrexone
• Diarrhea in carcinoid syndrome	Octreotide
• To prevent dehydration in diarrhea	ORS
• Crohn's disease	Corticosteroids
• Ulcerative colitis	5-ASA derivatives
• Hepatic encephalopathy	Lactulose

MULTIPLE CHOICE QUESTIONS

PEPTIC ULCER DISEASE

- Despite their short half-lives (2 hrs), proton pump inhibitors (PPIs) cause a prolonged suppression of acid secretion (up to 48 h) because: (AIIMS May 2012)
 - They are prodrugs and undergo activation gradually
 - They exit from the plasma and enter acid secretory canaliculi and stay there, blocking the secretion of acid for a long time
 - They irreversibly inhibit the proton pump molecule and hence, acid secretion requires synthesis of new proton pumps
 - They are available as enteric coated capsules, from which drug is gradually released
- Which of the following proton pump inhibitor has enzyme inhibitory activity? (AI 2010)
 - Rabeprazole
 - Lansoprazole
 - Pantoprazole
 - Omeprazole
- Drug not used in *H. pylori* is: (AIIMS May 2008) (AIIMS Nov., 2006)
 - Metronidazole
 - Omeprazole
 - Mosapride
 - Amoxicillin
- Which of the following drugs is not used for *H. pylori* treatment? (AI 2007)
 - Oxytetracycline
 - Bismuth compounds
 - Amoxicillin
 - Omeprazole
- Which of the following agents is beneficial in NSAID induced gastric ulcer? (AI 2007)
 - PGE₁ agonist
 - PGE₂ agonist
 - PGD₂ agonist
 - PGF_{2α} agonist
- A patient of peptic ulcer was prescribed ranitidine and sucralfate in the morning hours. Why is this combination incorrect? (AI 2004)
 - Ranitidine combines with sucralfate and prevents its action
 - Combination of these two drugs produces serious side effects like agranulocytosis
 - Ranitidine increases the gastric pH so sucralfate is not able to act.
 - Sucralfate inhibits the absorption of ranitidine
- Proton pump inhibitors are most effective when they are given: (AI 2002)
 - After meals
 - Shortly before meals
 - Along with H₂ blockers
 - During prolonged fasting periods
- A patient is taking famotidine, sucralfate and antacid tablets. This treatment is irrational because: (AI 2000)
 - Sucralfate decreases the absorption of famotidine
 - Sucralfate increases the toxicity of famotidine
 - Sucralfate decreases the absorption of antacids
 - Sucralfate polymerizes only when gastric pH is less than 4
- Gynaecomastia can occur as a side effect of:
 - Bromocriptine
 - Cimetidine
 - Famotidine
 - Levodopa
- Choose the CORRECT statement about H₂ receptor blockers:
 - They are the most efficacious drugs in inhibiting gastric acid secretion
 - They cause faster healing of duodenal ulcers
 - They prevent stress ulcers in the stomach
 - They afford the most prompt relief of ulcer pain
- Ranitidine differs from cimetidine in the following respect:
 - It is less potent
 - It is shorter acting
 - It does not have anti-androgenic action
 - It produces more CNS side effects
- The most efficacious drug for inhibiting round the clock gastric acid output is:
 - Omeprazole
 - Cimetidine
 - Pirenzepine
 - Misoprostol
- In peptic ulcer, antacids are now primarily used for:
 - Prompt pain relief
 - Ulcer healing
 - Preventing ulcer relapse
 - Control of bleeding from the ulcer
- The following anti ulcer drug DOES NOT act by reducing the secretion of or neutralizing gastric acid:
 - Megaldrate
 - Sucralfate

- (c) Misoprostol
(d) Omeprazole
15. Choose the CORRECT statement about colloidal bismuth subcitrate:
(a) It causes prolonged neutralization of gastric acid
(b) It has anti *H. pylori* activity
(c) It relieves peptic ulcer pain promptly
(d) All of the above are correct
16. The drugs employed for anti-*H. pylori* therapy include all of the following EXCEPT:
(a) Ciprofloxacin
(b) Clarithromycin
(c) Tinidazole
(d) Amoxicillin
17. The following is true of anti-*H. pylori* therapy EXCEPT:
(a) It is indicated in all patients of peptic ulcer
(b) Resistance to any single antimicrobial drug develops rapidly
(c) Concurrent suppression of gastric acid enhances the efficacy of the regimen
(d) Colloidal bismuth directly inhibits *H. pylori* but has poor patient acceptability
18. Drug of choice for the treatment of peptic ulcer caused due to chronic use of NSAIDs is:
(a) Pirenzepine
(b) Loxatidine
(c) Misoprostol
(d) Esomeprazole
19. Most specific drug for the treatment of peptic ulcer disease due to chronic use of aspirin is:
(a) Omeprazole
(b) Misoprostol
(c) Pirenzepine
(d) Ranitidine
20. M_1 blocker used in peptic ulcer disease is:
(a) Pirenzepine
(b) Pyridostigmine
(c) Atropine
(d) Oxybutynin
21. Choose the antiulcer drug that inhibits gastric acid secretion, stimulates gastric mucus and bicarbonate secretion and has cytoprotective action on gastric mucosa:
(a) Misoprostol
(b) Sucralfate
(c) Carbenoxolone sodium
(d) Colloidal bismuth subcitrate
22. Antacid combinations of magnesium and aluminium salts are superior to single component preparations because:
(a) They have rapid as well as sustained acid neutralizing action
(b) They are less likely to affect gastric emptying
(c) They are less likely to alter bowel movement
(d) All of the above
23. Cimetidine inhibits the metabolism of all of the following drugs EXCEPT: (DPG 1997)
(a) Phenytoin
(b) Warfarin
(c) Ketoconazole
(d) Diazepam
24. Drug used in the treatment of gastric ulcer due to *H. pylori* is: (TN 2006)
(a) Anticholinergics
(b) Carbenoxolone sodium
(c) Bismuth sub citrate
(d) Corticosteroid
25. Which one of the following is not an antacid? (TN 2008)
(a) Magnesium sulfate
(b) Magaldrate
(c) Magnesium carbonate
(d) Magnesium phosphate
26. NSAID induced ulcer are treated by: (RJ 2005)
(a) Antacids
(b) H_2 blockers
(c) Misoprostol
(d) PPI (proton pump inhibitors)
27. Which of the following is not the effect of ranitidine as compared to cimetidine? (MH 2003)
(a) Action on H_2 receptors
(b) Given orally
(c) Used with proton pump blockers
(d) Anti-androgenic action
28. Esomeprazole acts by inhibiting: (MH 2005)
(a) H^+K^+ ATPase pump
(b) H^+Na^+ ATPase pump
(c) H^+ pump
(d) Any of the above
29. Anti-peptic ulcer drug that can be given in patients with chronic renal failure (CRF) (MH 2005)
(a) Aluminium Hydroxide
(b) Magnesium Hydroxide
(c) Sucralfate
(d) None
30. Antacid drug that typically causes diarrhea? (MH 2007)
(a) Sodium bicarbonate
(b) Magnesium hydroxide
(c) Calcium bicarbonate
(d) Aluminium hydroxide
31. The inhibition of hydrochloric acid (HCl) secretion by omeprazole occurs within an hour, reaches a peak at 2 hours, and plateaus by 4th day. After how many days will the secretion gradually normalize: (MH 2008)
(a) < 24 hours
(b) 1-2 days

- (c) 3-5 days
- (d) 6-10 days

32. All are H_2 blocker except: (Jharkhand 2003, 2004)
- (a) Omeprazole
 - (b) Cimetidine
 - (c) Famotidine
 - (d) Ranitidine
33. The following appears to affect the integrity of the adherent gel of sucralfate interfering with its action: (TN 1991) (AP 2001)
- (a) Antacids
 - (b) Food
 - (c) Mucin
 - (d) Proteins in foodstuffs
34. A patient presents with Zollinger-Ellison syndrome due to gastrinoma. He has two bleeding ulcers and diarrhoea. A drug that irreversibly inhibits the H^+/K^+ ATPase in gastric parietal cells is: (Karnataka 2007)
- (a) Cimetidine
 - (b) Cisapride
 - (c) Glycopyrrolate
 - (d) Omeprazole
- ANTI-EMETICS AND GERD**
35. Which of the following is an antagonist of a peptide and is used to reduce chemotherapy induced nausea and vomiting?
- (a) Atrial natriuretic peptide
 - (b) Aprepitant
 - (c) Bradykinin
 - (d) Enalapril
36. Drug given for metoclopramide induced dystonic reaction is: (MPPG 2002)
- (a) Pheniramine
 - (b) Promethazine
 - (c) Chlorpromazine
 - (d) Prochlorperazine
37. Regarding aprepitant all are true except: (AI 2011)
- (a) Agonist at NK_1 receptors
 - (b) Crosses Blood Brain Barrier
 - (c) Ameliorate nausea and vomiting induced by chemotherapy
 - (d) Metabolized by CYP450 enzymes
38. An anti-emetic drug that also decreases acid secretion due to its action on H_1 receptors is: (AI 2010)
- (a) Promethazine
 - (b) Domperidone
 - (c) Metoclopramide
 - (d) Ondansetron
39. Metoclopramide (DPG 2009)
- (a) Inhibit cholinergic smooth muscle stimulation in the gastrointestinal tract
 - (b) Decrease lower esophageal sphincter pressure
 - (c) Stimulate D_2 receptor
 - (d) Enhance colonic motility
40. Drug implicated in prolonging QT interval is: (AI 2004) (RJ 2007)
- (a) Domperidone
 - (b) Metoclopramide
 - (c) Cisapride
 - (d) Omeprazole
41. For chemotherapy induced vomiting, $5HT_3$ antagonist having maximum potency is: (AIIMS Nov., 2007)
- (a) Ondansetron
 - (b) Granisetron
 - (c) Dolasetron
 - (d) Palonosetron
42. Which of the following drugs is not an antiemetic? (AIIMS May, 2007)
- (a) Ondansetron
 - (b) Domperidone
 - (c) Metoclopramide
 - (d) Cinnarizine
43. Anti emetic action is produced through: (PGI Dec. 2002)
- (a) Decreased CTZ stimulation
 - (b) H_1 agonistic action
 - (c) D_1 antagonistic action
 - (d) Olfactory apparatus stimulation
 - (e) $5HT_4$ agonistic action
44. Ondansetron acts by: (PGI June, 2002)
- (a) Acting on CTZ
 - (b) $5-HT_3$ antagonism
 - (c) D_1 and D_2 receptor antagonism
 - (d) Increasing GIT motility
 - (e) Blocking cholinergic receptors
45. In case of hill journey, antimotion sickness drugs are best administered at:
- (a) Twelve hours before commencing journey
 - (b) One hour before commencing journey
 - (c) Immediately after commencing journey
 - (d) At the first feeling of motion sickness
46. Metoclopramide has the following actions EXCEPT:
- (a) Increase lower esophageal sphincter tone
 - (b) Prokinetic action is blocked by atropine
 - (c) Increase gastric peristalsis
 - (d) Increase large intestinal peristalsis
47. Which of the following prokinetic drugs produces extrapyramidal side effects?
- (a) Metoclopramide
 - (b) Cisapride
 - (c) Domperidone
 - (d) All of the above
48. Which antiemetic drug selectively blocks levodopa induced vomiting without blocking its anti-Parkinsonian action?
- (a) Metoclopramide
 - (b) Cisapride
 - (c) Domperidone
 - (d) Ondansetron

49. The most effective antiemetic for controlling cisplatin induced vomiting is:

- (a) Prochlorperazine
- (b) Ondansetron
- (c) Metoclopramide
- (d) Aprepitant

50. Activation of the following type of receptors present on myenteric neurons by metoclopramide is primarily responsible for the enhanced acetylcholine release and improving gastric motility:

- (a) Muscarinic M_1
- (b) Serotonergic $5-HT_3$
- (c) Serotonergic $5-HT_4$
- (d) Dopaminergic D_2

51. Which of the following prokinetic drugs has been implicated in causing serious ventricular arrhythmias, particularly in patients concurrently receiving erythromycin or ketoconazole?

- (a) Domperidone
- (b) Cisapride
- (c) Mosapride
- (d) Metoclopramide

52. Indicate the drug which does not improve lower esophageal sphincter tone or prevent gastroesophageal reflux, but is used as the first line treatment of gastroesophageal reflux disease:

- (a) Sodium alginate + aluminium hydroxide gel
- (b) Omeprazole
- (c) Mosapride
- (d) Metoclopramide

53. A patient on cisplatin therapy develops intractable vomiting on the third day of treatment. Agent of choice for controlling this vomiting is:

- (a) Aprepitant
- (b) Ondansetron
- (c) Metoclopramide
- (d) Prochlorperazine

54. Ondansetron acts by inhibiting which of the following receptors?

- (a) $5-HT_1$ (RJ 2006, 2005)
- (b) $5-HT_2$ (TN 2002, Jhankhand 2004, 2005)
- (c) $5-HT_3$
- (d) $5-HT_4$

55. Drug stimulating $5HT_4$ receptors to act as prokinetic agents are all of the following Except:

- (a) Renzapride (MH 2006)
- (b) Metoclopramide
- (c) Domperidone
- (d) Cisapride

56. Which of the following drugs is not used for motion sickness:

- (a) Metoclopramide (Kolkata 2007)
- (b) Cyclizine
- (c) Cinnarizine
- (d) Scopolamine

■ DIARRHEA, CONSTIPATION, IBS

57. Drug used in irritable bowel syndrome with constipation is: (AI 2012)

- (a) Lubiprostone
- (b) Loperamide
- (c) Alosetron
- (d) Clonidine

58. Which of the following statements about octreotide is true? (AIIMS Nov. 2011)

- (a) Stimulates growth hormone
- (b) Used in secretory diarrhea
- (c) Used orally
- (d) Contraindicated in acromegaly

59. Which of the following agents are useful in medical treatment of variceal bleeding? (AI 2011)

- (a) Octreotide
- (b) Pantoprazole
- (c) Somatotropin
- (d) Dexamethasone

60. Which of the following laxatives lowers blood ammonia level in hepatic encephalopathy?

- (a) Bisacodyl
- (b) Liquid paraffin
- (c) Lactulose
- (d) Magnesium sulfate

61. Stimulant purgatives are contraindicated in the following:

- (a) Bed ridden patients
- (b) Before abdominal radiography
- (c) Subacute intestinal obstruction
- (d) All of these

62. The success of oral rehydration therapy of diarrhea depends upon which of the following processes in the intestinal mucosa?

- (a) Sodium pump mediated Na^+ absorption
- (b) Glucose coupled Na^+ absorption
- (c) Bicarbonate coupled Na^+ absorption
- (d) Passive Na^+ diffusion secondary to nutrient absorption

63. The concentration of sodium ions in the standard WHO oral rehydration solution is:

- (a) 40 m moles/L
- (b) 60 m moles/L
- (c) 90 m moles/L
- (d) 110 m moles/L

64. The new formula WHO-ORS differs from the older standard formula WHO-ORS in the following respect:

- (a) It has lower Na^+ and glucose concentration
- (b) It has higher K^+ concentration
- (c) It has no basic salt
- (d) Both (b) and (c) are correct

65. Which of the following statements is true about new formula WHO-ORS?
- It has Na^+ ion concentration of 75 mM/L
 - Its glucose concentration is 75 mM/L
 - Its total osmolarity is 245 mOsm/L
 - All of the above
66. Apart from diarrhea, oral rehydration solution has been employed in:
- Severe vomiting
 - Burn cases
 - Heat stroke
 - Both (b) and (c)
67. The therapeutic effect of sulfasalazine in ulcerative colitis is exerted by:
- Inhibitory action of the unabsorbed drug on the abnormal colonic flora
 - Breakdown of the drug in colon to release 5-aminosalicylic acid which suppresses inflammation locally
 - Release of sulfapyridine having antibacterial property
 - Systemic immunomodulatory action of the drug
68. The preferred drug for controlling an acute exacerbation of ulcerative colitis is:
- Prednisolone
 - Sulfasalazine
 - Mesalazine
 - Vancomycin
69. A small amount of atropine is added to diphenoxylate in order to:
- Suppress associated vomiting of gastroenteritis
 - Augment the anti-motility action of diphenoxylate
 - Block side effects of diphenoxylate
 - Discourage overdose and abuse of diphenoxylate
70. Choose the correct statement about the use of opioid anti-motility drugs in the management of diarrhea:
- They are used to control diarrhea irrespective of its etiology
 - They should be used only as a short term measure after ensuring that enteroinvasive organisms are not involved
 - They are used as adjuvant to antimicrobial therapy of diarrhea
 - They are the drug of choice in irritable bowel syndrome diarrhea
71. Aryan, a 14-year-old boy presented with chronic diarrhea and weight loss. History reveals that he has repeated attacks of respiratory tract infections with *Pseudomonas aeruginosa*. His younger brother died from a severe respiratory infection at the age of 7. Which of the following agents is most likely to improve this patient's condition?
- Octreotide
 - Pancreatic lipase
 - Metronidazole
 - Loperamide
72. A 46-year-old male presents to OPD with diarrhea and abdominal pain. On investigations, it was found to be non-infective and you proceed with diphenoxylate therapy in this patient. Which of the following is the primary target for the drug you prescribed to this patient?
- Secretion
 - Digestion
 - Inflammation
 - Motility
73. Bisacodyl is: (UP 2007)
- Bulk forming
 - Stool softner
 - Stimulant purgative
 - Osmotic purgative
74. Sulfa drug used in inflammatory bowel disease includes: (TN 2008)
- Sulfasalazine
 - Sulfamethoxazole
 - Sulfinpyrazone
 - Sulphadoxine
75. Best for treatment of irritable bowel syndrome with spastic colon is: (MH 2000)
- Liquid paraffin
 - Senna
 - Bisacodyl
 - Dietary fibers
76. Diarrhea (loose stools) is side effect of: (MH 2006)
- Omeprazole
 - Sucralfate
 - Metoclopramide
 - Misoprostol
77. Not true about the composition of ORS: (Kolkata 2005)
- NaCl -3.5g
 - KCl -1.5g
 - Bicarbonate -2g
 - Glucose -20g
78. Which one of the drugs is useful in treating Crohn's disease? (Karnataka 2006)
- Infliximab
 - Azathioprine
 - Tacrolimus
 - Cyclosporine
79. Drug useful in hepatic encephalopathy is: (DPG 2005)
- Magnesium sulphate
 - Lactulose
 - Bisacodyl
 - Biphosphonates

RECENT QUESTIONS ASKED BY NATIONAL BOARD

1. Which of the following stool softeners does not interfere with fat absorption?
 - (a) Docussates
 - (b) Phenolphthalein
 - (c) Liquid paraffin
 - (d) Castor oil
2. All of the following are true about ondansetron except:
 - (a) Drug of choice for chemotherapy induced vomiting
 - (b) Dopamine antagonist
 - (c) 5HT₃ antagonist
 - (d) Used to prevent relapse in alcohol dependence
3. Which of the following is the most potent 5HT₃ antagonist?
 - (a) Ondansetron
 - (b) Granisetron
 - (c) Dolasetron
 - (d) Palonosetron
4. Which drug is given in delayed vomiting after chemotherapy:
 - (a) Metoclopramide
 - (b) Hyoscine
 - (c) Domperidone
 - (d) Aprepitant
5. Antiemetic used in vomiting induced by anticancer drugs is:
 - (a) Ondansetron
 - (b) Cisapride
 - (c) Metoclopramide
 - (d) Trifluopromazine
6. Which is not an adverse effect of cimetidine?
 - (a) Impotence
 - (b) Gynaecomastia
 - (c) Atrophic gastritis
 - (d) Galactorrhea
7. Which of the following is not used in Crohn's disease?
 - (a) Infliximab
 - (b) Adalimumab
 - (c) Ustekinumab
 - (d) Natalizumab
8. Drug used in cancer chemotherapy induced vomiting is?
 - (a) Aprepitant
 - (b) Dexamethasone
 - (c) Ondansetron
 - (d) All of the above
9. Which laxative acts by opening of chloride channels?
 - (a) Docusate
 - (b) Anthraquinone
 - (c) Lubiprostone
 - (d) Bisacodyl
10. Primary role of antacids in peptic ulcer is:
 - (a) Pain relief
 - (b) Ulcer healing
 - (c) H Pylori eradication
 - (d) All of the above
11. Drug not used in the treatment of H.pylori is:
 - (a) Cisapride
 - (b) Clarithromycin
 - (c) Metronidazole
 - (d) Omeprazole
12. Which one of the following drugs increases gastrointestinal motility?
 - (a) Glycopyrrolate
 - (b) Atropine
 - (c) Neostigmine
 - (d) Fentanyl
13. All of the following are true for metoclopramide except:
 - (a) Chemically related to procainamide
 - (b) Speeds gastric emptying
 - (c) Stimulates chemoreceptor trigger zone
 - (d) Blocks D₂ receptors
14. Which of the following purgative increases the fecal bulk due to their water absorbing and retaining capacity:
 - (a) Methyl cellulose
 - (b) Lactulose
 - (c) Liquid paraffin
 - (d) Dioctyl sodium sulfosuccinate
15. A vitamin that is reducing agent, a property that may explain its function is:
 - (a) Nicotinamide
 - (b) Thiamine
 - (c) Vitamin B₁₂
 - (d) Vitamin C
16. Which of the following 5-HT receptors play an important role in causing emesis?
 - (a) 5HT₁
 - (b) 5HT_{2A/2C}
 - (c) 5HT₃
 - (d) 5HT₄
17. A prokinetic drug which lacks D₂ receptor antagonistic action is which one of the following:
 - (a) Metoclopramide
 - (b) Domperidone
 - (c) Cisapride
 - (d) Chlorpromazine
18. All of the following antibiotics have been used in treatment of H.pylori infection, except:
 - (a) Clarithromycin
 - (b) Amoxicillin
 - (c) Metronidazole
 - (d) Ciprofloxacin

19. All of the following statements about treatment of diarrhea are correct except:
 - (a) Opioids delay passage of gut contents by reducing peristalsis
 - (b) Loperamide is an opioid with anti motility action
 - (c) Anti motility drugs are best drugs for infective diarrhea
 - (d) Diphenoxylate overdose can cause respiratory depression
20. Which group of drugs is most effective for the healing of Non steroidal Anti Inflammatory Drug (NSAID) induced gastric ulcer:
 - (a) Prostaglandin analogues
 - (b) H_2 -receptor antagonists
 - (c) Proton pump inhibitors
 - (d) Antacids
21. All of the following are effective against cytotoxic drug induced emesis except:
 - (a) Dronabinol
 - (b) Hyoscine
 - (c) Metoclopramide
 - (d) Ondansetron
22. Effective ulcer treatment that works by inhibitory action on gastric acid secretion is:
 - (a) Lactulose
 - (b) Aluminium hydroxide
 - (c) Sucralfate
 - (d) Ranitidine
23. Sulfasalazine is used in:
 - (a) Ulcerative colitis
 - (b) Osteoarthritis
 - (c) Gouty arthritis
 - (d) Irritable bowel syndrome
24. Which of the following is the drug of choice for treatment of peptic ulcer disease?
 - (a) Omeprazole
 - (b) Pirenzepine
 - (c) Ranitidine
 - (d) Sucralfate
25. On chronic use which of the following drugs may cause reversible gynaecomastia?
 - (a) Cimetidine
 - (b) Omeprazole
 - (c) Pirenzepine
 - (d) Sucralfate
26. A 30 years old pregnant woman has a history of rheumatoid arthritis which has been managed successfully with NSAIDs. However, she has recently visited her general practitioner complaining of burning epigastric pain worsened by food intake. Which of the following ulcer medication is most likely contraindicated in this patient:
 - (a) Famotidine
 - (b) Omeprazole
 - (c) Misoprostol
 - (d) Ranitidine
27. Omeprazole act by inhibiting:
 - (a) $Na^+H^+ATPase$
 - (b) $Na^+K^+ATPase$
 - (c) Calcium channels
 - (d) $H^+K^+ATPase$
28. Glucose is added in ORS to:
 - (a) Improve taste
 - (b) Decrease bacterial colonization of GIT
 - (c) Increase the stability
 - (d) Increase the absorption of sodium

EXPLANATIONS

1. **Ans. (c) They irreversibly inhibit the proton pump molecule and hence, acid secretion requires synthesis of new proton pumps** (Ref: Rang and Dale 5/e p370-371, Goodman Gilman 12/e p1311-1312)

- Proton pump inhibitors (PPIs) are prodrugs that require activation in an acid environment.
- After absorption into the systemic circulation, the prodrug diffuses into the parietal cells of the stomach and accumulates in the acidic secretory canaliculi. Here, it is activated by proton-catalyzed formation of a tetracyclic sulfenamide, trapping the drug so that it cannot diffuse back across the canalicular membrane. This preferential accumulation in areas of very low pH, such as occur uniquely in the secretory canaliculi of gastric parietal cells, means that PPI have a specific effect on these cells.
- The activated form then binds covalently with sulfhydryl groups of cysteines in the H^+ , K^+ -ATPase, irreversibly inactivating the pump molecule. Acid secretion resumes only after new pump molecules are synthesized and inserted into the luminal membrane, providing a prolonged (up to 24- to 48-hour) suppression of acid secretion, despite the much shorter plasma half-lives (0.5-2 hours) of the parent compounds.
- Because they block the final step in acid production, the proton pump inhibitors are effective in acid suppression regardless of other stimulating factors.
- To prevent degradation of proton pump inhibitors by acid in the gastric lumen, oral dosage forms are supplied in enteric coated formulations. The enteric-coated tablets dissolve only at alkaline pH.
- Esomeprazole, pantoprazole and lansoprazole are approved for intravenous administration.
- Because an acidic pH in the parietal cell acid canaliculi is required for drug activation and food stimulates acid production, these drugs ideally should be given ~30 minutes before meals.
- Because not all pumps or all parietal cells are active simultaneously, maximal suppression of acid secretion requires several doses of the proton pump inhibitors. For example, it may take 2-5 days of therapy with once-daily dosing to achieve the 70% inhibition of proton pumps that is seen at steady state.

2. **Ans. (d) Omeprazole** (Ref: Katzung 11/e p1075)

- Omeprazole and esomeprazole are microsomal enzyme inhibitors. These may decrease the metabolism of diazepam.
- Lansoprazole enhances the metabolism of theophylline.

3. **Ans. (c) Mosapride** (Ref: KDT 6/e p645-646)

Mosapride is a 5-HT₄ agonist used for GERD. Other drugs given in the options are used for H. pylori.

4. **Ans. (a) Oxytetracycline** (Ref: KDT 6/e p637)

5. **Ans. (a) PGE₁ agonist** (Ref: KDT 6/e p634)

Misoprostol is a PGE₁ analog useful in peptic ulcer disease.

6. **Ans. (c) Ranitidine increases the gastric pH so sucralfate is not able to act** (Ref: KDT 6/e p636)

Sucralfate is an ulcer protective agent. It forms a coating over the ulcer base after polymerization. Sucralfate polymerizes only at acidic pH (<4). Ranitidine is an H₂ blocker that reduces the gastric acid secretion. If both of these drugs are combined, action of sucralfate will be abolished due to rise in pH by ranitidine.

7. **Ans. (b) Shortly before meals** (Ref: KDT 6/e p632)

Proton pump inhibitors are used just before meals. Food stimulates the secretion of gastric acid that will be reduced by PPIs if these are given just before meals.

8. **Ans. (d) Sucralfate polymerizes only when gastric pH is less than 4** (Ref: KDT 6/e p636)

9. **Ans. (b) Cimetidine** (Ref: KDT 6/e p629)

10. **Ans. (c) They prevent stress ulcers in the stomach** (Ref: KDT 6/e p631)

- H₂ receptor blockers like ranitidine are used to prevent stress ulcers.
- Most effective agents for inhibiting acid secretion and treatment of gastric as well as duodenal ulcers are PPIs.
- Antacids afford most prompt relief of ulcer pain.

11. Ans. (c) It does not have anti-androgenic action (Ref: KDT 6/e p629)

Cimetidine is rarely used now because:

- It is the least potent H_2 blocker
- It is a short acting agent
- It is a potent inhibitor of microsomal enzymes
- It can cause gynaecomastia
- It produces more CNS adverse effects

12. Ans. (a) Omeprazole (Ref: KDT 6/e p35)

13. Ans. (a) Prompt pain relief (Ref: KDT 6/e p636)

14. Ans. (b) Sucralfate (Ref: KDT 6/e p636)

- Megaldrate is an antacid. It acts by neutralizing the gastric acid.
- Omeprazole and misoprostol decrease the secretion of gastric acid.
- Sucralfate is an ulcer protective agent. It forms the protective coating over the ulcer base.

15. Ans. (b) It has anti-*H. pylori* activity (Ref: KDT 6/e p636, 637)

Colloidal bismuth subcitrate forms an acid resistant protective coating over the ulcer base. It also dislodges *H. pylori* from the surface of gastric mucosa.

16. Ans. (a) Ciprofloxacin (Ref: KDT 6/e p637)

17. Ans. (a) It is indicated in all patients of peptic ulcer (Ref: KDT 6/e p637, 638)

- Triple drug therapy for *H. pylori* is indicated in those patients in whom infection is detected by urea breath test. Since *H. pylori* becomes less virulent in the absence of acid, combination with PPI is more effective.
- Because resistance can develop to single agents, these are used in combination.
- Colloidal bismuth subcitrate dislodges *H. pylori* but produces metallic taste and blackening of tongue.

18. Ans. (d) Esomeprazole (Ref: KDT 6/e p632)

- Proton pump inhibitors are the drugs of choice for peptic ulcer disease due to any etiology.
- Misoprostol is the MOST SPECIFIC drug for the treatment of PUD due to chronic NSAID use because it is a PGE_1 analog.

19. Ans. (b) Misoprostol (Ref: KDT 6/e p633, 634)

20. Ans. (a) Pirenzepine (Ref: KDT 6/e p633)

21. Ans. (a) Misoprostol (Ref: KDT 6/e p633, 634)

22. Ans. (d) All of the above (Ref: KDT 6/e p635)

- $Mg(OH)_2$ has a quick onset whereas $Al(OH)_3$ acts for a long time.
- Magnesium salts cause osmotic diarrhea whereas aluminium salts cause constipation. Combination of these two agents minimizes the impact on bowel movements.

23. Ans. (c) Ketoconazole (Ref: KDT 6/e p630)

Cimetidine is a potent inhibitor of microsomal enzymes. It prolongs the half lives of warfarin, theophylline, phenytoin, oral hypoglycemic agents, alcohol and benzodiazepines.

24. Ans. (c) Bismuth sub citrate (Ref: KDT 6/e p636)

25. Ans. (a) Magnesium sulfate (Ref: KDT 6/e p635)

26. Ans. (d) PPI (Ref: KDT 6/e p632)

27. Ans. (d) Anti-androgenic action (Ref: KDT 6/e p629)

28. Ans. (a) H^+K^+ ATPase pump (Ref: KDT 6/e p631)

29. Ans. (c) Sucralfate (Ref: KDT 6/e p635-636)

30. Ans. (b) Magnesium hydroxide (Ref: KDT 6/e p635)

31. Ans. (c) 3-5 days (Ref: KDT 6/e p632)

32. Ans. (a) Omeprazole (Ref: KDT 6/e p628)

33. Ans. (a) Antacids (Ref: KDT 6/e p636)

34. Ans. (d) Omeprazole (Ref: KDT 6/e p631)

35. Ans. (b) Aprepitant (Ref: Goodman & Gilman 11/e p1005)

This drug is an antagonist of substance P. It is particularly useful in delayed phase of chemotherapy induced vomiting.

36. Ans. (b) Promethazine (Ref: KDT 6/e p157)

- "Acute muscle dystonia caused by antiemetic-antipsychotic drugs is promptly relieved by parenteral promethazine or hydroxyzine." This is based on central anti-cholinergic action of the drugs.
- Promethazine is a first generation anti-histaminic which has maximum penetration of blood brain barrier and maximum anticholinergic activity.

37. Ans. (a) Agonist at NK₁ receptors (Ref: Katzung, 11/e p1086, Goodman and Gilman, 11/e p650)

- Aprepitant is a highly selective NK₁ receptor antagonists, orally active, and enter the brain.
- It is used in treating and preventing chemotherapy-induced emesis.
- It is metabolized by CYP3A4 enzymes and can also inhibit the metabolism of drugs metabolized by this enzyme e.g. warfarin.

38. Ans. (a) Promethazine (Ref: Katzung 11/e p277)

- Promethazine is a first generation H₁-antihistaminic drug. It is indicated for treatment of allergic reactions. Because of its anticholinergic action and ability to cross blood brain barrier, it can be used as an antiemetic (particularly for prophylaxis of motion sickness) and as an anti-Parkinsonian drug (particularly in drug induced Parkinsonism).
- Acid secretion is reduced mainly by H₂-blocking drugs like ranitidine but even H₁-anti histaminics can also reduce acid secretion at high doses (due to lack of selectivity at such high dose).

39. Ans. (d) Enhances colonic motility (Ref: Katzung 10/e p1021; KDT 6/e p643)

- Metoclopramide is a D₂ receptor antagonist that increases cholinergic activity by inhibiting pre-synaptic D₂ receptors in GIT (D₂ receptor stimulation inhibits the release of ACh).
- It increase LES tone that is also responsible for anti-emetic action.
- It does not significantly increase colonic motility.
- But out of the four options, this is the best answer, because although not significantly but it can increase colonic motility, whereas other options are definitely wrong.

40. Ans. (c) Cisapride (Ref: KDT 6/e p645)

Cisapride is a 5HT₄ agonist that is useful as a prokinetic agent. At high plasma concentration, it can block cardiac K⁺ channels leading to polymorphic ventricular tachycardia (torsades de pointes). It is manifested in the ECG as QT prolongation. Therefore, cisapride should not be combined with microsomal enzyme inhibitors like erythromycin and ketoconazole. Other important drugs causing QT prolongation are

- Terfenadine
- Astemizole
- Ziprasidone

41. Ans. (d) Palonosetron (Ref: Katzung 10/e p1027)

42. Ans. (d) Cinnarizine (Ref: KDT, 6/e p641-642)

- Cinnarizine is an anti-vertigo drug.
- Metoclopramide and domperidone are antiemetic drugs. These act by blocking D₂ receptors.
- Ondansetron is an antagonist of 5 HT₃ receptors. It is the drug of choice for chemotherapy induced vomiting.

43. Ans. (a) Decreased CTZ stimulation; (e) 5-HT₄ agonistic action (Ref: KDT 6/e p643)

The mechanisms of actions of antiemetic drugs are:

- Anticholinergic (Inhibit muscarinic M₁ receptors) e.g. hyoscine.
- H₁ antihistaminics e.g. promethazine, diphenhydramine, cyclizine.
- 5-HT₃ antagonists e.g. ondansetron, Granisetron.

- Adjuvant antiemetics, e.g. Dexamethasone, benzodiazepines, cannabinoids.
- Prokinetics:
 - 5HT₄ agonists, e.g. cisapride
 - Motilin agonist, e.g. erythromycin
 - Somatostatin analogues, e.g. octreotide
- CTZ (chemoreceptor trigger zone) contains histamine (H₁), dopamine (D₃), cholinergic (M), opioid (μ) and serotonin (5-HT₃) receptors. Antiemetic acts by inhibiting the receptors at CTZ.

44. Ans. (a) Acting on CTZ ; (b) 5-HT₃ antagonism (Ref: KDT 6/e p646)

- Ondansetron blocks the depolarizing action of **serotonin through 5-HT₃ receptors** on vagal afferents in the gut as well as in NTS and CTZ.
- **It do not block dopamine receptors (D₁ and D₂) or ACh receptors.**

45. Ans. (b) One hour before commencing journey (Ref: KDT 6/e p641)

Hyoscine is administered half to one hour before journey for prevention of motion sickness. It has no role once the vomiting starts.

46. Ans. (d) Increase large intestine peristalsis (Ref: KDT 6/e p643)

- Metoclopramide is a prokinetic and anti-emetic drug. It acts by blocking D₂ and 5 HT₃ receptors and stimulating 5-HT₄ receptors. D₂ receptors are normally inhibitory to the release of ACh. Metoclopramide enhances ACh release by blocking these inhibitory D₂ receptors. Due to increased release of ACh, there is increase in gastric motility and LES tone. Prokinetic action can thus be blocked by atropine.
- Metoclopramide has no effect on colonic motility.

47. Ans. (a) Metoclopramide (Ref: KDT 6/e p643, 644)

- Metoclopramide and domperidone act by blocking D₂ receptors.
- Metoclopramide can cross BBB whereas domperidone cannot.
- Therefore, metoclopramide can produce extra-pyramidal adverse effects while domperidone is devoid of it.
- Cisapride acts as 5HT₄ agonist. It can cause torsades de pointes.

48. Ans. (c) Domperidone (Ref: KDT 6/e p645)

- Levo-dopa induced vomiting is due to stimulation of D₂ receptors in CTZ whereas its antiparkinsonian action is due to agonistic action on D₂ receptors in the nigrostriatal pathway.
- Both metoclopramide and domperidone inhibit D₂ receptors in CTZ and thus counteract vomiting induced by l-dopa.
- Metoclopramide also crosses BBB and thus abolishes the therapeutic action of l-dopa by inhibiting central D₂ receptors.
- Domperidone cannot cross BBB, thus does not interfere with antiparkinsonian action of l-dopa.
- Cisapride (5HT₄ agonist) and ondansetron (5HT₃ antagonist) do not affect dopaminergic pathway.

49. Ans. (b) Ondansetron (Ref: KDT 6/e p646)

5HT₃ antagonists like ondansetron, granisetron and topisetron are the agents of choice for chemotherapy induced vomiting.

50. Ans. (c) Serotonergic 5-HT₄ (Ref: KDT 6/e p646, 647)

Gastric motility is increased by ACh. Release of this neurotransmitter is enhanced by 5HT₄ receptor stimulation and 5 HT₃ and D₂ receptor antagonism.

51. Ans. (b) Cisapride (Ref: KDT 6/e p645)

- Cisapride is a 5HT₄ agonist that can block cardiac K⁺ channels at high concentration. When these are administered with microsomal enzyme inhibitors (like erythromycin or ketoconazole), polymorphic ventricular tachycardia can result.
- Mosapride and tegaserod are other 5HT₄ agonists that are devoid of arrhythmogenic action.

52. Ans. (b) Omeprazole (Ref: KDT 6/e p648)

Treatment of GERD can be accomplished by

- Increasing GI motility with prokinetic drugs (like metoclopramide and mosapride) or
- By decreasing gastric acid secretion with PPIs like omeprazole.

53. Ans. (a) Aprepitant (Ref: Katzung 10/e p1027, 1028)

Cisplatin induced vomiting has two phases.

1. **EarlyPhase:** It occurs within first 24 hours. 5 HT₃ antagonists like ondansetron are the agents of choice for this condition.
2. **Delayed Phase:** Vomiting occurring after 24 hours is less responsive to ondansetron and other drugs. It is best controlled by substance P antagonist like aprepitant.

54. Ans. (c) 5HT₃ (Ref: KDT 6/e p646)

55. Ans. (c) Domperidone (Ref: KDT 6/e p645)

56. Ans. (a) Metoclopramide (Ref: KDT 6/e p641-642)

57. Ans. (a) Lubiprostone (Ref: Katzung 11/e p1080)

Lubiprostone acts by stimulating Cl⁻ channel opening in the intestine, increasing liquid secretion in gut and decreasing transit time, therefore used for chronic constipation. It has also been approved for constipation dominant irritable bowel syndrome in women.

58. Ans (b) Used in secretory diarrhea (Ref: Katzung 11/e p1081)

59. Ans. (a) Octreotide (Ref: Harrison's Principles of Medicine 17/e p1977)

Management of Variceal Bleeding

A. Prevention of re-bleeding

- Non selective beta blockers (e.g. propranolol)
- Variceal band ligation

B. Management of acute bleed

- Stabilize with fluids and blood
- Octreotide
- Vasopressin (Not preferred now)
- Balloon tamponade:
 - i. Sengstaken-Blackmore
 - ii. Minnesota Tube
- Variceal ligation
- Variceal sclerotherapy

60. Ans. (c) Lactulose (Ref: KDT 6/e p655)

Lactulose is degraded to lactic acid that converts NH₃ to NH₄⁺. As ionic molecules cannot cross biological membranes, it is not absorbed and is thus excreted.

61. Ans. (c) Subacute intestinal obstruction (Ref: KDT 6/e p655, 656)

Stimulant (or irritant) purgatives are contra-indicated in pregnancy and intestinal obstruction (both subacute as well as chronic).

62. Ans. (b) Glucose coupled Na⁺ absorption (Ref: KDT 6/e p657)

63. Ans. (c) 90 mmoles/L (Ref: KDT 6/e p658, 659)

Concentration of Na⁺ is 90 mmol/L in standard WHO-ORS whereas it is 75 mmol/L in New formula ORS.

64. Ans. (a) It has lower Na⁺ and glucose concentration (Ref: KDT 6/e p659)

- New formula ORS contains less Na⁺ and glucose than standard formula ORS.
- Total osmolality is decreased to 245 mmol/L in New formula WHO ORS.

65. Ans. (d) All of the above (Ref: KDT 6/e p659)

66. Ans. (d) Both (b) and (c) (Ref: KDT 6/e p659)

Non-diarrheal uses of ORS include:

- Maintenance of hydration in postsurgical, postburn and post-trauma patients
- Heat stroke
- During changeover from total parenteral nutrition to enteral nutrition.

67. Ans. (b) Breakdown of the drug in colon to release 5-ASA which suppresses inflammation locally (Ref: KDT 6/e p661, 662)

68. Ans. (a) Prednisolone (Ref: KDT 6th, 663)

Corticosteroids are the mainstay of treatment of acute exacerbation of ulcerative colitis.

Review of Pharmacology

69. **Ans. (d) Discourage overdose and abuse of diphenoxylate** (Ref: KDT 6/e p664)
For explanation, refer to text
70. **Ans. (b) They should be used only as a short-term measure after ensuring that enteroinvasive organisms are not involved** (Ref: KDT 6/e p663, 664)
71. **Ans. (b) Pancreatic lipase** (Ref: Katzung 11/e p1093)
In a young male, a history of recurrent respiratory infections with *P. aeruginosa*, chronic diarrhea, weight loss, and death of a sibling due to respiratory infection suggests a diagnosis of cystic fibrosis (CF). Chronic diarrhea and weight loss in patients with CF are typically caused by malabsorption secondary to pancreatic insufficiency and can be corrected by pancreatic enzyme supplementation.
72. **Ans. (d) Motility** (Ref: Katzung 11/e p1080-1081)
Diphenoxylate is an opioid; it binds to mu receptors in the GIT and slows motility.
73. **Ans. (c) Stimulant purgative** (Ref: KDT 6/e p653)
74. **Ans. (a) Sulfasalazine** (Ref: KDT 6/e p661)
75. **Ans. (d) Dietary fibers** (Ref: KDT 6/e p655)
76. **Ans. (d) Misoprostol** (Ref: KDT 6/e p634)
77. **Ans. (c) Bicarbonate -2 g** (Ref: KDT 6/e p659)
78. **Ans. (a) Infliximab** (Ref: KDT 6/e p663)
79. **Ans. (b) Lactulose**
- Lactulose is a laxative that acts by conversion to short chain fatty acids in the colon.
 - These fatty acids result in decrease in pH of intestinal juice.
 - At low pH, ammonia becomes ionized (NH_4^+) and thus cannot be absorbed.

ANSWERS OF RECENT QUESTIONS ASKED BY NATIONAL BOARD

- Ans. (a) Docussates** (Ref: KDT 7/e p673-674)
 - Phenolphthalein and castor oil are stimulant purgatives whereas docussates (DOSS) and liquid paraffin are stool softeners. Liquid paraffin may cause deficiency of fat soluble vitamins.
- Ans. (b) Dopamine antagonist** (Ref: KDT 7/e p668)
- Ans. (d) Palonosetron** (Ref: KDT 7/e p669)
- Ans. (d) Aprepitant** (Ref: KDT 7/e p669)
- Ans. (a) Ondansetron** (Ref: KDT 6/e p646)
- Ans. (d) Galactorrhea** (Ref: KDT 7/e p650)
- Ans. (c) Ustekinumab** (Ref: CMDT 2014 p620)
 - Ustekinumab is a monoclonal antibody used in psoriasis
 - Natalizumab can be used in multiple sclerosis and Crohn's disease.
- Ans. (d) All of the above** (Ref: KDT 7/e p876)
 - Ondansetron is drug of choice for chemotherapy induced vomiting
 - Dexamethasone, lorazepam and aprepitant are also used for chemotherapy induced vomiting.
- Ans. (c) Lubiprostone** (Ref: KDT 7/e p674)
- Ans. (a) Pain relief** (Ref: KDT 7/e p656)
- Ans. (a) Cisapride** (Ref: KDT 7/e p657)
- Ans. (c) Neostigmine** (Ref: KDT 7/e p103)
- Ans. (c) Stimulates chemoreceptor trigger zone** (Ref: KDT 7/e p664-665)
- Ans. (a) Methyl cellulose** (Ref: KDT 7/e p672)
- Ans. (d) Vitamin C** (Ref: KDT 7/e p916)
- Ans. (c) 5HT₃** (Ref: KDT 7/e p172)

17. Ans. (c) **Cisapride** (Ref: KDT 7/e p667)
18. Ans. (d) **Ciprofloxacin** (Ref: KDT 7/e p657-658)
19. Ans. (c) **Anti motility drugs are best drugs for infective diarrhea** (Ref: KDT 7/e p686)
20. Ans. (c) **Proton pump inhibitors** (Ref: KDT 7/e p652)
21. Ans. (b) **Hyoscine** (Ref: KDT 7/e p670, 668, 666)
22. Ans. (d) **Ranitidine** (Ref: KDT 7/e p649)
23. Ans. (a) **Ulcerative colitis** (Ref: KDT 7/e p683)
24. Ans. (a) **Omeprazole** (Ref: KDT 7/e p652)
25. Ans. (a) **Cimetidine** (Ref: KDT 7/e p650)
26. Ans. (c) **Misoprostol** (Ref: KDT 7/e p654)
27. Ans. (d) **H⁺ – K⁺ ATPase** (Ref: KDT 7/e p651)
28. Ans. (d) **Increase the absorption of sodium** (Ref: KDT 7/e p678)

NOTES

Gastrointestinal Tract

Chemotherapy A: General Considerations and Non-specific Antimicrobial Agents

Antibiotics are the substances produced by microorganisms, which suppress the growth of or kill other microorganisms at very low concentrations.

GENERAL CONSIDERATIONS

Drug Resistance

Drug resistance in bacteria may be natural or acquired. Development of acquired resistance may be due to **single step mutation** (as seen with *streptomycin* and *rifampicin*) or **multi step mutation** (*erythromycin*, *tetracycline* and *chloramphenicol*).

Drug resistance can be transferred from one microorganism to other by gene transfer (also called infectious resistance) via conjugation, transduction or transformation.

- **Conjugation:** It is due to the physical contact between bacteria and is responsible for multidrug resistance. This is a very important mechanism for the development of resistance against *chloramphenicol* and *streptomycin*.
- **Transduction:** It is the transfer of resistance gene through bacteriophage e.g. *penicillin*, *erythromycin* and *chloramphenicol*.
- **Transformation:** It is the transfer of resistance gene through environment and is not significant clinically e.g. *penicillin G*.

Resistance once acquired becomes prevalent due to *selection pressure* of a widely used antimicrobial agent i.e. antimicrobials allow resistant organisms to grow preferentially.

MECHANISM OF RESISTANCE

Microorganism may develop resistance due to

- **Decreased affinity for the target** e.g. pneumococci and staphylococci may develop altered penicillin binding proteins.
- Development of **alternative metabolic pathway** e.g. sulfonamide resistant organisms start utilizing preformed folic acid in place of synthesizing it from PABA.
- Elaboration of the **enzymes which inactivate the drug** e.g. β -lactamases (penicillins and cephalosporins), chloramphenicol acetyl transferase (chloramphenicol) and aminoglycoside inactivating enzymes (aminoglycosides).
- **Decreased drug permeability** due to the loss of specific channels e.g. *aminoglycosides* and *tetracyclines* attain much lower drug concentration in the resistant organisms than in the sensitive organisms.
- Development of **efflux pumps** (*tetracyclines*, *erythromycin* and *fluoroquinolones*) results in active extrusion of the drug from the resistant microorganisms.

Superinfection

It refers to the appearance of a new infection as a result of antimicrobial therapy. Normal microbial flora contributes to host defense by development of bacteriocins. Pathogens also have to compete with the normal flora for nutrients. **Broad spectrum antibiotics** (*tetracyclines*, *chloramphenicol*, *clindamycin*, *aminoglycosides* and *ampicillin*) may kill the normal flora and result in the development of new infection. Superinfection is more commonly seen in



Transfer of antimicrobial drug resistance

Conjugation

- Multiple drug resistance

Transduction

- Staph. aureus

Transformation

- Pneumococci
- Neisseria



Drug resistance by inactivating enzymes

A – Aminoglycosides

B – Beta lactams

C – Chloramphenicol

immunocompromised patients. Oropharynx, intestine, respiratory and genitourinary tracts are common sites for the development of new infection. The organisms frequently involved are *Candida albicans*, *Clostridium difficile*, staphylococci, proteus and pseudomonas. *Clostridium difficile* superinfection may result in **pseudomembranous colitis** (most commonly due to third generation cephalosporins) for which **metronidazole is the drug of choice** (alternative drug is *vancomycin*). Further, due to the loss of commensal flora, there may be decreased formation of vitamin K leading to enhanced anticoagulant effects of warfarin.

Concentration Dependent Killing (CDK) and Time Dependent Killing (TDK)

- **CDK** means that killing effect of a drug is high when ratio of peak concentration to MIC is more. This type of killing behaviour is exhibited by **aminoglycosides and fluoroquinolones**. These drugs produce better action when **used as a large single dose** as compared to same daily dose divided into 2-3 portions.
- **TDK** means antimicrobial action depends on the length of time the concentration remains above the MIC. This is exhibited by **β -lactams and macrolides**. For these drugs **multiple daily doses** are preferred over single dose.
- **Post antibiotic effect (PAE)**: After exposure of an organism to the antibiotic, its growth stops. When it is placed in the antibiotic free medium, the growth resumes but only after a lag period. This signifies that inhibitory effect of antibiotics is present even when their concentration is below MIC. This period is known as PAE. *Most of the antimicrobials have long PAE (≥ 1.5 hours) against gram positive bacteria.* **Carbapenems and drug affecting protein synthesis** (aminoglycosides, chloramphenicol, tetracyclines) or **DNA synthesis** (Quinolones, rifampicin) have **long PAE against gram -ve bacteria also**. *Rifampicin prolongs the PAE of isoniazid.* Due to this reason isoniazid can be given thrice weekly when given in combination with rifampicin in short course chemotherapy of tuberculosis (it needs to be administered daily if used alone).

Combined Use of Antibiotics

Though every combination is unique but the general guidelines are that:

- Two bacteriostatic agents often show *additive effect*.
- Two bactericidal agents are *additive if the organism is sensitive to both* e.g. isoniazid and rifampicin in tuberculosis.
- Combination of a bactericidal with a bacteriostatic drug is *additive if the organism has low sensitivity to the cidal drug* e.g. streptomycin + tetracycline for brucellosis.
- Combination of bactericidal with bacteriostatic agent is *antagonistic if the organism has high sensitivity to cidal drug* e.g. penicillin + tetracycline (or chloramphenicol) for pneumococci.

Factors Affecting the Choice of an Antimicrobial Agent

1. AGE

- *Chloramphenicol* in new born may cause *grey baby syndrome*.
- *Sulfonamides* in new born may cause *kernicterus*.
- Half life of aminoglycosides is prolonged in the elderly.
- *Tetracyclines* are contra-indicated in children below 6 years because it accumulates in the developing *teeth and bone*.

2. PREGNANCY

All antibiotics pose risk to the fetus when used in pregnancy. *Penicillins, most cephalosporins and macrolides (PCM) appear safe.*

3. IMPAIRED HOST DEFENSES

Bactericidal drugs are must in immunocompromised patients.

Pseudomembranous Colitis

- Most common organism implicated: *Clostridium difficile*.
- Most common antimicrobial implicated: Third generation cephalosporins > Clindamycin
- Treatment of choice: Metronidazole
- Treatment of choice for severe cases: Vancomycin

Drugs having

- **CDK**
 - Aminoglycosides
 - Fluoroquinolones
- **TDK**
 - Beta lactams
 - Vancomycin
- **Prolonged PAE against gram -ve bacteria**
 - Carbapenems
 - Tetracyclines
 - Chloramphenicol
 - Aminoglycosides
 - Fluoroquinolones
 - Rifampicin

4. RENAL FUNCTION

Drugs contra indicated in renal disease	Dose reduction required in renal failure
Cephalothin	Aminoglycosides
Cephaloridine	Amphotericin B
Nitrofurantoin	Vancomycin
Nalidixic acid	Ethambutol
Tetracyclines (except doxycycline)	

Note: Penicillins and rifampicin do not require dose adjustment in renal disease.

5. LIVER FUNCTION

Drugs contra-indicated in liver disease	Dose reduction required in liver failure
Erythromycin estolate	Chloramphenicol
Tetracyclines	Isoniazid
Pyrazinamide	Rifampicin
Pefloxacin	Clindamycin

Antimicrobials secreted in bile

- **Penicillins**
 - Ampicillin
 - Nafcillin
- **Cephalosporins**
 - Ceftriaxone
 - Cefoperazone
- Doxycycline
- Rifampicin
- Erythromycin

6. GENETICS FACTORS

Antimicrobials producing **hemolysis in glucose-6-phosphate dehydrogenase (G-6PD) deficient patients** are *primaquine, chloroquine, quinine, chloramphenicol, nitrofurantoin, fluoroquinolones, dapsone and sulfonamides* etc.

CLASSIFICATION OF ANTIMICROBIAL AGENTS

Antimicrobials can be classified according to several characteristics:

Based On the Mechanism of Action

A. DRUGS INHIBITING CELL WALL SYNTHESIS

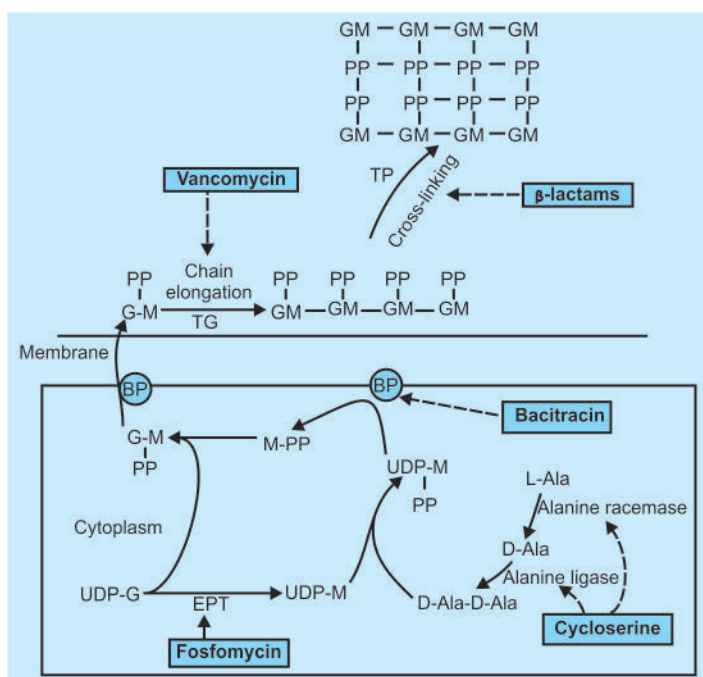


Fig. 13.1: Biosynthesis of bacterial cell wall

EPT - Enolpyruvate transferase;
PP - Pentapeptide;
BP - Bactoprenol;
G - N-Acetylglucosamine;
M - N-Acetylmuramic acid;
TG - Transglycosylase;
TP - Transpeptidase.

Bacterial cell wall is composed of peptidoglycan that contains N-acetylmuramic acid and N-acetylglucosamine. It also contains a pentapeptide unit which is attached to N-acetylmuramic acid. Cell wall synthesis starts by conversion of UDP-N-acetylglucosamine (UDP-G) to UDP-N-acetylmuramic acid (UDP-M) in the presence of enzyme **enolpyruvate transferase**. UDP-M then acquires the pentapeptide. **Alanine racemase and alanine-alanine ligase helps in the formation of pentapeptide unit**. UDP is then removed from UDP-M-pentapeptide by bactoprenol (membrane lipid carrier) and N-acetylglucosamine is added to it (which is carried by UDP-G). These all reactions occur in the cytoplasm. The resulting molecule formed is **transported across the plasma membrane by bactoprenol**. **Elongation** of the peptidoglycan chain occurs with the help of enzyme **transglycosylase**. Strength to peptidoglycan chain is provided by **cross linking** of elongated chains with the help of **transpeptidase**.

Various antibiotics can act by inhibiting one of these steps in cell wall synthesis as shown in Table 13.1 below. All of these are **bactericidal drugs**.

Table 13.1: Mechanism of action of cell wall synthesis inhibiting antimicrobial drugs

	Drug	Step in cell wall synthesis inhibited
Firmly	Fosfomycin	Enolpyruvate transferase
Bind to	Beta lactam antibiotics	Transpeptidase
Bacterial	Bacitracin	Dephosphorylation of bactoprenol
Cell	Cycloserine	Alanine racemase and alanine ligase
Wall	Vancomycin	Transglycosylase

B. DRUGS INHIBITING TRANSLATION (PROTEIN SYNTHESIS)

Protein synthesis in the bacteria is accomplished with the use of 70S ribosome, mRNA and tRNA. 70S ribosome consists of two subunits 30S and 50S. Latter (50S subunit) contains two sites; *A site (acceptor)* and *P site (peptidyl)*. Nascent (already formed) peptide chain is attached to P site. Next amino acid is transported to the A site by tRNA having complementary base pairs (anticodons). Peptide bond forms between the peptide chain and the newly attached amino acid with the help of enzyme *peptidyl transferase*. The nascent peptide chain is thus shifted from P site to A site. For further elongation of the peptide chain, A site must be free because the next amino acid attaches to A site only. This is carried out by *translocation* of the peptide chain from A site to P site. Ribosome moves forward along the mRNA to expose the next codon. All of these steps keep on repeating till there is a termination codon on the mRNA (at this point protein synthesis stops). *All drugs inhibiting protein synthesis are bacteriostatic except aminoglycosides and streptogramins.*

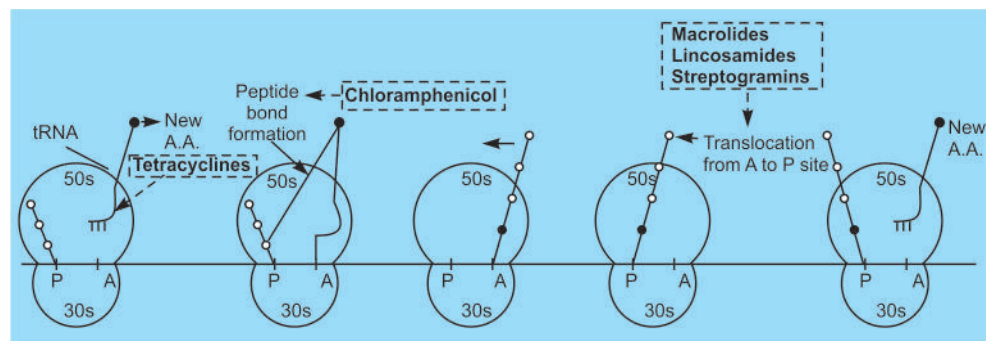


Fig. 13.2: Steps of protein synthesis and the mechanism of action of drugs

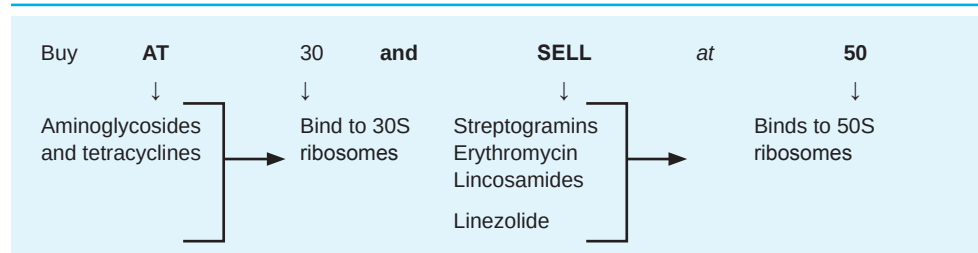
Table 13.2: Mechanism of action of protein synthesis inhibiting antimicrobial drugs

Drugs	Binds to	Mechanism of action
1. Aminoglycosides	Several sites at 30 S and 50 S subunits as well as to their interface	- Freezing of initiation - Interference with polysome formation - Misreading of mRNA code

contd...

contd...

	Drugs	Binds to	Mechanism of action
2.	Tetracyclines and Glycylcyclines	30S ribosome	*Inhibit aminoacyl-tRNA attachment to A Site *Inhibit aminoacyl-tRNA attachment to A Site
3.	Chloramphenicol	50S ribosome	*Inhibits peptidyl transferase that results in the inhibition of peptide bond formation and transfer of peptide chain from P to A site
4.	Macrolides Lincosamides Streptogramins	50S ribosome	*Inhibit translocation of peptide chain from A site to P site
5.	Linezolid	23S fraction of 50S ribosome	• Inhibits initiation

Mnemonics

Puromycin resembles 3'-end of aminoacyl-tRNA. It enters the A-site and transfers to growing chain (forming covalent bond) and causes premature chain termination. It inhibits protein synthesis in both prokaryotes as well as eukaryotes.

C. DRUGS AFFECTING CELL MEMBRANE

These drugs act by causing disruption of cell membrane and leakage of ions and molecules from the cell. The drugs include

- **Polypeptide antibiotics:** *Polymyxin B, colistin and tyrothricin* (bacitracin is also a polypeptide but acts by inhibiting cell wall synthesis)
- **Polyene antibiotics:** *Amphotericin B, nystatin, hamycin, natamycin*
- **Azoles:** *Ketoconazole, fluconazole, itraconazole*

D. DRUGS AFFECTING NUCLEIC ACIDS (DNA AND RNA)

These drugs include:

- **DNA gyrase inhibitors:** DNA replication occurs on the straight strands of DNA and in this process positive supercoils are introduced. DNA gyrase *nicks* the double stranded DNA, *introduces negative supercoils* and then *reseals* the nicked ends. This prevents excessive supercoiling. In gram positive bacteria, same function is carried out by a similar enzyme topoisomerase IV. The drugs inhibiting DNA gyrase or topoisomerase are *quinolones (nalidixic acid and fluoroquinolones)* and *novobiocin*.
- **RNA polymerase inhibitors:** *Rifampicin* inhibits transcription by inhibiting DNA dependent RNA polymerase.
- **Drugs destroying DNA:** *Metronidazole* generates reactive nitro radicals (in anaerobic conditions) that results in DNA helix destabilization and strand breakage. *Nitrofurantoin* is also considered to be acting by the destruction of DNA.
- **Nucleotide/Nucleoside analogues:** Drugs that are structurally similar to nucleosides (nitrogen base plus sugar) or nucleotides (nitrogen base plus sugar plus phosphate) gets incorporated in the DNA or RNA. This results in the formation of faulty nucleic acids that may be non-functional or unstable (degrade easily). *Idoxuridine, acyclovir, NRTI* etc are analogues of nucleosides/nucleotides.

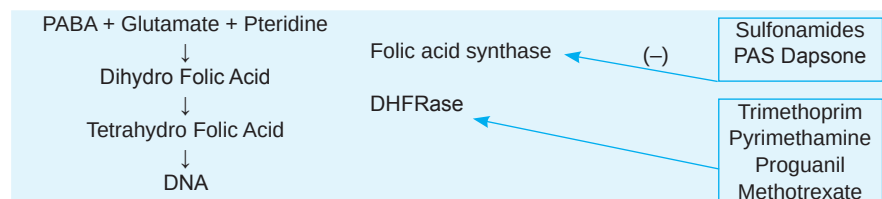
E. DRUGS AFFECTING INTERMEDIARY METABOLISM

Most important metabolic step amenable to inhibition by the drugs is folic acid synthesis.

- **Drugs inhibiting folic acid synthesis:** Folic acid synthase (dihydropteroate synthase) results in the formation of folic acid by incorporation of PABA. *Sulfonamides, dapsone*

and paraaminosalicylic acid (PAS) are structural analogues of paraaminobenzoic acid (PABA). These drugs act as competitive inhibitors of folic acid synthase.

- **Dihydrofolate reductase (DHFRase) inhibitors:** DHFRase is the enzyme responsible for conversion of dihydrofolic acid to tetrahydrofolic acid. Latter is the active form required for the transfer of one carbon units. Drugs inhibiting this enzyme are trimethoprim, pyrimethamine, proguanil and methotrexate.



- **Arabinogalactan synthesis inhibitors:** Ethambutol inhibits arabinogalactan synthesis and thus incorporation of mycolic acid in the cell wall of mycobacteria.

Based on the Type of Action

According to this classification, drugs may be bacteriostatic or bactericidal (see Table 13.3). Minimum bactericidal concentration (MBC) of an antibiotic is the concentration which **kills** 99.9% of the bacteria whereas minimum inhibitory concentration (MIC) of the antibiotic is the concentration which **prevents visible growth** of bacteria in culture plates using serial dilutions. A small difference between MIC and MBC indicates that the antibiotic is primarily bactericidal, whereas a large difference indicates bacteriostatic action. In immunocompromised patients (patients with HIV, on steroid therapy, neutropenic etc.), only bactericidal drugs should be used.

Table 13.3: Classification of antibiotics according to the type of action

Bacteriostatic	Bactericidal
Protein synthesis inhibitors • Tetracyclines • Tigecycline • Chloramphenicol • Macrolides • Lincosamides • Linezolid	Protein synthesis inhibitors • Aminoglycosides • Streptogramins
Drugs affecting DNA • Nitrofurantoin • Novobiocin	Drugs affecting DNA • Quinolones • Metronidazole
Drugs affecting metabolism • Sulfonamides • Dapsone • PAS • Trimethoprim • Ethambutol	Polypeptide antibiotics • Polymixin B • Colistin • Amphotericin B
	Cell wall synthesis inhibitors • Fosfomycin • Cycloserine • Bacitracin • Vancomycin • Penicillins • Cephalosporins
	First line ATT drugs (except Ethambutol) • Rifampicin • Isoniazid • Pyrazinamide • Streptomycin (aminoglycoside)

Based on the Therapeutic Index (TI)

High TI	Low TI	Very low TI
Penicillins	Chloramphenicol	Polymyxin B
Cephalosporins	Aminoglycosides	Vancomycin
Macrolides	Tetracyclines	Amphotericin B

DRUGS INHIBITING CELL WALL SYNTHESIS**Beta – Lactam Antibiotics**

Beta lactam antibiotics are those drugs that contain **β -lactam ring** in their structure. These drugs act by inhibiting the cell wall synthesis and include

- Penicillins
- Cephalosporins
- Monobactams e.g. aztreonam
- Carbapenems e.g. imipenem

All β -lactam antibiotics are **bactericidal** drugs. These bind to specific receptors (penicillin binding proteins; PBPs) on bacterial cell membrane and **inhibit transpeptidase** enzyme responsible for the cross linking of peptidoglycan chains. Bacteria formed in the presence of these drugs are without cell wall and die due to imbibition of water (cell wall provides turgidity).

PENICILLINS

Penicillin G is commercially obtained from *Penicillium chrysogenum*. It had a lot of limitations in its clinical use. Important among these are:

- It is **not effective orally** because of breakdown by acid in the stomach.
- It has **short duration of action** due to its rapid excretion from kidney through tubular secretion.
- It has **narrow spectrum** of activity covering mainly gram positive bacteria.
- Even, gram positive bacteria have now become **resistant** to penicillin G mainly due to development of penicillinase (β -lactamase) or altered penicillin binding proteins (PBPs).
- It can cause hypersensitivity reactions.

Newer penicillins have been designed to overcome these shortcomings

1. Penicillin G is not effective orally due to acid lability. New penicillins have been developed that are acid-resistant and can be given orally. These include: penicillin V, oxacillin, dicloxacillin, cloxacillin, amoxycillin and ampicillin.
2. Penicillin G is short acting. To overcome this problem:
 - (a) Benzathine and procaine group can be added to penicillin G to make it long acting. Benzathine penicillin G is longest acting penicillin.
 - (b) Probenecid can be administered with penicillins. Former inhibits the tubular secretion.
 - (c) Penicillins have wide therapeutic index. A high initial dose can be used.
3. Penicillin G has narrow spectrum of antibacterial activity. Several new penicillins with extended spectrum have been developed.

These include:

Aminopenicillins:	Ampicillin Amoxycillin
Carboxypenicillins:	Carbenicillin Ticarcillin
Ureidopenicillins:	Mezlocillin Azlocillin Piperacillin

**Acid resistant penicillins**

V – Penicillin V
O – Oxacillin
D – Dicloxacillin
K – Cloxacillin
A – Amoxycillin and Ampicillin



Penicillinase resistant penicillins

Cloxacillin
Oxacillin
Nafcillin
Dicloxacillin
Methicillin
C O N D O M



Methicillin resistance occurs due to altered PBPs, thus no penicillin, (infact no β -lactam antibiotic) is useful against methicillin-resistant *Staphylococcus aureus* (MRSA) infections.



Anti-pseudomonal penicillins

C – Carbenicillin
T – Ticarcillin
M – Mezlocillin
A – Azlocillin
P – Piperacillin

Mnemonic: A CT MAP

- All of these are effective against gram negative bacteria like *E.coli*, salmonella, shigella (except amoxycillin) etc.
 - Last five penicillins (CT MAP) are effective against *Pseudomonas*.
 - Last three (MAP) are effective against *Klebsiella* also.
4. Problem of resistance can be tackled by:
 - (a) Adding β -lactamase inhibitors to penicillins. These inhibit the bacterial enzyme and penicillins escape degradation.
 - (b) By administering penicillinase resistant penicillins like cloxacillin, oxacillin, nafcillin, dicloxacillin or methicillin.
 5. **Hypersensitivity reactions** can occur with any penicillin. Infact, penicillins are the most common drugs responsible for anaphylactic shock. If a person is severely allergic to any penicillin, no β -lactam (except monobactams) should be administered to that person. Intra-dermal skin testing can be used to prevent severe allergic reactions.

Pharmacokinetics

- One gram of penicillin is equivalent to 1.6 million units.
- Gastric acid breaks down penicillins and results in decreased oral bioavailability. Penicillin G can be used orally only for infections in which clinical experience has proven efficacy.
- Ampicillin and nafcillin are excreted partly in the bile.
- Benzyl penicillin (Penicillin G) is given by i.m. injection. It has small $t_{1/2}$ so given 6-12 hourly whereas procaine penicillin (12-24 hourly) and **benzathine penicillin (longest acting)** are long acting due to slow release. **Procaine** helps to **prolong the duration** of action.

Clinical Uses

- **Penicillin G:** It is the *drug of choice for syphilis*. Benzathine penicillin G is used for primary, secondary and early latent syphilis (2.4 million units i.m.) as single dose and late latent and tertiary syphilis for 3 weeks (once weekly). **Aqueous penicillin G is DOC for neurosyphilis** (benzathine penicillin has little entry in brain). It can also be used for gram positive bacteria like streptococci and meningococci. **Penicillin G** is also the *drug of choice for meningococcus, actinomycosis, tetanus (now metronidazole is preferred), gas gangrene, rat bite fever, yaws, leptospirosis, group A and B streptococcal infections and viridans streptococcal endocarditis*. Most staphylococci and gonococci are now resistant. It is effective against *anaerobic bacteria except bacteroides*.
- **Methicillin, nafcillin, oxacillin and cloxacillin:** Main use of these drugs is for the treatment of *Staphylococcus aureus* infections although organisms resistant to these drugs also have been isolated. **Methicillin resistance is developed due to the formation of alternative penicillin binding proteins that have less affinity for the drugs.** Organisms resistant to methicillin (MRSA) are resistant to all other beta lactam drugs. These resistant organisms are treated by vancomycin or teicoplanin. Vancomycin resistant staphylococcus (VRSA) can be treated by linezolid or streptogramins.
- **Ampicillin, amoxicillin:** These are wide spectrum penicillinase sensitive antibiotics. In addition to gram positive organisms, these are also effective against enterococci, listeria and haemophilus organisms. The activity of these drugs is enhanced when used with beta lactamase inhibitors like sulbactam or clavulanic acid. **Ampicillin is drug of choice for listeria meningitis (cephalosporins are not effective) and UTI caused by E. faecalis.**
- **Piperacillin, ticarcillin, carbenicillin, azlocillin and mezlocillin:** These possess activity against gram negative rods including pseudomonas. These are used with beta lactamase inhibitors and with aminoglycosides. Ureidopenicillins (piperacillin, azlocillin and mezlocillin) are also highly effective against klebsiella species.
- MRSA is not susceptible to β -lactam antibiotics.

Toxicity

- Main toxicity is hypersensitivity including serum sickness. **Anaphylaxis** is most commonly associated with these drugs; therefore intra-dermal sensitivity testing is must before administration of penicillins. *If a patient develops severe hypersensitivity reaction to a penicillin, all other beta lactam antibiotic are contra-indicated except aztreonam* (cross sensitivity is not present).
- Ampicillin* is involved in causing maculopapular skin rash in the patients with viral diseases like infectious mononucleosis.
- Methicillin* is the most common antibiotic implicated in causing *interstitial nephritis*.
- Nausea and diarrhea may be caused by oral drugs like amoxicillin and ampicillin. *Ampicillin causes diarrhea* more frequently, because it is incompletely absorbed and causes more suppression of normal microbial flora. It can also cause pseudomembranous colitis.
- Procaine penicillin* in high doses can result in seizures and CNS abnormalities (due to procaine).
- Oxacillin* can cause hepatitis and *nafcillin* is involved in causing neutropenia.
- Carbenicillin* in high dose can result in bleeding.

M

Nafcillin can cause Neutropenia

M

Ampicillin should be avoided in patients with viral illness particularly EBV because it can cause rash in these patients.

CEPHALOSPORINS

These are β -lactam antibiotics having 7-aminocephalosporanic acid nucleus. These are classified into four generations.

First Generation		Second Generation		Third Generation		Fourth Generation	Fifth Generation
Oral	Parenteral	Oral	Parenteral	Oral	Parenteral	Parenteral	Parenteral
Cephalexin Cefadroxil Cephadrine	Cefazolin	Cefaclor Cefuroxime axetil Loracarbef Cefprozil	Cefuroxime Cefotetan Cefoxitin Cefmetazole	Cefixime Cefpodoxime Ceftibuten Cefditoren Cefdinir	Cefotaxime Ceftizoxime Ceftriaxone Ceftazidime Cefoperazone Moxalactam	Cefepime Cefpirome	Ceftaroline Ceftobiprole

Pharmacokinetics

- Most cephalosporins are excreted via kidney through tubular secretion.
- Ceftriaxone and cefoperazone** are secreted in the bile.
- Nephrotoxicity* of these drugs is increased with loop diuretics.

M

- All cephalosporins having A after cef are 1st generation (except cefaclor)
- Cephalosporins containing PI are 4th gen. (cefePIme, cefPIrome)
- Cephalosporins ending with ME are 3rd gen. except. cefuroxiME.

Antibacterial Spectrum

Useful spectrum of cephalosporins		
Generation	Organism	Remarks
First	Gram +ve Cocci • Streptococci • Staphylococci	Not active against penicillin resistant strains
Second	Gram -ve bacilli • E. coli • Klebsiella • Proteus • H. influenza • M. catarrhalis • Bacteroides	Only cefoxitin, cefmetazole and cefotetan are effective against Bacteroides

Contd...

Contd...

Useful spectrum of cephalosporins		
Generation	Organism	Remarks
Third	Gram +ve cocci - Streptococci - Staphylococci Gram -ve cocci - Gonococci Gram -ve bacilli - Enterobacteriaceae - Serratia - Pseudomonas Anaerobes - Bacteroides	- Only ceftazidime and cefoperazone are effective against <i>Pseudomonas</i> - Activity against gram +ve cocci is same as 1st generation agents - Activity against <i>Bacteroides</i> is less than cefoxitin
Fourth	Same as 3rd Generation	More resistant to β -lactamases

Clinical Uses

First Generation

These are active against gram positive cocci including staphylococci. MRSA is resistant to cephalosporins also. **Cefazolin is the drug of choice for surgical prophylaxis.**

Second Generation

This group of drugs is less active against gram positive organisms than first generation agents but has extended gram negative coverage. **Cefotetan, cefmetazole and cefoxitin are active against anaerobes like *Bacteroides fragilis*.** Cefuroxime attains higher CSF levels as compared to other second generation cephalosporins.

Third Generation

- These are active against gram negative organisms resistant to other beta lactam antibiotics.
- These can also penetrate the blood brain barrier (except cefoperazone and cefixime).
- Ceftazidime (maximum), ceftolozane and cefoperazone are active against pseudomonas.**
- Ceftazidime** is drug of choice for melioidosis (caused by *Burkholderia pseudomallei*).
- Ceftizoxime** has maximum activity against *Bacteroides*.
- Ceftriaxone** is the first choice drug for gonorrhoea, salmonellosis (including typhoid), *E. coli* sepsis, *Proteus*, *Serratia*, *Haemophilus* and empirical therapy for bacterial meningitis.
- Long term use of > 2g/d of **ceftriaxone** is associated with **biliary sludging syndrome** and cholelithiasis due to precipitation in bile.
- Most of these drugs are reserved for serious infections.
- Ceftriaxone has long plasma half life.
- Cefotaxime is metabolized to an active metabolite (desacetyl-cefotaxime).

Fourth Generation

These drugs possess activity against gram negative organisms (including pseudomonas) resistant to 3rd generation cephalosporins. Their efficacy against gram positive cocci is similar to 3rd generation compounds. However, these are not active against anaerobes.

MNEMONICS

1. Which generation?

- All drugs having 'a' after cef are 1st generation except cefactor [e.g. cefazolin, cefadroxil]

Contd...

Ceftaroline and ceftobiprole are fifth generation cephalosporins approved for treatment of community acquired pneumonia and MRSA infections. Ceftobiprole is also effective against MRSA and pseudomonas.

Ceftriaxone and cefoperazone are secreted in the bile.

Cefazolin is the drug of choice for surgical prophylaxis.

Cefotetan, cefmetazole and cefoxitin are active against anaerobes like *Bacteroides fragilis*.

Contd...

- Drugs with 'PI' in the name are 4th generation (cefe PIme and cef PIrome)
- Drugs with 'ROL' in the name are 5th generation [CeftibipRoLe, ceftaROLine]
- Drugs ending with ME except cefuroxime (CefixiME, CefpodoxiME, CeftazidiME, CefotaxiME, CeftizoxiME), ONE (ceftriaxONE, CefoperazONE) or TEN (ceftibutTEN, CefdfiTorEN) are 3rd generation.
- Rest of the drugs (except cefdinir and moxalactam) are 2nd generation.

2. Whether oral or Parenteral?

- Drugs with OR in the name are ORal (e.g. CefaclOR, CefditORen, LORarcarbef)
- Apart from these, drugs having 't' in the name are injectable except ceftibuten (CefoTetan, CefTazidime, CefoTaxime, CefTizoxime, CefTriaxone, moxalacTam, CefTaroline, CefTobiprole)

Note:

- Cefotaxime and ceftriaxone are most active cephalosporins against penicillin resistant pneumococci.
- No cephalosporin is active against *Enterococcus faecalis*, MRSA and *Listeria monocytogenes*.
- **Ceftazidime plus aminoglycoside is the treatment of choice for pseudomonas infections.**

Toxicity

- Cephalosporins can cause *hypersensitivity* reactions. There is complete cross reactivity between different cephalosporins and also 5-10 % cross-reactivity with penicillins.
- Drugs containing a methylthiotetrazole group like *cefamandole*, *cefoperazone*, *moxalactam* and *cefotetan* may cause *hypoprothrombinemia* (bleeding) and *disulfiram* like reaction with alcohol.
- *Ceftazidime* is implicated in causing *neutropenia*.

Note:

No cephalosporin is active against

- Penicillin resistant *Pneumococci*
- MRSA
- *Enterococcus*
- *Listeria*
- *Legionella*
- *Xanthomonas*
- *Campylobacter*
- *Clostridium difficile*

OTHER BETA LACTAM ANTIBIOTICS

Monobactams

This group includes **aztreonam**. This is active against β -lactamase producing *gram negative rods* including *pseudomonas* but has no activity against gram positive organisms or anaerobes. It is administered i.v. and its half life is prolonged in renal failure. **It is the only beta lactam antibiotic that can be used in patients having severe allergy to penicillins or cephalosporins** (as it is not cross allergenic).

Carbapenems

These include *imipenem*, *doripenem*, *meropenem* and *ertapenem*. These have *wide spectrum* of activity including gram positive cocci, gram negative rods as well as anaerobes. For the treatment of *pseudomonas* (meropenem is most active whereas ertapenem is least) infections, these drugs should be combined with aminoglycosides. Carbapenems are β -lactamase resistant and are *drugs of choice for Enterobacter, Klebsiella and acinetobacter species*. These are the **only β -lactams which are reliably efficacious against ESBL** (extended spectrum β -lactamase) producing organisms. **Imipenem** is rapidly **inactivated by renal dehydropeptidase I**, so

Aztreonam is the only beta lactam antibiotic that can be used in patients having severe allergy to penicillins or cephalosporins.



Carbapenems are the only β -lactams which are reliably efficacious against ESBL (extended spectrum β -lactamase) producing organisms.

it is **combined with cilastatin**, an inhibitor of this enzyme. Cilastatin increases the half life of imipenem and also *inhibits the formation of nephrotoxic metabolite*. Main adverse effects of imipenem-cilastatin combination include **seizures** and gastrointestinal distress. *Meropenem, doripenem and ertapenem are not metabolized by renal dehydropeptidase and are less likely to cause seizures*. Ertapenem is very long acting and is inactive against *Pseudomonas*.

Loracarbef: It is chemically *similar to cefaclor*. It can be administered orally and its uses and spectrum resembles second generation cephalosporins. *Its overdose can cause seizures*.

Beta lactamase inhibitors

- These include *clavulanic acid, sulbactam, tazobactam and avibactam*. These are more active against plasmid encoded beta-lactamases (produced by gonococci and *E. coli*) than against inducible chromosomal beta-lactamases (produced by *pseudomonas* and *enterobacter*)
 - Amoxicillin* is combined with *clavulanic acid* (Co-amoxyc-clav).
 - Ampicillin* is combined with *sulbactam* (Sultamicin).
 - Piperacillin* is combined with *tazobactam*.
 - Ceftazidime-avibactam combination** is recently approved for complicated UTI (including pyelonephritis) and complicated intra-abdominal infections.

Beta-Lactamases

These are the enzymes that hydrolyze beta-lactam antimicrobials. These enzymes may be located on chromosome (e.g. SHV-1 enzyme mediating resistance to Ampicillin and ticarcillin in *Klebsiella*) or on the plasmid (e.g. enzyme mediating penicillin resistance in *Staphylococci*). Further, these can be inducible (the production is initiated when bacteria is exposed to beta-lactams e.g. in penicillin resistance in *Staphylococci*) or constitutive (bacteria continue to produce them whether exposed to beta-lactams or not e.g. SHV-1).

Two major schemes are adopted to classify beta lactamases:

- Molecular classification (Amber classification):** It is based on structure (amino acid sequence). Beta lactamases are classified into four categories; A, B, C and D. Class A, C and D enzymes require serine residue to hydrolyze beta lactams whereas Class B require zinc ions (therefore also known as metallo-beta lactamases).
- Functional classification (Bush Classification):** This classification is based on the type of substrate of beta lactamase (i.e. which beta-lactam is hydrolyzed). It also takes into consideration whether the enzyme is *inhibited by clavulanic acid* or other drugs. According to this scheme, beta lactamases are classified into three (previously there were four) categories: 1, 2 and 3.

Beta-lactamase	Functional Group	Molecular Group	Inhibited by	Substrates	Example
Cephalo-sporinase	1	C	None	Cephalosporins, cephamycins, Aztreonam	Amp C
Serine β -lactamases	2	A or D	CA and TZB		
Penicillinase	2a	A	CA and TZB	Penicillin G	PCI
	2b	A	CA and TZB	Penicillin and early cephalosporins*	TEM-1, TEM-2, SHV-1
Extended Spectrum Beta-lactamases (ESBL)	2be	A	CA and TZB	Penicillins, Cephalosporins, Oxyimino beta lactams** NOT cephamycins and carbapenems	TEM-3, SHV-2
Carbenicillinase	2c	A	CA and TZB	Carbenicillin	CARB-1
Oxacillinase	2d	D	CA and TZB	Cloxacillin, Oxacillin	OXA-1



CA is Clavulanic acid, TZB is Tazobactam, EDTA is chelating agent

- Cephamycins include cefoxitin, cefmetazole and cefotetan
- *Early cephalosporins include cephaloridine, cefazolin and cephalothin
- **Oxyimino beta-lactams include cefotaxime, ceftazidime, ceftriazone, cefepime and aztreonam.

Contd...

Contd...

Beta-lactamase	Functional Group	Molecular Group	Inhibited by	Substrates	Example
	2e	A	CA and TZB	Most cephalosporins but not aztreonam	Cep A
	2f	A	TZB	Carbapenems, Cephamycins. Oxyimino-beta lactams	KPC-2
Metallo- β lactamases	3	B	EDTA	Carbapenems	IMP-1

Extended Spectrum Beta Lactamases (ESBL)

These are the enzymes that confer resistance to most beta lactams antibiotics including penicillins, cephalosporins and monobactams. ESBL have been found exclusively in gram negative organisms primarily in *Klebsiella* and *E. coli*. The important characteristics of ESBL are:

- These belong to functional (Bush) group 2be and molecular (Amber) group A.
- These can be inhibited by clavulanic acid or tazobactam.
- These can hydrolyze penicillins, cephalosporins (including cefotaxime, ceftazidime, ceftriazone, cefepime) as well monobactams (aztreonam).
- These cannot hydrolyze cephamycins (cefoxitin, cefotetan and cefmetazole).
- These cannot hydrolyze carbapenems (imipenem, meropenem etc.)
- **Carbapenems are drug of choice for treatment of infections caused by a bacteria producing ESBL.**

Other Cell Wall Synthesis Inhibitors**VANCOMYCIN AND OTHER GLYCOPEPTIDES**

- It is a bactericidal *glycopeptide antibiotic* that inhibits cell wall synthesis by *inhibiting transglycosylase enzyme* (involved in chain elongation).
- It has narrow spectrum and is effective against gram positive organisms including MRSA, penicillin resistant pneumococci and *Clostridium difficile*. It is *drug of choice for MRSA, Corynebacterium jeikeium and for serious infections in penicillin allergic patients*.
- **Teicoplanin** is another glycopeptide with similar characteristics but can be given once daily due to **long $t_{1/2}$** (45-70 hours).
- These are administered parenterally (*vancomycin by i.v. route and teicoplanin by i.v. or i.m. route*) and are excreted unchanged in urine.
- Rapid i.v. infusion of high doses of vancomycin can cause **RED MAN SYNDROME** (diffuse flushing due to histamine release). It is the **most common adverse reaction** to vancomycin.
- Other toxic effects of vancomycin are *chills, ototoxicity and nephrotoxicity*. Its dose should be decreased in renal failure. Teicoplanin does not cause red man syndrome or nephrotoxicity.
- Vancomycin is used **ORALLY** to treat *pseudomembranous colitis* by *Clostridium difficile* because it is not absorbed from the gastrointestinal tract and higher concentration reaches the colon.
- **Oritavancin** is a newer glycopeptide antibiotic that is being developed for the treatment of MRSA infections.
- **Telavancin** has been approved for complicated skin and skin structure infections. It is effective against MRSA. Apart from vancomycin like mechanism, it also disrupts membrane potential.
- **Dalbavancin** is **once-weekly** drug being developed for MRSA and VRSA acting by same mechanism as vancomycin.



Vancomycin is drug of choice for

- MRSA
- *Corynebacterium jeikeium*
- Serious infections in penicillin allergic patients.

FOSFOMYCIN

It inhibits cell wall synthesis by *inhibiting enolpyruvate transferase*. *Diarrhea* is quite common with its use. It is drug of choice (along with nitrofurantoin), for uncomplicated urinary tract infections.

BACITRACIN

It also inhibits cell wall synthesis but because of *marked nephrotoxicity*, it is indicated *only for topical use*. It is selectively active against gram positive bacteria.

CYCLOSERINE

It also inhibits cell wall synthesis. It has potential neurotoxic effects (tremors and seizures). It also causes **neuropsychiatric symptoms**. It is one of the **second line drugs for the treatment of tuberculosis**.

Cycloserine has potential neurotoxic effects (tremors and seizures). It also causes **neuropsychiatric symptoms**.

DRUGS INHIBITING PROTEIN SYNTHESIS

According to spectrum of activity, these may be classified as:

- **Broad spectrum:** Chloramphenicol and tetracyclines
- **Moderate spectrum:** Macrolides and ketolides
- **Narrow spectrum:** Lincosamides, streptogramins and oxazolidinones

Chloramphenicol

It inhibits protein synthesis by binding to 50S ribosomal subunit and causing the *inhibition of peptidyl transferase*. Chloramphenicol **undergoes enterohepatic circulation** and is mainly inactivated by hepatic glucuronidation. It is a *bacteriostatic* drug with wide spectrum of antimicrobial activity. *Resistance* develops to this drug due to the formation of *inactivating enzyme* acetyl transferase. Because of the rapid development of resistance and high toxicity, this drug has very few systemic uses. Earlier, it was the drug of choice for typhoid fever (enteric fever) but due to the development of resistance, ceftriaxone or ciprofloxacin are now the preferred drugs. It is also *active against anaerobes*. Due to its wide spectrum, it may cause superinfection diarrhea. It can also cause dose dependent and **reversible bone marrow suppression** as well as idiosyncratic, **irreversible myelosuppression** (can occur even after ocular administration). Neonates and premature infants are deficient in hepatic glucuronyl transferase and because it is excreted in the kidney after glucuronidation, these are very sensitive to its toxicity. In such patients, it may lead to **grey baby syndrome** characterized by decreased RBCs, cyanosis and cardiovascular collapse.

Tetracyclines

Tetracyclines bind to 30S ribosomal subunit and *inhibit the binding of aminoacyl-tRNA to the A site*. These are classified into three groups

- **Group I :** Tetracycline, chlortetracycline, oxytetracycline
- **Group II :** Demeclocycline, lymecycline
- **Group III :** Doxycycline, minocycline

Pharmacokinetics

- Oral *absorption* of tetracyclines is *impaired by food and multivalent cations* (calcium, iron, aluminium etc.). Yoghurt decreases the absorption of tetracyclines because it contains cations like calcium and magnesium.
- Tetracyclines *cross the placenta* and affect the fetus, if administered to a pregnant female.
- All tetracyclines undergo *enterohepatic circulation*.
- All tetracyclines are excreted primarily in the urine except doxycycline. **Doxycycline** is excreted in the feces and thus **can be used in the presence of renal failure**.
- *Half life of doxycycline and minocycline is longer than other tetracyclines.*

Chloramphenicol may lead to grey baby syndrome and bone marrow suppression.

Clinical Uses

Tetracyclines are broad spectrum *bacteriostatic* drugs. Development of **resistance** to tetracyclines is mainly due to the development of **efflux pumps**. **Tetracyclines are first choice drugs for**

- Lymphogranuloma venereum (LGV)
- Granuloma inguinale
- Atypical pneumonia due to chlamydia
- Cholera
- Brucellosis (with rifampicin)
- Plague prophylaxis (Drug of choice for treatment is streptomycin)
- Relapsing fever (Doxycycline)
- Lyme's disease (Doxycycline)
- Rickettsial infections (Doxycycline)
- Chlamydial infections (Doxycycline)



All tetracyclines are excreted primarily in the urine except doxycycline. Doxycycline is excreted in the feces and thus can be used in the presence of renal failure.

Other uses of individual tetracyclines include

- Meningococcal carrier state (Minocycline)
- Malaria prophylaxis (Doxycycline)
- Amoebiasis (Doxycycline)
- Syndrome of inappropriate ADH secretion (Demeclocycline)
- As secondary drugs for gonorrhoea, syphilis and chlamydial infections
- For pleurodesmosis in malignant pleural effusion.
- Leprosy (minocycline)
- Peptic ulcer by *H. pylori* (tetracycline)

Toxicity

- Tetracyclines may cause *superinfection diarrhea and pseudomembranous colitis*. Gastrointestinal side effects are most common adverse effects.
- These are contra-indicated in pregnancy due to the risk of *fetal tooth enamel dysplasia and irregularities in the fetal bone growth*.
- Treatment of *young children (< 8 years)* with tetracyclines may cause *dentition abnormalities*. Doxycycline is less likely to cause this adverse effect.
- High dose of tetracyclines may lead to *hepatic necrosis* especially in pregnant females.
- *Outdated* tetracycline use may lead to *Fanconi's syndrome* (a type of renal tubular acidosis).
- Tetracyclines may *exacerbate pre-existing renal dysfunction* although these are not directly nephrotoxic.
- *Demeclocycline (maximum)* and doxycycline can result in *photosensitivity*.
- **Minocycline** may lead to dose dependent **vestibular toxicity** (more in women).
- **Diabetes insipidus** may be precipitated **by** ADH antagonistic action of **demeclocycline**.
- Tetracyclines also possess anti-anabolic effects.



T Tetracyclines are used for
E — Rickettsia, Relapsing fever
T — Atypical pneumonia
R — Cholera
A — LYme's disease
C — Chlamydia
Y — LGV
L — Inguinale (granuloma)
I — Epidemics of plaque
N
E

Mnemonic:

- K** — Kidney Failure (All are contra-indicated except doxycycline)
- A** — Antianabolic effect
- P** — Photosensitivity (Maximum with demeclocycline)
- I** — Insipidus (diabetes insipidus; maximum with demeclocycline)
- L** — Liver Toxicity (hepatic necrosis)
- D** — Dentition and Bone defects (contra-indicated in pregnancy and children)
- E** — Expired drugs can cause Fanconi's syndrome
- V** — Vestibular dysfunction (maximum with minocycline)

GLYCYLCYCLES

This new group of antibiotics includes **tigecycline**, which acts by inhibiting protein synthesis via a mechanism *similar to tetracyclines*. But these are *more resistant* than tetracyclines to *efflux pumps* developed by the microorganisms. Their main indication is *serious complicated skin and skin structures infections* and intra-abdominal infections. It has a broad spectrum including MRSA, VRSA, streptococci, enterococci, anaerobes, rickettsia, chlamydia, legionella and rapidly growing mycobacteria. However, it is ineffective against *Proteus* and *Pseudomonas*.

Macrolides

These antibiotics have large cyclic lactone ring structure with attached sugars. The drugs included in this group are *erythromycin*, *azithromycin*, *roxithromycin* and *clarithromycin*. An immunosuppressant drug, **tacrolimus** is also a **macrolide** antibiotic. These drugs bind to 50S ribosome and **block the translocation** of peptide chain from A to P site. *Ketolides* and *lincosamides* have similar mechanism of action.

Pharmacokinetics

These drugs are well absorbed orally. **Erythromycin** is excreted by **biliary route** and clarithromycin by both renal and biliary routes. Excretion of **azithromycin** is quite slow (**longest half life**) and mainly in the urine. Erythromycin is administered four times a day whereas azithromycin is administered as a single daily dose.

Clinical Uses

Macrolides are the **drug of choice** for (remembered as **CLAW**)

- Chancroid by *Haemophilus ducreyi* (Azithromycin single dose), *Corynebacterium* (diphtheria), *Campylobacter*
- Legionella infections
- Atypical pneumonia
- Whooping cough by *Bordetella pertussis*

It can also be used for diphtheria and the infections caused by chlamydia and gram positive organisms (as second choice drugs to penicillins).

Clinical uses of Azithromycin and clarithromycin

- C – Chlamydia
- H – H.influezae
- A – MAC
- T – Toxoplasma

- Azithromycin has similar spectrum but is more active against *H. influenza* and *Neisseria*. Because of its long $t_{1/2}$, a single dose is effective in the treatment of urogenital infections caused by chlamydia. It can be used once weekly in the prophylaxis of MAC infections.
- Roxithromycin has similar spectrum as that of azithromycin.
- *Clarithromycin* is approved for the prophylaxis and treatment of *Mycobacterium avium* complex and in the treatment of peptic ulcer caused by *H. pylori*.
- Macrolides have **anti-inflammatory** action due to their effect on neutrophils and inflammatory cytokines. This action is responsible for the use of macrolides in the prevention of cystic fibrosis exacerbation.
- **Spiramycin** is another macrolide antibiotic that is the **drug of choice for the treatment of toxoplasmosis in pregnancy**.
- **Fidaxomicin** is a non-absorbed macrolide approved for treatment of *C. difficile* infection.

M

Adverse Effect of Macrolides

- M – Motilin receptor agonists
- A – Allergy
- C – Cholestasis
- R } Reversible
- O } Ototoxicity

Toxicity

- Erythromycin can cause *diarrhea* by the stimulation of **motilin receptors**. *Gastro-intestinal effects* are most common side effects of all macrolides.
- **Erythromycin estolate** is implicated in the causation of **acute cholestatic hepatitis** especially in pregnant females. Other salts of erythromycin are safe.

- Erythromycin, roxithromycin and clarithromycin inhibit CYP3A4. If administered to patients receiving terfenadine, astemizole or cisapride (substrates of CYP3A4), these drugs may lead to prolongation of QT interval and serious polymorphic ventricular tachycardia (*torsades de pointes*). **Azithromycin is not an enzyme inhibitor** and is free from these drugs interactions.
- Intravenous erythromycin (not oral) can cause dose dependent reversible ototoxicity.
- Erythromycin also increases the plasma concentration of theophylline by inhibiting CYP1A2.

Ketolides

This group includes *telithromycin*. It has the same mechanism of action and indications as macrolides. It is excreted in the bile and urine and is a potent inhibitor of CYP3A4.

Lincosamides

This group includes *clindamycin* and *lincomycin*. These have same mechanism of action as macrolides. Main use of clindamycin is against *anaerobes like bacteroides* and propionibacterium (responsible for acne). It is also a drug of choice for treatment of severe, invasive group A streptococcal infections along with penicillin. It was also active against *Pneumocystis jirovecii* (previously called *P. carinii*) and *Toxoplasma gondii*. It is used as an alternative to amoxycillin or ampicillin for prophylaxis against endocarditis following dental procedures. It was the **most common antibiotic implicated in causing pseudomembranous colitis but now second and third generation cephalosporins (particularly cefotaxime, cefuroxime, ceftriaxone and ceftazidime) are most frequently responsible**. It can also cause hepatic dysfunction.

Streptogramins

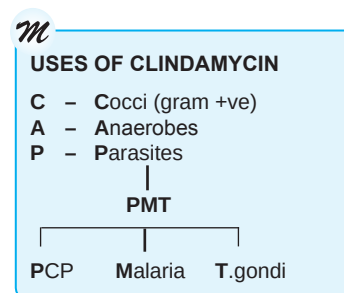
These are **bactericidal** for most susceptible organisms. These drugs bind to 50S ribosomal subunit and constrict the exit channel on the ribosome through which nascent polypeptides are extruded. These drugs also inhibit tRNA synthetase activity. **Quinpristin – dalfopristin** is a bactericidal combination of two streptogramins with prolonged PAE. Resistance to macrolides, lincosamides and streptogramins may be inherited together (**MLS-B resistance**). Quinpristin- dalfopristin combination is **effective against penicillin resistant pneumococci, Methicillin resistant Enterococcus faecium (not faecalis), MRSA as well as VRSA**. These drugs are potent inhibitors of CYP3A4, therefore drug interactions are possible. *Venous irritation* is very common side effect (mostly required to be given by central line). Other adverse effects include *arthralgia myalgia syndrome*.

Oxazolidinones

This group includes the drugs **linezolid** and **tedizolid**. These act by *binding to 23S part of 50S ribosomal subunit* and inhibits the initiation of protein synthesis. These have *no cross resistance with other protein synthesis inhibiting drugs*. These are **active against MRSA, VRSA and vancomycin resistant Enterococcus faecium as well as faecalis**. Major adverse effect of linezolid is *thrombocytopenia and neutropenia*. Blood counts should be monitored if duration of therapy exceeds one week. It also possesses MAO inhibitory activity and can cause **serotonin syndrome** if administered with SSRI or other serotonergic drugs. Optic neuritis, peripheral neuropathy and lactic acidosis have also been reported with this drug.

Aminoglycosides

These include *streptomycin*, *gentamicin*, *kanamycin*, *tobramycin*, *amikacin*, *sisomicin*, *netilmicin*, *neomycin* and *framycetin*. These drugs **exhibit CDK** and have **prolonged PAE**, therefore are administered as *single daily dose*. Aminoglycosides are **bactericidal** inhibitors of protein synthesis. *Their penetration across the cell wall is dependent on the oxygen dependent transport*, therefore these drugs are **inactive against anaerobes**. Their transport is enhanced if used



Aminoglycosides exhibit CDK and have prolonged PAE, therefore are administered as single daily dose.

along with cell wall synthesis inhibitors like penicillins. These bind to 30S and 50S ribosomes and freeze initiation, interfere with polysome formation and cause misreading of mRNA code.

Pharmacokinetics

These are *not absorbed orally* and do not cross blood brain barrier. These are *excreted primarily by glomerular filtration* and the dose should be decreased in renal insufficiency.

Resistance to these drugs develops due to the formation of **inactivating enzymes** which acetylate, phosphorylate or adenylate the aminoglycosides. All aminoglycosides except amikacin and netilmicin are susceptible to these enzymes. Thus *amikacin and netilmicin may be effective against organisms resistant to other aminoglycosides.*

Clinical Uses

- Gentamicin, tobramycin and amikacin are effective against *gram negative organisms* including pseudomonas (*except salmonella*). However these are not reliable for gram positive organisms if used alone.
- Aminoglycosides produce synergistic effects against gram positive bacteria when combined with β -lactams or vancomycin.
- Streptomycin is the first line drug for the treatment of tuberculosis, plague and tularemia.
- Amikacin is a second line drug for the treatment of tuberculosis and is also used for MDR tuberculosis.
- Netilmicin is used for serious infections only.
- Neomycin and framycetin are used only topically because of their high toxic potential.
- Neomycin can also be used orally for gut sterilization in hepatic encephalopathy.
- **Spectinomycin** is a drug related to aminoglycosides, which is used as a **single dose treatment** for penicillinase producing *Neisseria gonorrhoea* (PPNG) and for gonorrhea in penicillin -allergic patients.

Note: Tobramycin is much less active against enterococcal endocarditis than gentamicin or streptomycin.

Toxicity

- **Ototoxicity:** It can occur due to damage to hair cells. This adverse effect is more likely with prolonged use, high serum concentrations (especially with renal impairment), hypovolemia and other ototoxic medications (like ethacrynic acid). *Amikacin, kanamycin and neomycin are more likely to cause hearing loss whereas streptomycin and gentamicin cause predominantly vestibular dysfunction.* Tobramycin cause both abnormalities equally. Ototoxicity is largely **irreversible** and progress from base of cochlea (high frequency) to the apex (low frequencies). Very early changes can be reversed by Ca^{2+} . Amikacin cause maximum hearing loss whereas streptomycin is most vestibulotoxic. Netilmicin is least ototoxic aminoglycoside.
- **Nephrotoxicity:** It results from toxicity to proximal tubular cells and is almost always **reversible**. Risk factors for nephrotoxicity include *hypokalemia, pre-existing renal disease and concomitant nephrotoxic medications* (like AMB, vancomycin etc.). Neomycin is most nephrotoxic and is not indicated for systemic use. Among the systemically used aminoglycosides, gentamicin is most nephrotoxic followed by tobramycin. Streptomycin is least nephrotoxic.
- **Neuromuscular blockade:** This adverse effect can lead to rare but severe respiratory depression. It can occur due to *inhibition of pre-synaptic release of ACh* and partly by *decreased sensitivity of post-synaptic receptors*. **Hypocalcemia, peritoneal administration, use of neuromuscular blockers and pre-existing respiratory depression** constitutes risk factors. This complication can be avoided by slow i.v. infusion (over 30 min.) or by i.m. route. If *respiratory depression occurs, it is reversed by i.v. administration of calcium.* Neomycin (not used) and streptomycin have maximum

potency of causing neuromuscular block whereas tobramycin is least potent in this regard. These drugs are therefore contra-indicated in myasthenia gravis.

	Maximum	Minimum
Nephrotoxicity	Neomycin > Gentamicin	Streptomycin
Ototoxicity	Amikacin (Auditory)	Netilmicin
	Streptomycin (vestibular)	
Neuromuscular blockade	Neomycin > Streptomycin	Tobramycin



Puromycin is structurally similar to amino-acyl tRNA. It enters the A site and transfers to growing chain causing premature chain release. It is not selective for either prokaryotes or eukaryotes.

Pleuromutins

Retapamulin is a new drug of this class approved for *topical treatment of impetigo due to methicillin-sensitive Staphylococcus aureus or Streptococcus pyogenes*. It acts by inhibiting protein synthesis after binding to 50S ribosomes.

ANTIMETABOLITES

The drugs that are able to interfere with the role of an endogenous compound in the cellular metabolism are called antimetabolites e.g. *sulfonamides, trimethoprim, pyrimethamine, proguanil and methotrexate*.

Sulfonamides

- These drugs are *bacteriostatic* agents and act by *inhibiting folate synthase competitively*.
- The selective toxicity to bacteria is due to the reason that mammalian cells do not synthesize folic acid and utilize preformed folic acid in the diet.
- Sulfonamides are **not effective in the presence of pus** because it contains large amount of PABA.
- These drugs undergo hepatic metabolism by **ACETYLATION** (*Drugs undergoing acetylation are SHIP: Sulfonamides including dapsone, Hydralazine, Isoniazid and Procainamide*) and can cause SLE.
- The solubility of sulfonamides decrease in the acidic urine, which may result in precipitation of the drug causing **crystalluria**. Risk is **minimum with** soluble drugs like **sulfisoxazole**.
- **Sulfadoxine** is **longest acting** whereas **sulfacytine** is **shortest** acting sulfonamide.



Sulfisoxazole is most soluble sulfonamide. Thus it has minimum risk of causing crystalluria.

Classification

- **For systemic use as oral agents**
 - Short acting:* Sulfisoxazole, sulfamethiazole, Sulfacytine
 - Intermediate acting:* Sulfamethoxazole, Sulfadiazine
 - Long acting:* Sulfadoxine
- **For use in GIT:** Sulfasalazine, olsalazine
- **For topical use:** Sulfacetamide, silver sulfadiazine, mafenide

Clinical Uses

- Sulfacetamide is used for *ocular infections* whereas mafenide and silver sulfadiazine are used in *burn patients* as topical agents.
- Sulfadiazine can be used for *nocardiosis* and sulfisoxazole for *urinary tract infections*.
- Sulfasalazine and olsalazine are used for the treatment of *ulcerative colitis*.
- Sulfadoxine plus pyrimethamine is used for *malaria*.
- Sulfadiazine and pyrimethamine combination can be used for the *treatment of toxoplasmosis* and *prophylaxis of Pneumocystis jiroveci pneumonia* in AIDS patients.



Sulfonamides commonly cause rash, so to remember adverse effects of sulfonamides, one must know ABC of RASH.

- A** – Aplastic anemia
- B** – Bilirubin displacement (kernicterus)
- C** – Crystalluria
- R** – Rash (MC side effect)
- A** – Acetylation
- S** – SLE
- H** – Hemolysis in G-6-PD deficiency



Cotrimoxazole is the drug of choice for pneumocystosis and nocardiosis.



Indications of Cotrimoxazole

- S** – STD's (Chancroid, LGV)
- E** – Enteritis (E.coli, Shigella)
- P** – PCP
- T** – Typhoid
- R** – RTI
- A** – Acute uncomplicated UTI
- N** – Nocardia

Toxicity

- Skin rash due to hypersensitivity is the *most common* adverse effect.
- These can also cause *granulocytopenia, thrombocytopenia and aplastic anemia* (more common in HIV infected patients).
- Sulfonamides can cause acute *hemolysis* in patients with G-6 PD deficiency.
- These can precipitate in the urine at acidic pH and may result in *crystalluria* and hematuria.
- These can displace bilirubin from plasma protein binding sites and may result in *kernicterus in the new born* (if given in third trimester of pregnancy).

Trimethoprim

It is a **bacteriostatic antimetabolite** that *inhibits dihydrofolate reductase*. It attains high concentrations in the prostate and vaginal fluids. For most of the indications, it is combined with sulfonamides; however it can be used alone in prostatitis and UTI. It can cause *megaloblastic anemia* (can be ameliorated by folic acid), leucopenia and pancytopenia. It can also result in *hyperkalemia* (due to amiloride like action i.e., inhibition of epithelial Na⁺ channels in CD).

Note:

- Other DHFRase inhibitors are pyrimethamine, methotrexate, proguanil and pentamidine.
- All DHFRase inhibitors can cause megaloblastic anemia.

Cotrimoxazole

This is a fixed dose combination of sulfamethoxazole and trimethoprim in a ratio of 5:1. Both drugs have similar half life and the combination is **bactericidal** to most pathogens. Due to different bioavailability (more for sulfamethoxazole), *plasma concentration* of the two drugs attained is 20:1. The bactericidal activity is due to **sequential blockade** at two steps in the DNA synthesis (sulfamethoxazole inhibits folate synthase and trimethoprim inhibits DHFRase). Cotrimoxazole is effective in UTI, respiratory tract infections, MRSA, middle ear and sinus infections caused by hemophilus and moraxella. It is the *drug of choice for pneumocystosis and nocardiosis*. Adverse effects are similar to sulfonamides and trimethoprim.

FLUOROQUINOLONES

These drugs act by **inhibiting DNA gyrase** (topoisomerase II) and topoisomerase IV resulting in the inhibition of DNA replication. These drugs have *long PAE*. On the basis of the spectrum of antibacterial activity, these drugs are classified as

- **First generation:** Norfloxacin, lomefloxacin (Narrow spectrum; mainly gram negative).
- **Second generation:** Ciprofloxacin and ofloxacin
- **Third generation:** Levofloxacin, gatifloxacin, pefloxacin, sparfloxacin (More active against gram positive)
- **Fourth generation:** Moxifloxacin, fleroxacin, garenoxacin, gemifloxacin and trovafloxacin (BROADEST SPECTRUM).

Pharmacokinetics

- These have *good oral bioavailability* (except norfloxacin) but like tetracycline multivalent cations interfere with absorption.
- **Excretion** of moxifloxacin and trovafloxacin is by *hepatic* metabolism and biliary excretion. Sparfloxacin and pefloxacin are excreted by *both* renal and hepatic route. All other drugs (ciprofloxacin, gatifloxacin, levofloxacin, lomefloxacin, norfloxacin and ofloxacin) are excreted by *tubular secretion in the kidneys*. Probenecid inhibits tubular secretion of these drugs. *Dose adjustment is required in renal disease for all fluoroquinolones except pefloxacin, moxifloxacin and trovafloxacin* (remembered as PMT).
- Sparfloxacin, moxifloxacin and trovafloxacin have **long half-lives** and can be administered once daily. **Sparfloxacin** has *longest* half-life among fluoroquinolones.

Clinical uses

- Quinolones are the oral agents with greatest activity against pseudomonas (maximum with ciprofloxacin).
- First generation drugs like *norfloxacin* have narrow spectrum. The concentration of norfloxacin reached in urine is bactericidal, thus it can be used for UTI but it is not effective for systemic use.
- Second generation drugs like ciprofloxacin and ofloxacin are effective against gonorrhoea and other gram negative organisms including pseudomonas. **Ciprofloxacin** is the drug of choice for prophylaxis and treatment of anthrax and for prophylaxis of meningococcal meningitis.
- **Ciprofloxacin** and **levofloxacin** are the only fluoroquinolones effective against *Pseudomonas*.
- Levofloxacin is l-isomer of ofloxacin and is effective against infections caused by atypical microorganisms like mycoplasma. Sparfloxacin has greater activity against gram positive organisms but is not effective against pseudomonas.
- *Levofloxacin, gatifloxacin, gemifloxacin and moxifloxacin* are called **respiratory fluoroquinolones** due to their enhanced activity against gram positive and atypical organisms (like chlamydia, mycoplasma and legionella).
- Moxifloxacin and trovafloxacin have widest spectrum including gram negative and gram positive micro-organisms as well as anaerobes.
- Fluoroquinolones (*ciprofloxacin, levofloxacin and moxifloxacin*) are also effective in tuberculosis and can be used for the prophylaxis of neutropenic patients.
- Finafloxacin is a fluoroquinolone that has been approved recently for topical treatment of acute otitis externa caused by *Pseudomonas* and *Staphylococcus*.
- **T. Pallidum and Nocardia are resistant to all fluoroquinolones.**

Toxicity

- GI distress is the most common side effect followed by CNS side effects (headache and dizziness; rarely seizures also).
- These may also cause cartilage problems, thus are not advocated in children less than 18 years old and in pregnancy. However when benefits outweighs risks, these can be indicated e.g. in adolescent patients with cystic fibrosis who have pulmonary exacerbations.
- Tendinitis resulting in tendon rupture can be seen rarely in adults.
- These drugs can also cause phototoxicity, the incidence of which is maximum with lomefloxacin and sparfloxacin.
- Gatifloxacin has recently been withdrawn from India due to its dysglycemic effects. Moxifloxacin can also cause hypoglycemia.
- Sparfloxacin and gatifloxacin prolong QTc interval (*grepafloxacin* was withdrawn because of arrhythmias caused due to prolongation of QT interval). Gatifloxacin can also result in hypo or hyperglycemia.
- Trovafloxacin has hepatotoxic potential.
- Fluoroquinolones particularly ciprofloxacin or pefloxacin increase the plasma concentration of methylxanthines like theophylline and thus enhance their toxicity.
- NSAIDs increase CNS toxicity (seizures) of these drugs. Fluoroquinolones are contraindicated in epilepsy.
- Several fluoroquinolones have been **withdrawn** from the market like **temafloxacin** (immune hemolytic anemia), **trovafloxacin** (hepatotoxicity), **grepafloxacin** (cardiotoxicity; increase QT interval) and **clinafloxacin** (phototoxicity).
- Recently, FDA has issued warning regarding **Peripheral Neuropathy** caused by fluoroquinolones.

Gatifloxacin has recently been withdrawn from India due to its dysglycemic effects.

NSAIDs increase CNS toxicity (seizures) of fluoroquinolones.

Recently, FDA has issued warning regarding peripheral neuropathy caused by fluoroquinolones.

URINARY ANTISEPTICS

These are oral drugs that are rapidly excreted in the urine and suppress the bacterial growth in urinary tract. These are *more effective in acidic urine because low pH is an independent inhibitor of bacterial growth*. Nitrofurantoin, methanamine mandelate and nalidixic acid are three important urinary antiseptic drugs.

NITROFURANTOIN

After reduction by bacterial enzymes, nitrofurantoin result in DNA damage. It is active against most urinary pathogens *except pseudomonas and proteus*. Resistance against it develops slowly. Now it is used infrequently. Adverse effects include diarrhea, phototoxicity, neurotoxicity and *hemolysis in G-6-PD deficient patients*.

METHANAMINE MANDELATE

Methanamine *release formaldehyde at low pH* (below 5.5), which is the major compound having antibacterial activity. *Mandelate salt is used because it itself is urine acidifying agent*. This drug is *not effective against proteus* because it releases NH_3 and alkalinizes the urine. Insoluble complex forms between formaldehyde and sulfonamides, so methanamine *should not be used with sulfonamides*.

NALIDIXIC ACID

This is a **quinolone** drug and acts by *inhibiting DNA gyrase*. This too is not effective against *pseudomonas and proteus*. Resistance emerges rapidly and *main adverse effect is neurotoxicity*.

PHENAZOPYRIDINE

It is not a urinary antiseptic but possesses analgesic action and alleviates symptoms of dysuria, frequency, burning and urgency.

OTHER ANTIBACTERIAL DRUGS

These include daptomycin, mupirocin, polypeptide antibiotics, fusidic acid, teicoplanin and glycyclines.

DAPTOMYCIN

It is a **lipopeptide** bactericidal drug that acts by *causing depolarization of bacterial cell membranes* with K^+ efflux and rapid cell death. It is used for serious gram positive infections including *penicillin resistant pneumococci, MRSA and VRSA*. It is also **effective against organisms resistant to linezolid and streptogramins**. *Myopathy* is the dose limiting toxicity of this drug. **Pulmonary surfactant** *antagonizes daptomycin*, therefore, the latter should not be used to treat pneumonia.

MUPIROCIN (PSUDOMONIC ACID)

It acts on gram positive organisms by inhibiting protein synthesis due to binding with isoleucyl-tRNA. It is active against most gram positive cocci including MRSA (but not enterococci). It is *used topically* or nasally for eliminating staphylococcal nasal carriage.

POLYPEPTIDE ANTIBIOTICS

These include *polymyxin B, bacitracin, colistin and tyrothricin*. **All of these except bacitracin affect cell membrane**. Bacitracin inhibits cell wall synthesis. *Because of neurotoxicity and renal damage, these antibiotics are used only topically*.

FUSIDIC ACID

It acts by blocking protein synthesis and is used *topically* for staphylococcal infections.

IMPORTANT POINTS ABOUT ANTIMICROBIALS

1. MAJOR ROUTES OF DRUG ELIMINATION

Renal	Hepatic/Biliary	
Aminoglycosides	M	Metronidazole
Amphotericin B	E	Erythromycin
Beta lactams	T	Ceftriaxone
Quinolones	A	Azithromycin
Sulfonamides	B	noVObiocin
Tetracyclines	O	
	L	Linezolid
	I	Isoniazid
	S	Streptogramins
	M	Moxifloxacin
	Can	Clindamycin
	Prevent	Cefoperazone
	Dose	Doxycycline
	Adjustment	Ampicillin
	iN	Nafcillin
	Renal	Rifampicin
	Conditions	Chloramphenicol

2. DRUGS EFFECTIVE AGAINST ANAEROBIC ORGANISMS

• Clindamycin	• Cefotetan	• Moxifloxacin
• Cefmetazole	• Trovafloxacin	• Cefoxitin
• Metronidazole	• Chloramphenicol	• Vancomycin

Note: Aminoglycosides are not effective against anaerobic micro-organisms.

3. DRUGS EFFECTIVE AGAINST PSEUDOMONAS

Beta lactam antibiotics

- Carboxypenicillins (*Carbenicillin, ticarcillin*)
- Ureidopenicillin (*Piperacillin, azlocillin and mezlocillin*)
- Carbapenems (*Imipenem, doripenem, meropenem*)

- Monobactams (*Aztreonam*)
- Cephalosporins (*Ceftazidime, cefoperazone, moxalactam, cefepime, ceftipime*).

Fluoroquinolones

- Ciprofloxacin, Pefloxacin

Polypeptide Antibiotics

- Colistin, Polymixin B.

Aminoglycosides

Note:

- Vancomycin is not active against pseudomonas.
- Ceftazidime plus aminoglycoside is the treatment of choice for pseudomonas infections.

4. DRUGS EFFECTIVE AGAINST MRSA

• Vancomycin	• Teicoplanin	• Oritavancin	• Telavancin
• Dalbavancin	• Streptogramins	• Linezolid	• Daptomycin
• Cotrimoxazole	• Rifampicin	• Tetracyclines	

Note: No β -lactam is effective against MRSA except 5th generation cephalosporins.

5. ANTIMICROBIALS OF CHOICE FOR PROPHYLAXIS

(Ref. Katzung 12th/912)

Cholera:	Tetracycline
Rheumatic fever:	Benzathine penicillin
Tuberculosis:	Isoniazid alone or with rifampicin
Meningococcal meningitis:	Rifampicin/Ciprofloxacin/Ceftriaxone
Gonorrhoea / Syphilis:	Procaine Penicillin
Rickettsial infections:	Tetracyclines
Malaria:	Chloroquine/Mefloquine/Doxycycline
Influenza A and B	<i>Osetamivir</i>
Surgical prophylaxis:	Cefazolin
Anthrax	Ciprofloxacin/Doxycycline
Diphtheria	Penicillin/Erythromycin
Endocarditis	Amoxycillin/Clindamycin
Herpes Simplex	Acyclovir
Group B streptococcal infection	Ampicillin
Hemophilus influenza type B	Rifampicin
Mycobacterium avium complex (MAC)	Azithromycin/Clarithromycin/Rifabutin
Otitis media	Amoxicillin
Pertussis	Azithromycin
Plague	Tetracycline
Pneumocystis jiroveci	Cotrimoxazole/Dapsone/Atovaquone
Toxoplasmosis	Cotrimoxazole
Urinary tract infections	Cotrimoxazole

6. MOST IMPORTANT MECHANISM OF DRUG RESISTANCE

Beta lactams	Inactivating enzyme (beta lactamase)
Tetracyclines	Efflux pump (decreased concentration in the cell)
Chloramphenicol	Inactivating enzyme (acetyl transferase)
Aminoglycosides	Inactivating enzyme
Macrolides	Decreased permeability or efflux pumps
Sulfonamides	Form large amount of PABA
	Decreased activity of folate synthase
Fluoroquinolones	<i>Altered DNA gyrase</i> with reduced affinity

Note: Transfer of resistance against all antibiotics is plasmid mediated except fluoroquinolones (due to chromosomal mutation).

7. DRUGS OF CHOICE FOR SUSPECTED OR PROVED MICROBIAL PATHOGENS

(Ref. CMDT, 2015)

Organism	Drug of Choice
Gram-positive cocci	
Streptococcus	
• <i>S. pneumoniae</i>	• Penicillin G ¹
• Hemolytic, groups A, B, C, G	• Penicillin G ¹
• <i>S. viridans</i>	• Penicillin G ^{1, 2}
Staphylococcus	
• Non penicillinase producing	• Penicillin G ¹
• Penicillinase producing	• Penicillinase resistant penicillin (cloxa, oxa, naf or dicloxacillin)
• Methicillin resistant (MRSA)	• Vancomycin
• Coagulase negative	• Vancomycin
Enterococcus	
• faecalis	• Ampicillin ³
• faecium	• Vancomycin ³
Gram-positive bacilli	
• Actinomyces	• Penicillin G
• Bacillus	
- Anthracis	• Ciprofloxacin or Doxycycline
- Cereus and others	• Penicillin G
• Clostridium	• Penicillin G
• Corynebacterium	• Erythromycin ⁴
• Listeria	• Ampicillin ⁵
Gram-negative cocci	
• Neisseria	
- meningitidis	• Penicillin G
- gonorrhoeae	• Ceftriaxone + Azithromycin/Doxycycline
• Moraxella	• Fluoroquinolones
Gram-negative bacilli	
• Campylobacter	• Macrolides
• Legionella	• Macrolides
• Bordetella	• Macrolides
• Brucella	• Doxycycline + Rifampicin
• Acinetobacter	• Carbapenems
• Hemophilus	
- Serious infections like meningitis	• Ceftriaxone
- Respiratory infections, otitis	• Cotrimoxazole
- Ducreyi (chancroid)	• Azithromycin
• Prevotella	• Clindamycin
• Bacteroides	• Metronidazole
• Pseudomonas	• Anti-Pseudomonal β -lactam (piperacillin or ceftazidime or cefepime or imipenem) + Gentamicin

• Burkholderia	
- mallei (glanders)	• Streptomycin + Tetracycline
- pseudomallei (melioidosis)	• Ceftazidime
• Helicobacter pylori	• Clarithromycin + Amoxicillin + Proton pump inhibitor
• Enterobacteriaceae	
- Salmonella	• Ceftriaxone
- E. coli sepsis	• Ceftriaxone ⁶
- Klebsiella	• Ceftriaxone ⁷
- Proteus vulgaris	• Ceftriaxone ⁸
- Enterobacter	• Carbapenems
- Serratia	• Carbapenems
- Shigella	• Fluoroquinolones
- Yersinia	• Streptomycin + tetracycline
Spirochetes	
• Treponema	
- pallidum (syphilis)	• Penicillin G
- pertenue (yaws)	• Penicillin G
• Leptospira	• Penicillin G
• Borrelia	
- burgdorferi (Lyme's)	• Doxycycline
- recurrentis (Relapsing fever)	• Doxycycline
Chlamydiae	
• C. psittaci	• Doxycycline
• C. trachomatis	• Doxycycline
• C. pneumoniae	• Doxycycline
Rickettsiae	
• R. prowazekii (Epidemic typhus)	• Doxycycline
• R. typhi (Endemic typhus)	• Doxycycline
• Orientia tsutsugamushi (scrub typhus)	• Doxycycline
• R. rickettsii (Rocky mounted spotted fever)	• Doxycycline
• R. akari (Rickettsial pox)	• Doxycycline
• Rickettsia fever	• Doxycycline
• Ehrlichia	• Doxycycline
• Coxiella burnetii (Q fever)	• Doxycycline
Mycoplasma	• Azithromycin
Nocardia	• Cotrimoxazole

1. Oral penicillin V can be used for mild cases
2. Addition of gentamicin decreases the duration of treatment
3. Gentamicin is added for meningitis or endocarditis
4. For *C. jejuni*, vancomycin is drug of choice
5. Gentamicin is added for first few days
6. For UTI by *E. coli*, nitrofurantoin or fosfomycin are used
7. For ESBL producing strains, carbapenems are drug of choice
8. For *P. mirabilis*, ampicillin is drug of choice

8. EXAMPLES OF INITIAL ANTIMICROBIAL THERAPY FOR ACUTELY ILL, HOSPITALIZED ADULTS PENDING IDENTIFICATION OF CAUSATIVE ORGANISM *(Ref. CMDT 2014)*

Clinical Diagnosis	Empirical antimicrobial of choice
• Bacterial Meningitis	
- Age 18-50 years	• Vancomycin + ceftriaxone
- >50 years	• Vancomycin + ceftriaxone + ampicillin (to cover <i>Listeria</i>)
- Post-operative or post-traumatic	• Vancomycin + cefepime
• Brain Abscess	• Vancomycin + ceftriaxone + metronidazole
• Pneumonia	
- Community acquired	• Respiratory fluoroquinolone ^{1,2}
- Nosocomial	
*Low risk of MDR organisms	• Respiratory fluoroquinolone ¹
*High risk of MDR organisms	• [Ceftazidime + gentamicin] to cover <i>Pseudomonas</i> + Vancomycin for MRSA
• Endocarditis	• Vancomycin + gentamicin
• Septic thrombophlebitis	• Vancomycin + ceftriaxone
• Osteomyelitis	• Nafcillin ³
• Septic Arthritis	• Ceftriaxone
• Pyelonephritis	• Ceftriaxone
• Febrile neutropenia	• Ceftriaxone
• Intra-abdominal sepsis	• Ertapenem

1. Respiratory fluoroquinolones include levofloxacin, moxifloxacin and gemifloxacin.
2. Azithromycin plus ceftriaxone is also first line treatment.
3. Cefazolin can also be used as first line drug.

9. EXAMPLE OF EMPIRIC CHOICES OF ANTIMICROBIALS FOR ADULT OUTPATIENT INFECTIONS *(Ref. CMDT 2015)*

Clinical Diagnosis	Likely Etiologic Diagnosis
• Streptococcal skin infections	
- Erysipelas	Penicillin V
- Impetigo	
- Cellulitis	
- Lymphangitis	
• Staphylococcal skin infection	
- Furuncle	• Dicloxacillin
• Pharyngitis	• Penicillin V
• Otitis media	• Amoxicillin
• Malignant otitis externa	• Ciprofloxacin
• Acute sinusitis	• Amoxicillin
• Pneumonia	
- Aspiration	• Clindamycin
- Community acquired	• Doxycycline or azithromycin

Contd...

Contd...

Clinical Diagnosis	Likely Etiologic Diagnosis
• Urinary tract infections	
- Cystitis	• Nitrofurantoin or Fosfomycin
- Pyelonephritis	• Fluoroquinolone
• Gastroenteritis	
- <i>Salmonella</i>	• No treatment
- <i>Shigella</i>	• Ciprofloxacin
- <i>Campylobacter</i>	• Ciprofloxacin
- <i>Entamoeba</i>	• Metronidazole
• Urethritis or epididymitis	
- Gonococcal	• Ceftriaxone + Azithromycin
- Chlamydial	• Doxycycline
Pelvic inflammatory Disease (PID)	• Fluoroquinolone + Metronidazole
• Syphilis	
- Early (Primary, secondary, latent < 1 year)	• Benzathine Penicillin G once
- Latent > 1 year	• Benzathine Penicillin G × 3 weeks
- Cardiovascular	• Benzathine Penicillin G × 3 weeks
- Neurosyphilis	• Aqueous penicillin G × 10-14 days

MULTIPLE CHOICE QUESTIONS

GENERAL AND CLASSIFICATION

- Time dependent killing and prolonged post-antibiotic effect is seen with:** (AIIMS May 2013)
 - Fluoroquinolones
 - Beta-lactam antibiotics
 - Clindamycin
 - Erythromycin
- All of the following drugs are bactericidal except:** (AI 2012)
 - Isoniazid
 - Tigecycline
 - Daptomycin
 - Ciprofloxacin
- Drug resistance transmitting factor present in bacteria is:** (AI 2012)
 - Plasmid
 - Chromosome
 - Introns
 - Centromere
- True statement regarding development of drug resistance in MRSA is?** (AI 2011)
 - Results due to penicillinase enzyme production
 - Occurs due to change in penicillin binding proteins
 - Chromosome mediated
 - Treated with amoxicillin + clavulanic acid
- Enzyme inactivation is the main mode of resistance to:** (Delhi PG - 2011)
 - Aminoglycosides
 - Quinolones
 - Rifamycins
 - Glycopeptides
- Which of the following antibiotics acts by inhibiting cell wall synthesis?** (AIIMS May 2008)
 - Cefepime
 - Aminoglycosides
 - Erythromycin
 - Doxycycline
- Which antibiotic acts by inhibiting protein synthesis?** (AI-2008)
 - Cefotetan
 - Doxycycline
 - Ciprofloxacin
 - Oxacillin
- Which of the following drugs require dose adjustment in renal failure?** (AI-2008)
 - Cefoperazone
 - Doxycycline
 - Streptomycin
 - Rifampicin
- Antimicrobial agent acting by inhibition of cell wall synthesis is:** (AI 2007) (AIIMS Nov. 2006)
 - Erythromycin
 - Tetracycline
 - Lomefloxacin
 - Cefepime
- All of the following antibacterial agents act by inhibiting cell wall synthesis EXCEPT:** (AI 2006)
 - Carbapenems
 - Monobactams
 - Cephalosporins
 - Nitrofurantoin
- A post operative patient developed septicemia and was empirically started on combination chemotherapy by a new resident doctor. However, when the patient did not respond even after 10 days of antibiotics treatment, the review of the charts was done. It was found that the resident doctor had started the combination of antibiotics which was mutually antagonistic in action. Which of the following is the most likely combination that was given?** (AI 2004)
 - Vancomycin and Amikacin
 - Cephalexin and Gentamicin
 - Ampicillin and Chloramphenicol
 - Ciprofloxacin and Piperacillin
- All of the following drugs act on cell membrane EXCEPT:** (AI 2003)
 - Nystatin
 - Griseofulvin
 - Amphotericin B
 - Polymyxin B
- Bacitracin acts on:** (AI 2003)
 - Cell wall
 - Cell membrane
 - Nucleic acid
 - Ribosome
- Which of the following drugs combination shows antimicrobial synergism?** (PGI June, 2005)
 - Penicillin + Streptomycin in SABE
 - Ampicillin + Tetracycline in endocarditis
 - Sulfamethoxazole + Trimethoprim in UTI
 - Amphotericin B + Flucytosine in cryptococcal meningitis
- All of the following antibiotics act by interfering with cell wall formation EXCEPT:**
 - Ceftriaxone
 - Vancomycin
 - Cycloserine
 - Clindamycin

16. The persistent suppression of bacterial growth that may occur after limited exposure to some antimicrobial drug is called:
 (a) Time dependent killing
 (b) Post antibiotic effect
 (c) Concentration dependent killing
 (d) Sequential blockade
17. Which of the following is not an established antimicrobial drug synergism at clinical level?
 (a) Amphotericin B and flucytosine in cryptococcal meningitis
 (b) Carbenicillin and gentamicin in pseudomonal infections
 (c) Penicillin and tetracycline in bacterial meningitis
 (d) Trimethoprim and sulfamethoxazole in coliform infections
18. Which of the following drugs is NOT excreted in bile:
 (a) Erythromycin
 (b) Ampicillin
 (c) Rifampicin
 (d) Gentamicin
19. Multiple drug resistance is transferred through:
 (a) Transduction (DPG 2008)
 (b) Transformation
 (c) Conjugation
 (d) Mutation
20. Most common mechanism for transfer of resistance in *Staphylococcus aureus* is:
 (a) Conjugation (DPG 2009, DPG 2007)
 (b) Transduction
 (c) Transformation
 (d) Mutation
21. Elaboration of inactivating enzymes are the important mechanism of drug resistance among all of these antibiotics EXCEPT:
 (a) Quinolones (DPG 2000, DPG 2007)
 (b) Penicillin
 (c) Chloramphenicol
 (d) Aminoglycosides
22. Pneumococcal resistance to penicillin G is mainly acquired by:
 (a) Conjugation (DPG 2006)
 (b) Transduction
 (c) Transformation
 (d) All of the above
23. A bactericidal drug would be preferred over a bacteriostatic drug in a patient with:
 (a) Neutropenia (DPG 2005)
 (b) Cirrhosis
 (c) Pneumonia
 (d) Heart disease
24. Which of the following antibiotic acts by inhibiting cell wall synthesis?
 (a) Chloramphenicol (DPG 2002)
 (b) Gentamicin
 (c) Erythromycin
 (d) Penicillin
25. Which of the following drugs acts by inhibiting cell wall synthesis?
 (a) Erythromycin (DPG 1997)
 (b) Cephalosporins
 (c) Chloramphenicol
 (d) Sulfonamides
26. In *Staphylococci*, plasmids encoding beta-lactamase are transmitted by:
 (a) Conjugation (MPPG 2007)
 (b) Transduction
 (c) Transposon
 (d) Transformation
27. Which of the following drug is bactericidal?
 (a) Sulfonamides (UIP 2006)
 (b) Erythromycin
 (c) Chloramphenicol
 (d) Cotrimoxazole
28. Superinfection is common in:
 (a) Narrow spectrum antibiotics (UIP 2006)
 (b) Immunocompromised host
 (c) Low spectrum antibiotics
 (d) Nutritional deficiency
29. Which of the following is a broad spectrum antibiotic?
 (a) Erythromycin (RJ 2005)
 (b) Streptomycin
 (c) Tetracycline
 (d) All
30. Which of the following antibiotic does not act by inhibiting protein synthesis?
 (a) Vancomycin (MH 2005)
 (b) Tetracycline
 (c) Streptomycin
 (d) Azithromycin

CELL WALL SYNTHESIS INHIBITORS

31. Which of the following antimicrobial is effective against an organism producing extended spectrum beta lactamase?
 (a) Amoxicillin-Clavulanic acid (AIIMS Nov 2012)
 (b) Cefepime
 (c) Piperacillin-Tazobactam
 (d) Ceftriaxone
32. Which of the following statement about Penicillin G is true?
 (a) It is commonly administered orally (AIIMS Nov 2012)
 (b) It has a broad spectrum of antibacterial activity
 (c) It can be used for the treatment rate bite fever
 (d) Concomitant probenecid decreases its duration of action

33. Which of the following statement is false about extended spectrum beta-lactamases (ESBL)? (AIIMS May 2011)
- These can hydrolyze penicillins, cephalosporins as well as monobactams
 - Carbapenems are sensitive to ESBL
 - Amber classification of ESBL is based on structural differences
 - Third and fourth generation cephalosporins are used for detection of ESBL.
34. Which of the following beta-lactam antibiotics can be safely used in a patient with a history of allergy to penicillins? (Delhi PG 2011)
- Aztreonam
 - Cefepime
 - Loracarbef
 - Ceftriaxone
35. All of the following statements about penicillin binding proteins are true EXCEPT: (AI 2010)
- Present on cell surface
 - Mutation in PBPs gives rise to resistance
 - These are target site of vancomycin
 - These are targeted by imipenem
36. All are true about cephalosporins, EXCEPT: (AIIMS May 2009)
- Ceftazidime is a 3rd generation cephalosporin.
 - Cefoperazone has got antipseudomonal effect.
 - Cefoxitin has got no activity against anaerobes.
 - Cephalosporins act by inhibiting cell wall synthesis.
37. Cephalosporin that does not require dose reduction in patient with any degree of renal impairment is: (AI 2009, AIIMS Nov 2008)
- Cefuroxime
 - Cefoperazone
 - Ceftazidime
 - Cefotaxime
38. Extended spectrum beta lactamases (ESBLs) are characterized by activity against all except: (DPG 2009)
- Penicillinases
 - Cephalosporinases
 - Oxymino-cephalosporinases
 - Carbapenems
39. All of the following statements about penicillin G are true EXCEPT: (AI-2008)
- It is actively secreted in tubules
 - It is never administered orally
 - It is effective against gram positive as well as some gram negative bacteria
 - It acts by inhibiting cell wall synthesis
40. All of the following are the therapeutic uses of penicillin G EXCEPT: (AI 2006)
- Bacterial meningitis
 - Rickettsial infection
 - Syphilis
 - Anthrax
41. Which one of the following drugs is an antipseudomonal penicillin? (AI 2006)
- Cephalexin
 - Cloxacillin
 - Piperacillin
 - Dicloxacillin
42. One of the following is not penicillinase susceptible? (AI 2005)
- Amoxicillin
 - Penicillin G
 - Piperacillin
 - Cloxacillin
43. Which of the following antimicrobials has antipseudomonal action? (AI 2004)
- Cefpodoxime proxetil
 - Cephadrine
 - Cefotetan
 - Cefoperazone
44. Which of the following is a fourth generation cephalosporin? (AIIMS May, 2004)
- Ceftriaxone
 - Cefaclor
 - Cefepime
 - Cefuroxime
45. All of the following cephalosporins have good activity against *Pseudomonas aeruginosa* EXCEPT: (AIIMS May, 2003)
- Cephadroxil
 - Cefepime
 - Cefoperazone
 - Ceftazidime
46. Which of the following statements are true regarding cefepime: (PGI Dec. 2001)
- It is a fourth generation cephalosporin
 - Once a day dose is sufficient
 - It possess antipseudomonal action
 - Its dose should not be reduced in renal pathology
 - It is a prodrug
47. Which of the following statements about the biodisposition of penicillins and cephalosporins is NOT accurate?
- Oral bioavailability is affected by lability to gastric acid
 - Procaine penicillin G is used via intramuscular injection
 - Renal tubular reabsorption of beta-lactams is inhibited by probenecid
 - Nafcillin and ceftriaxone are eliminated mainly via biliary secretion
48. The mechanism of antibacterial action of cephalosporins involves:
- Inhibition of the synthesis of precursors of peptidoglycan
 - Interference with the synthesis of ergosterol
 - Inhibition of transpeptidation reaction
 - Inhibition of beta-lactamase

49. Which of the following statements about imipenem is most accurate?
- The drug has a narrow spectrum of antibacterial action
 - It is used in fixed dose combination with sulbactam
 - In renal dysfunction, dosage reductions are necessary to avoid seizures
 - Imipenem is active against methicillin-resistant staphylococci
50. Methicillin resistant staphylococci do not respond to β -lactam antibiotics because:
- They produce a β -lactamase which destroys methicillin and related drugs
 - They elaborate an amidase which destroys methicillin and related drugs
 - They have acquired penicillin binding protein which has low affinity for β -lactam antibiotics
 - They are less permeable to β -lactam antibiotics
51. The penicillin G preparation with the longest duration of action is:
- Benzathine penicillin
 - Sodium penicillin
 - Potassium penicillin
 - Procaine penicillin
52. Amoxicillin + clavulanic acid is active against the following organisms EXCEPT:
- Methicillin resistant *Staph. aureus*
 - Penicillinase producing *Staph. aureus*
 - Penicillinase producing *N. gonorrhoea*
 - β -lactamase producing *E. coli*
53. The following is true of vancomycin EXCEPT:
- It is a bactericidal antibiotic active primarily against gram positive bacteria
 - It acts by inhibiting bacterial protein synthesis
 - It is an alternative to penicillin for enterococcal endocarditis
 - It can cause deafness as a dose related toxicity
54. TRUE statement regarding vancomycin is:
- It is bacteriostatic
 - It has the advantage of high oral bioavailability
 - It is not susceptible to penicillinases
 - Staphylococcal enterocolitis occurs commonly with its use
55. This drug has activity against many strains of *P. aeruginosa*. However, when it is used alone, resistance has emerged during the course of treatment. The drug should not be used in penicillin-allergic patients. Its activity against gram-negative rods is enhanced if it is given in combination with tazobactam. Which of the following drugs is being described?
- Amoxicillin
 - Aztreonam
 - Piperacillin
 - Vancomycin
56. A 36 years old woman recently treated for leukemia is admitted to the hospital with malaise, chills and high fever. Gram stain of blood reveals the presence of gram negative bacilli. The initial diagnosis is bacteremia and parenteral antibiotics are indicated. The record of the patient reveals that she had severe urticarial rash, hypotension and respiratory difficulty after oral penicillin V about 6 months ago. The most appropriate drug should be:
- Ampicillin plus sulbactam
 - Aztreonam
 - Cefazolin
 - Imipenem plus cilastatin
57. Not true about cefepime is: (DPG 2004)
- 4th generation cephalosporin
 - Useful in hospital acquired infection
 - Inhibits transpeptidase
 - Given twice daily orally
58. Antipseudomonas are all, EXCEPT: (DPG 2003)
- Cephalexin
 - Carbenicillin
 - Piperacillin
 - Ceftazidime
59. Cilastatin is given along with: (DPG 1999)
- Imipenem
 - Amoxicillin
 - Erythromycin
 - Ampicillin
60. Which of the following cephalosporins is active against *Pseudomonas aeruginosa*? (DPG 1997)
- Ceftriaxone
 - Cephalothin
 - Ceftazidime
 - Cefotaxime
61. Which of the following is NOT true about penicillins? (DPG 1997)
- Penicillin V is absorbed orally
 - Benzathine penicillin is short acting penicillin
 - Cloxacillin is β -lactamase and acid resistant
 - Ampicillin is not resistant to β -lactamases
62. Mechanism of action of vancomycin is: (MPPG 2003) (UP 2007)
- Inhibition of cell wall synthesis
 - Inhibition of protein synthesis
 - Leakage from cell membrane
 - Inhibition of DNA gyrase
63. Carbenicillin: (MPPG 2002)
- Is effective in pseudomonas infection
 - Has no effect in *Proteus* infection
 - Is a macrolide antibiotic
 - Is administered orally

64. A potent inhibitor of beta-lactamase is: (MPPG 2002)
 (a) Carbenicillin
 (b) Clavulanic acid
 (c) Cefamandole
 (d) Idoxuridine
65. All are true about cefuroxime Except: (UP 2008)
 (a) Inhibit cell wall synthesis
 (b) Third generation cephalosporin
 (c) Some acquired resistance with penicillin
 (d) More active against gram negative organisms
66. Amoxycillin is better than ampicillin due to:
 (a) Better bioavailability if taken with food
 (b) Lesser bioavailability if taken with food
 (c) Incidence of diarrhea is higher (UP 2008)
 (d) More active against Shigella and H. influenza
67. Mechanism of action of penicillins and cephalosporins is to inhibit: (UP 2005)
 (a) Cell wall synthesis
 (b) Leakage from cell membrane
 (c) Protein synthesis
 (d) DNA gyrase
68. The following organisms are known to develop resistance to Penicillin except: (AP 1979) (TN 2000)
 (a) Staphylococcus
 (b) Streptococcus
 (c) Pneumococcus
 (d) Treponema
69. Ceftriaxone is: (TN 2005)
 (a) IInd generation short acting cephalosporin
 (b) Has activity against beta lactamase producing bacteria
 (c) IVth generation long acting cephalosporin
 (d) IIIrd generation long acting cephalosporin
70. Acid susceptible penicillin is: (RJ 2003)
 (a) Methicillin
 (b) Ampicillin
 (c) Amoxicillin
 (d) Cloxacillin
71. All are first generation cephalosporins except: (RJ 2003)
 (a) Cefadroxil
 (b) Cefazolin
 (c) Cephalexin
 (d) Cefaclor
72. Which is not a beta lactum antibiotic? (RJ 2008)
 (a) Penicillin
 (b) Carbapenem
 (c) Monobactam
 (d) Azithromycin
73. Second generation cephalosporin that can be used orally is: (MH 2003)
 (a) Cefepime
 (b) Cefalothin
 (c) Cefaclor
 (d) Cefadroxil
74. Third generation cephalosporin that can be given orally is: (MH 2003)(MH 2006)
 (a) Cefixime
 (b) Cefpirome
 (c) Cefaclor
 (d) Cefadroxil
75. Ampicillin is not given in EB virus infection due to: (Bihar 2003)
 (a) Due to increased toxicity
 (b) Skin rash
 (c) Blindness
 (d) Convulsions
76. Which among the following is not a beta lactamase inhibitor? (Jharkhand 2006)
 (a) Sulbactam
 (b) Calvulanic acid
 (c) Piperacillin
 (d) None
77. Oral cephalosporin among these is: (AP 2003)
 (a) Cefatoxime
 (b) Ceftriaxone
 (c) Cefaclor
 (d) Ceftazidime
78. Beta lactam antibiotics act by inhibiting (AP 2004)
 (a) Cell wall synthesis
 (b) Protein synthesis
 (c) RNA synthesis
 (d) DNA synthesis
79. Which one of the following is a fourth generation cephalosporin? (MP 2008)
 (a) Cefuroxime
 (b) Ceftazidime
 (c) Cefepime
 (d) Cefamandole
80. Neutropenia is associated with: (Kolkata 2009)
 (a) Nafcillin
 (b) Methicillin
 (c) Carbencillin
 (d) Ampicillin
81. Third-generation cephalosporins include all of the following EXCEPT: (Karnataka 2007)
 (a) Ceftizoxime
 (b) Cefoperazone
 (c) Cefoxitin
 (d) Cefixime
82. Which one of the following statement about imipenem is most accurate? (Karnataka 2005)
 (a) The drug has a narrow spectrum of anti-bacterial action
 (b) It is used in fixed combination with sulbactam
 (c) Imipenem is highly susceptible to beta lactamase produced by enterobacteriaceae
 (d) In renal dysfunction, dosage reduction are necessary to avoid seizures

83. Which of the following is fourth generation cephalosporin? *(Karnataka 2002)*

- (a) Cefamandole
- (b) Cefpirome
- (c) Cephalexin
- (d) Cefuroxime

PROTEIN SYNTHESIS INHIBITORS

84. Which of the following mechanism is mainly responsible for gentamicin induced ototoxicity? *(AIIMS Nov 2012)*

- (a) Direct hair cell toxicity
- (b) Binding to and inhibition of hair cell $\text{Na}^+ \text{K}^+$ ATPase
- (c) Non-cumulative toxicity
- (d) Bind to Ca^{2+} channels

85. Tetracycline is used for the prophylaxis of? *(AI 2011)*

- (a) Cholera
- (b) Brucellosis
- (c) Leptospirosis
- (d) Meningitis

86. Which of the following should be monitored if linezolid is given for more than 14 days? *(AI 2010)*

- (a) Liver function tests
- (b) Kidney function test
- (c) Platelet count
- (d) Audiometry

87. Erythromycin is given in intestinal hypomotility because: *(AIIMS Nov 2009)*

- (a) It increases bacterial count
- (b) It decreases bacterial count
- (c) It binds to adenyl cyclase
- (d) It binds to motilin receptors

88. True about aminoglycosides is all EXCEPT: *(AIIMS May 2008)*

- (a) Are bacteriostatic
- (b) Distributed only extracellularly
- (c) Excreted unchanged in urine
- (d) Teratogenic

89. Which of the following is not true regarding tetracycline? *(AI-2008)*

- (a) It is not teratogenic
- (b) It can cause tooth discoloration
- (c) It can result in superinfection
- (d) It can lead to pseudomembranous colitis

90. The group of antibiotics that possesses additional anti-inflammatory and immunomodulatory activities is: *(AI 2005)*

- (a) Tetracyclines
- (b) Polypeptide antibiotics
- (c) Fluoroquinolones
- (d) Macrolides

91. All of the following are risk factors for renal toxicity caused by aminoglycosides EXCEPT: *(AI 2002)*

- (a) Elderly patient
- (b) Hypokalemia
- (c) Simultaneous use of penicillin
- (d) Aminoglycoside administration in recent past

92. Tetracyclines inhibit protein synthesis by: *(AI 2001, AIIMS Nov, 2005)*

- (a) Inhibition of initiation and misreading of mRNA
- (b) Binding to 30 S subunit and inhibiting the binding of aminoacyl-tRNA to A site
- (c) Inhibiting peptidyl transferase activity
- (d) Inhibiting translocation

93. The antibiotic that inhibits protein synthesis by premature termination and which structurally resembles amino acyl t-RNA is:

- (a) Tetracycline *(DPG 2009) (AIIMS Nov, 2002)*
- (b) Chloramphenicol
- (c) Puromycin
- (d) Erythromycin

94. Ototoxicity of aminoglycoside is increased with concurrent use of which of the following drug (s): *(PGI Dec. 2004)*

- (a) Cisplatin
- (b) Furosemide
- (c) Vancomycin
- (d) Vincristine
- (e) Erythromycin

95. Which one of the following statements about doxycycline is FALSE?

- (a) It is bacteriostatic
- (b) It is excreted mainly in the feces
- (c) It is more active than tetracycline against *H. pylori*
- (d) It is used in Lyme's disease

96. Concerning streptogramins, which one of the following statements is FALSE?

- (a) They are active against methicillin-resistant staphylococci
- (b) They may cause a syndrome of arthralgia and myalgia
- (c) They induce formation of hepatic drug metabolizing enzymes
- (d) They are used in the management of infections caused by vancomycin-resistant enterococci

97. Which of the following statements about the clinical uses of the aminoglycosides is FALSE?

- (a) Owing to their polar nature, aminoglycosides are not absorbed following oral administration
- (b) Aminoglycosides are often used in combination with cephalosporins in the empirical treatment of life-threatening bacterial infections
- (c) The spectrum of antimicrobial activity of aminoglycosides includes *Bacteroides fragilis*
- (d) Gentamicin is used with ampicillin for synergistic effects in the treatment of enterococcal endocarditis

98. Regarding the antibacterial action of gentamicin, which of the following statements is most accurate?
- Efficacy is directly proportionate to the time that the plasma level of the drug is greater than the minimal inhibitory concentration
 - Gentamicin continues to exert antibacterial effects even after plasma levels decrease below detectable range
 - Antibacterial activity is often reduced by the presence of an inhibitor of cell wall synthesis
 - The antibacterial action of gentamicin is time dependent
99. The following tetracycline has the potential to cause vestibular toxicity:
- Minocycline
 - Demeclocycline
 - Doxycycline
 - Tetracycline
100. The most suitable tetracycline for use in a patient with impaired renal function is:
- Tetracycline
 - Demeclocycline
 - Oxytetracycline
 - Doxycycline
101. The most important mechanism by which gram negative bacilli acquire chloramphenicol resistance is:
- Decreased permeability into the bacterial cell
 - Acquisition of a plasmid encoded for chloramphenicol acetyl transferase
 - Lowered affinity of the bacterial ribosome for chloramphenicol
 - Switching over from ribosomal to mitochondrial protein synthesis
102. Bactericidal inhibitors of protein synthesis are:
- Tetracyclines
 - Aminoglycosides
 - Macrolides
 - Lincosamides
103. Hepatitis with cholestatic jaundice occurs most frequently as an adverse reaction to the following preparation of erythromycin:
- Erythromycin base
 - Erythromycin stearate
 - Erythromycin estolate
 - Erythromycin ethyl succinate
104. The tetracycline with highest antileprotic activity is:
- Minocycline
 - Doxycycline
 - Demeclocycline
 - Oxytetracycline
105. Which of the following drugs is most effective against an organism producing aminoglycoside inactivating enzymes?
- Amikacin
 - Streptomycin
 - Gentamicin
 - Tobramycin
106. The mechanism of action of tetracyclines involves:
- Binding of a component of the 50S ribosomal subunits
 - Inhibition of translocase activity
 - Blockade of binding of aminoacyl-tRNA to bacterial ribosomes
 - Selective inhibition of ribosomal peptidyl transferase
107. This inhibitor of bacterial protein synthesis has a narrow spectrum of antibacterial activity. It has been used in the management of abdominal abscess caused by *Bacteroides fragilis*, but antibiotic associated colitis has occurred. Which of the following drugs is being described?
- Clarithromycin
 - Clindamycin
 - Minocycline
 - Ticarcillin
108. Which of the following drugs act by inhibiting bacterial protein synthesis? (DPG 2000)
- Bacitracin
 - Dapsone
 - Ethambutol
 - Streptomycin
109. Tetracyclines are not useful for: (TN 2007)
- Trichomonas
 - Chlamydia
 - Syphilis
 - Rickettsia
110. The following drug interferes with translocation of protein synthesis: (TN 2003)
- Erythromycin
 - Tetracycline
 - Chloramphenicol
 - Penicillins
111. Chloramphenicol act through action on: (RJ 2001)
- 50S ribosome
 - 30S ribosome
 - Nucleus
 - Mitochondria
112. Tetracyclines can be given in all forms except: (RJ 2004)
- Oral
 - Intravenous
 - Topical in eye
 - Topical in open wound
113. All are aminoglycosides except: (RJ 2009)
- Netilmicin
 - Streptomycin
 - Kanamycin
 - Azithromycin

- 114. Which of the following aminoglycosides has highest nephrotoxicity?** (MH 2003)
 (a) Paramomycin
 (b) Streptomycin
 (c) Amikacin
 (d) Neomycin
- 115. Auditory toxicity is maximum with:** (MH 2005)
 (a) Streptomycin
 (b) Kanamycin
 (c) Tobramycin
 (d) Amikacin
- 116. Erythromycin acts by interfering with:** (MH 2007)
 (a) Translocation of 50S ribosome
 (b) Translocation of 50S ribosome
 (c) Transcription of 50 S ribosome
 (d) Signal transduction of 50 S ribosome
- 117. Single dose aminoglycoside administration is more preferable than 8 hourly dose because of:** (Bihar 2004)
 (a) MIC
 (b) Increase perfusion of renal cortex
 (c) Post antibiotic effect
 (d) None
- 118. Linezolid is best used for:** (Bihar 2005)
 (a) MRSA
 (b) VRSA
 (c) K.pneumoniae
 (d) E.coli
- 119. Doxycycline is used in the treatment of following diseases EXCEPT:** (Karnataka 2008)
 (a) Leptospirosis
 (b) Q fever
 (c) Borreliosis
 (d) All of the above
- ANTIMETABOLITES, FLOUROQUINOLONES AND MISCELLANEOUS ANTIMICROBIALS**
- 120. Fluoroquinolone having longest half-life is:** (AI 2012)
 (a) Levofloxacin
 (b) Lomefloxacin
 (c) Ciprofloxacin
 (d) Moxifloxacin
- 121. Cotrimoxazole can be used for the treatment of all of the following except:** (AIIMS May 2011)
 (a) Chancroid
 (b) Lower urinary tract infections
 (c) Prostatitis
 (d) Typhoid
- 122. A girl on sulphonamides developed abdominal pain and presented to emergency with seizure. What is the probable cause?** (AIIMS Nov 2008)
 (a) Acute intermittent porphyria
 (b) Congenital erythropoietic porphyria
 (c) Infectious mononucleosis
 (d) Kawasaki's disease
- 123. Folic acid metabolism is inhibited by:** (PGI June, 2003)
 (a) Sulfonamides
 (b) Methotrexate
 (c) Nitrous oxide
 (d) Trimethoprim
 (e) 5-Flucytosine
- 124. Which of the following blocks replication without getting involved in the DNA strand?** (PGI Dec. 2007)
 (a) Cytarabine
 (b) Nalidixic acid
 (c) Ciprofloxacin
 (d) 5-Fluorouracil
 (e) 6-Mercaptopurine
- 125. In unconjugated hyperbilirubinemia the risk of kernicterus increases with the use of:** (AI 2005)
 (a) Ceftriaxone
 (b) Phenobarbitone
 (c) Ampicillin
 (d) Sulfonamide
- 126. All of the following are topically used sulfonamides EXCEPT:** (AI 2005)
 (a) Sulfacetamide
 (b) Sulfasalazine
 (c) Silver sulfadiazine
 (d) Mafenide
- 127. Which of the following statements is NOT true regarding sulfonamides?** (AI 2004)
 (a) Sulfasalazine is absorbed well from GIT
 (b) Crystalluria can occur with sulfonamide administration
 (c) Sulfonamide administration to newborn may cause kernicterus
 (d) Sulfonamides are of value in treatment of infections due to *Nocardia* species.
- 128. Which of the following fluoroquinolones does not require dose adjustment in a patient with creatinine clearance of < 50 mg/min?** (AI 2004)
 (a) Ciprofloxacin
 (b) Trovafloxacin
 (c) Lomefloxacin
 (d) Sparfloxacin
- 129. Sparfloxacin and astemizole can cause:** (AIIMS Nov, 2003)
 (a) Ventricular arrhythmia
 (b) Myopathy
 (c) Electrolyte imbalance
 (d) Nephropathy

- 130. Which of the following statements about sulfonamides is FALSE?**
- Sulfonamides inhibit bacterial dihydrofolate reductase
 - Dysfunction of the basal ganglia may occur in the newborn if sulfonamides are administered late in pregnancy
 - Sulfonamide crystalluria is most likely to occur at low urinary pH
 - Sulfonamides are antimetabolites
- 131. Which of the following statements about the fluoroquinolones is FALSE?**
- Gonococcal resistance to fluoroquinolones may involve changes in DNA gyrase
 - Modification of fluoroquinolones dosage is required in patients if creatinine clearance is less than 50 mL/min
 - A fluoroquinolone is the drug of choice for treatment of an uncomplicated urinary tract infection in a 7 year-old girl
 - Fluoroquinolones inhibit relaxation of positively supercoiled DNA
- 132. Which of the following adverse effects is most likely to occur with sulfonamides?**
- Neurologic effects including headache, dizziness, and lethargy
 - Hematuria
 - Fanconi's anemia
 - Skin reactions
- 133. Which fluoroquinolone is highly active against *Mycobacterium leprae* and is being used in alternative multidrug therapy regimens:**
- Norfloxacin
 - Ofloxacin
 - Ciprofloxacin
 - Lomefloxacin
- 134. Maximum incidence of phototoxicity is associated with:**
- Norfloxacin
 - Sparfloxacin
 - Lomefloxacin
 - Cotrimoxazole
- 135. Methanamine salts are used as urinary antiseptics. The reason they lack systemic antibacterial action is that they are:**
- Not absorbed into systemic circulation after oral use
 - Rapidly metabolized by liver drug metabolizing enzymes
 - Converted to formaldehyde at low urinary pH
 - Substrates for active tubular secretion
- 136. A contraindication to the use of ciprofloxacin is a history of:**
- Epilepsy
 - Deep vein thrombosis
 - Gout
 - G-6 PD deficiency
- 137. The combination of trimethoprim and sulfamethoxazole is effective against which of the following opportunistic infections in the AIDS patient?**
- Disseminated *Herpes simplex*
 - Cryptococcal meningitis
 - Pneumocystis jiroveci*
 - Tuberculosis
- 138. Ciprofloxacin should not be given to an asthmatic using theophylline because:** (DPG 2003)
- Ciprofloxacin inhibit theophylline metabolism
 - Theophylline inhibits ciprofloxacin metabolism
 - Ciprofloxacin decreases effect of theophylline
 - Theophylline induces metabolism of ciprofloxacin
- 139. Mechanism of action of fluoroquinolones is:** (UP 2005 (DPG 2000))
- Inhibits cell wall synthesis
 - Inhibits protein synthesis
 - Inhibits DNA gyrase
 - Interferes with intermediary metabolism
- 140. Eye drops of which sulphonamide is used clinically?** (MH 2000)
- Sulfacetamide
 - Sulfamethoxazole
 - Sulfinpyrazone
 - All
- 141. Which is of the following can be used safely in renal failure?** (Kolkata 2005)
- Ciprofloxacin
 - Ofloxacin
 - Lomefloxacin
 - Pefloxacin

CLINICAL USES OF ANTIMICROBIALS

- 142. Drug-induced colitis is most frequently associated with:** (AIIMS May 2012)
- Neomycin
 - Vancomycin
 - Clindamycin
 - Chloramphenicol
- 143. A 26 year old patient presents with suspected pneumococcal meningitis. CSF culture is sent for antibiotic sensitivity. Which empirical antibiotic should be given till culture sensitivity result come?** (AIIMS May 2012)
- Penicillin G
 - Ceftriaxone + metronidazole
 - Doxycycline
 - Cefotaxime + vancomycin
- 144. A patient develops an infection of methicillin resistant *Staphylococcus aureus*. All of the following can be used to treat this infection except:** (AI 2012) (AIIMS Nov. 2011)
- Cotrimoxazole
 - Cefaclor
 - Ciprofloxacin
 - Vancomycin

145. Drug of choice for syphilis in a pregnant lady is: (AI 2012)
 (a) Penicillin
 (b) Azithromycin
 (c) Tetracycline
 (d) Ceftriaxone
146. A patient diagnosed as having ventilator associated pneumonia, is on treatment with ceftriaxone and amikacin. Culture and sensitivity turned out to be positive for ESBL producing *Klebsiella* infection. The most appropriate next action should be: (AIIMS Nov 2010)
 (a) Continue same antibiotic but at higher dose
 (b) Replace ceftazidime for ceftriaxone
 (c) Remove amikacin and add quinolone
 (d) Change over to imipenem.
147. Which of the following antibiotic is used in the treatment of *Clostridium difficile* associated diarrhea? (Delhi PG - 2011)
 (a) Ciprofloxacin
 (b) Metronidazole
 (c) Piperacillin
 (d) Clindamycin
148. Which of the following drug should not be used to treat *Klebsiella* infection? (Delhi PG - 2011)
 (a) Ampicillin
 (b) Amikacin
 (c) Imipenem
 (d) Tigecycline
149. Drug of choice for chlamydial infection in pregnancy is: (AI 2010)
 (a) Doxycycline
 (b) Tetracycline
 (c) Erythromycin
 (d) Ciprofloxacin
150. Which of the following drugs is effective against *Pseudomonas* infection? (DPG 2009)
 (a) Ampicillin
 (b) Ceftriaxone
 (c) Colistin
 (d) Cefixime
151. Drug of choice for treatment of infection caused by methicillin resistant *Staphylococcus aureus* is: (DPG 2009)
 (a) Macrolides
 (b) Third generation cephalosporins
 (c) Carbapenems
 (d) Glycopeptides
152. Methicillin resistant *Staphylococcus aureus* is not expected to respond to: (DPG 2009)
 (a) Aminoglycoside
 (b) Lincosamide
 (c) Oxazolidinone
 (d) Carbapenem
153. Fixed drug eruptions can be seen more frequently with: (DPG 2009)
 (a) Penicillin
 (b) Sulfonamide
 (c) Cetrizine
 (d) Roxithromycin
154. Which of the following penicillins is effective against *pseudomonas*? (AI-2008)
 (a) Piperacillin
 (b) Amoxycillin
 (c) Ampicillin
 (d) Oxacillin
155. Drug of choice for prophylaxis of diphtheria is: (AI-2008)
 (a) Tetracycline
 (b) Erythromycin
 (c) Ciprofloxacin
 (d) Amikacin
156. Which of the following is least nephrotoxic? (AI-2008)
 (a) Streptomycin
 (b) Gentamicin
 (c) Polymixin B
 (d) Doxycycline
157. Drug commonly used against enteric fever are all EXCEPT: (AI 2008)
 (a) Amikacin
 (b) Ciprofloxacin
 (c) Ceftriaxone
 (d) Azithromycin
158. Which of the following is an antipseudomonal antibiotic? (AI 2007)
 (a) Ciprofloxacin
 (b) Vancomycin
 (c) Cefaclor
 (d) Tetracycline
159. Which of the following drugs is not used for MRSA? (AIIMS May 2007, AI 2007)
 (a) Cefaclor
 (b) Cotrimoxazole
 (c) Ciprofloxacin
 (d) Vancomycin
160. Which of the following medications is contraindicated in patients with allergy to sulfonamides? (AI 2006)
 (a) Levobunolol
 (b) Bimatoprost
 (c) Brinzolamide
 (d) Brimonidine
161. A diabetic patient develops cellulitis due to *Staphylococcus aureus* that was found to be methicillin resistant on the antibiotic sensitivity testing. All of the following antibiotics will be appropriate EXCEPT: (AI 2006)
 (a) Vancomycin
 (b) Imipenem
 (c) Teicoplanin
 (d) Linezolid

162. All of the following drugs can cause renal failure EXCEPT: (AI 2002)
- Cephaloridine
 - Amphotericin B
 - Cefoperazone
 - Gentamicin
163. The treatment of contacts of meningococcal meningitis is by: (AI 2000)
- Rifampicin
 - Erythromycin
 - Penicillin
 - Cephalosporin
164. Which of the following is not an anti-pseudomonal agent? (AI 2000) (Jharkhand 2006)
- Vancomycin
 - Ticarcillin
 - Ceftazidime
 - Tobramycin
165. A patient has hepatic encephalopathy. The drug of choice for gut sterilization in this patient is: (AI 2000)
- Neomycin
 - Netilmicin
 - Bleomycin
 - None of the above
166. Which of the following drug causes pseudotumor cerebri? (AIIMS May, 2004)
- Sparfloxacin
 - Tetracycline
 - Gentamicin
 - Clofazimine
167. In a chronic alcoholic patient all of the following drugs should be avoided EXCEPT: (AIIMS Nov, 2001)
- Cefamandole
 - Metronidazole
 - Chlorpropamide
 - Beclomethasone
168. Drugs that can be used for out patient treatment of community acquired pneumonia are: (PGI Dec. 2007)
- Ceftriaxone
 - Cefazolin
 - Imipenem
 - Azithromycin
 - Doxycycline
169. Drugs used in the treatment of MRSA are: (PGI June, 2006)
- Quinupristin/dalfopristin
 - Linezolid
 - Teicoplanin
 - Penicillin G
 - Piperacillin
170. Drugs that should be avoided in a patient with seizure disorder are: (PGI June, 2004)
- Ciprofloxacin
 - Cycloserine
 - Glucocorticoids
 - Ketoconazole
171. Treatment of penicillinase producing *Neisseria gonorrhoeae* is/are: (PGI Dec. 2004)
- Amoxycillin
 - Ciprofloxacin
 - Cefotaxime
 - Doxycycline
 - Azithromycin
172. Drugs useful for treatment of anaerobic infections are: (AIIMS Nov, 2001) (DPG 2001)
- Metronidazole
 - Imipenem
 - Aztreonam
 - Clotrimazole
 - Vancomycin
173. Which of these antibiotics are safe in renal failure? (PGI June, 2002)
- Cephalexin
 - Tetracycline
 - Nitrofurantoin
 - Gentamicin
 - Doxycycline
174. Treatment of choice for *Salmonella typhi* is: (PGI Dec. 2001)
- Cephalexin
 - Gentamicin
 - Streptomycin
 - Tetracycline
 - Ciprofloxacin
175. Drug of choice for methicillin resistant staphylococcus aureus (MRSA) is: (PGI Dec 2001) (MPPG 2002)
- Amoxicillin-Clavulanate
 - Vancomycin
 - Flucloxacillin
 - Clindamycin
 - Erythromycin
176. Which of the following drugs is most likely to cause loss of equilibrium and auditory damage?
- Amikacin
 - Ethambutol
 - Isoniazid
 - Rifabutin
177. Which of the following drugs is LEAST likely to require dosage reduction in renal dysfunction?
- Amikacin
 - Ciprofloxacin
 - Clindamycin
 - Vancomycin
178. Antimicrobials effective against anaerobic bacteria include the following EXCEPT:
- Tobramycin
 - Clindamycin
 - Chloramphenicol
 - Metronidazole

179. Select the antimicrobial agent that can be used to treat both methicillin resistant and vancomycin resistant *Staphylococcus aureus* infections:
- Clarithromycin
 - Clindamycin
 - Linezolid
 - Lincomycin
180. For a 23 old pregnant female having severe sensitivity to amoxicillin, drug used to treat gonorrhoea in a single dose should be
- Ceftriaxone
 - Tetracycline
 - Ciprofloxacin
 - Spectinomycin
181. The drug that should be used for prophylaxis of close contacts of a patient suffering from meningococcal meningitis is:
- Rifampicin
 - Dapsone
 - Erythromycin
 - Amikacin
182. A 14 year old boy present with headache, fever and cough for 2 days. Sputum is scant and non-purulent and gram stain reveals many white cells but no organisms. The treatment should be initiated with:
- Cefazolin
 - Erythromycin
 - Amikacin
 - Trovaflaxacin
183. Drugs that can be used to treat infections caused by *Bacteroides fragilis* are all EXCEPT:
- Metronidazole
 - Trovaflaxacin
 - Vancomycin
 - Amikacin
184. A patient needs antibiotic treatment for artificial valve, culture-positive infective enterococcal endocarditis. His medical history includes severe anaphylactic reaction to penicillin G during the past year. The best approach would be treatment with:
- Amoxicillin-clavulanic acid
 - Aztreonam
 - Cefazolin plus gentamicin
 - Vancomycin
185. In a patient with culture-positive enterococcal endocarditis who has failed to respond to vancomycin because of resistance, the treatment most likely to be effective is:
- Clarithromycin
 - Linezolid
 - Minocycline
 - Ticarillin
186. Select the drug which is used to treat antibiotic associated pseudomembranous enterocolitis and is a component of anti *H. pylori* triple drug regimen:
- Amoxicillin
 - Vancomycin
 - Metronidazole
 - Clotrimazole
187. This drug depolarizes cell membranes of aerobic gram positive bacteria. It is effective against vancomycin resistant enterococcal infections. It may cause myopathy especially in patients taking statins. It is:
- Teicoplanin
 - Daptomycin
 - Linezolid
 - Streptogramin
188. A patient of abdominal sepsis was started on empirical treatment with intravenous ampicillin and gentamicin. Regarding the treatment of this patient, which statement is most accurate?
- Empirical treatment of abdominal sepsis should always include a third generation cephalosporin
 - A drug active against anaerobe should be included in the antibiotic regimen
 - Combination of ampicillin and gentamicin provides good coverage for all likely pathogens
 - If the patient is severely allergic to ampicillin, then ceftriaxone should be used
189. Guddu, a 5-year-old female was brought to the emergency with fever, headache and confusion. A provisional diagnosis of bacterial meningitis was made. The baby developed a severe allergic reaction to penicillin around six months back. She was admitted and intravenous antibiotics were started. Few days later her investigations revealed as:
- | | |
|-------------------|-------------------------------|
| Hemoglobin | 6.0 g/L |
| Erythrocyte count | $1.2 \times 10^6/\text{mm}^3$ |
| Platelets | $60000/\text{mm}^3$ |
| Leukocyte count | $1500/\text{mm}^3$ |
- Which of the following is the most likely drug responsible for the above findings?
- Gentamicin
 - Chloramphenicol
 - Doxycycline
 - Vancomycin
190. Red man syndrome occurs with: (Karnataka 2009, 2004)
- Clindamycin
 - Teicoplanin
 - Vancomycin
 - Polymyxin
191. Which of the following antimicrobials needs dose reduction even in mild renal failure? (DPG 2006)
- Ciprofloxacin
 - Carbenicillin
 - Cefotaxime
 - Ethambutol

192. Which of the following drug can cause cartilage damage in children? (DPG 2006)
 (a) Cotrimoxazole
 (b) Penicillin
 (c) Ciprofloxacin
 (d) Metronidazole
193. Gray baby syndrome is caused by: (DPG 2006) (MPPG 2002, TN 2005)
 (a) Chlorpromazine
 (b) Chloramphenicol
 (c) Phenytoin
 (d) Gentamycin
194. Macrocytic anaemia is caused by all EXCEPT: (DPG 2005)
 (a) Pyrimethamine
 (b) Methotrexate
 (c) Pentamidine
 (d) Trimethoprim
195. Which of the following drugs is most commonly associated with *Clostridium difficile* colitis? (DPG 2001)
 (a) Vancomycin
 (b) Metronidazole
 (c) Clindamycin
 (d) Erythromycin
196. Which of the following is not nephrotoxic? (DPG 2000)
 (a) Tobramycin
 (b) Kanamycin
 (c) Ampicillin
 (d) Amphotericin B
197. Dose of which of the following antibiotic does not require alteration in renal failure? (DPG 2000)
 (a) Vancomycin
 (b) Ethambutol
 (c) Erythromycin
 (d) Metronidazole
198. Drug of choice for sore throat caused by Group A beta hemolytic streptococcus is: (DPG 1997)
 (a) Erythromycin
 (b) Penicillin
 (c) Ceftriaxone
 (d) Sulfonamides
199. Nephrotoxicity is seen with: (MPPG 2004)
 (a) Doxycycline
 (b) Aminoglycosides
 (c) Erythromycin
 (d) Rifampicin
200. Drug which should not be given in renal disease is: (MPPG 2003)
 (a) Gentamicin
 (b) Nitroprusside
 (c) Doxycycline
 (d) Ceftriaxone
201. Drug causing megaloblastic anemia is: (MPPG 2003)
 (a) INH
 (b) Chloramphenicol
 (c) Pyrimethamine
 (d) Methyl dopa
202. All are hepatotoxic drugs Except: (UP 2008)
 (a) Erythromycin estolate
 (b) Rifampicin
 (c) Tetracycline
 (d) None
203. Jarisch-Herxheimer reaction is seen in syphilis with: (UP 2005)
 (a) Tetracyclines
 (b) Penicillins
 (c) Co-trimoxazole
 (d) Sulfonamides
204. Which of the following drug is not used against *Pseudomonas*? (UP 2005)
 (a) Piperacillin
 (b) Carbenicillin
 (c) Ticarcillin
 (d) Oxacillin
205. Red cell aplasia can be caused by: (UP 2006)
 (a) Aminoglycosides
 (b) Chloramphenicol
 (c) Penicillins
 (d) Ciprofloxacin
206. Which of the following drug is safe during pregnancy? (UP 2006)
 (a) Aminoglycoside
 (b) Ampicillin
 (c) Chloramphenicol
 (d) Cotrimoxazole
207. Which one of the following is used in the prophylaxis of streptococcal sore throat? (TN 2000)
 (a) Phenoxy methyl penicillin
 (b) Inj. Benzathine Penicillin
 (c) Crystalline penicillin
 (d) Both A and B are true
208. Drug of choice for plague is: (TN 2000, RJ 2009)
 (a) Erythromycin
 (b) Tetracyclines
 (c) Ampicillin
 (d) Cotrimoxazole
209. Which one of the following is primarily bacteriostatic? (TN 2002)
 (a) Ciprofloxacin
 (b) Chloramphenicol
 (c) Vancomycin
 (d) Rifampicin
210. Drug of choice for prophylaxis of meningococcal meningitis is: (TN 2005)
 (a) Penicillin
 (b) Erythromycin
 (c) Septran
 (d) Rifampicin

Review of Pharmacology

211. Drug with high degree of photosensitivity is: (TN 2006)
 (a) Tetracycline
 (b) Doxycycline
 (c) Minocycline
 (d) Methacycline
212. Drug used for treatment of methicillin resistant staphylococcus aureus is: (TN 2006)
 (a) Teicoplanin (RJ 2006, Bihar 2006)
 (b) Vancomycin
 (c) Both
 (d) None
213. Drug of choice in pertussis is: (RJ 2001)
 (a) Penicillin
 (b) Doxycycline
 (c) Erythromycin
 (d) Ciprofloxacin
214. Drug effective against pseudomonas is: (AI 2005) (MH 2000)
 (a) Penicillin G
 (b) Gentamicin
 (c) Tetracycline
 (d) Chloramphenicol
215. Treatment of choice for chancroid is: (MH 2002)
 (a) Penicillin
 (b) Chloramphenicol
 (c) Tetracyclines
 (d) Erythromycin
216. Pseudomembranous colitis is associated mostly with which drug? (MH 2002)
 (a) Erythromycin
 (b) Ampicillin
 (c) Vancomycin
 (d) Ciprofloxacin
217. Drug of choice for primary syphilis is: (MH 2003)
 (a) Ampicillin
 (b) Benzathine penicillin
 (c) Erythromycin
 (d) Tetracycline
218. Drug of choice for syphilis during pregnancy is: (MH 2003)
 (a) Ampicillin
 (b) Erythromycin
 (c) Benzathine penicillin
 (d) Tetracyclines
219. Drug that is NOT contraindicated in G-6 PD deficiency is: (MH 2003)
 (a) Primaquine
 (b) Nitrofurantoin
 (c) Dapsone
 (d) INH
220. Which of the following drug is contraindicated in pregnancy? (MH 2005)
 (a) Chloroquine
 (b) Erythromycin
 (c) Ampicillin
 (d) Primaquine
221. Absorption of which of the following drug increases with food intake? (MH 2005)
 (a) Tetracycline
 (b) Diazepam
 (c) Griseofulvin
 (d) Ampicillin
222. Which of the following prokinetic drug acts on motilin receptors? (MH 2008)
 (a) Erythromycin
 (b) Metoclopramide
 (c) Loxiglumide
 (d) Cisapride
223. The antibiotic which can be given safely in a pregnant women is: (Bihar 2003)
 (a) Ciprofloxacin
 (b) Cefuroxime
 (c) Metronidazole
 (d) Chloramphenicol
224. Drug of choice for Mycoplasma pneumoniae infection is: (AP 2005)
 (a) Gentamicin
 (b) Amoxycillin
 (c) Azithromycin
 (d) Cefotaxime
225. Drug of choice for acute (pneumococcal) lobar pneumonia is: (Karnataka 2002)
 (a) Amoxicillin clavulanic acid combination
 (b) Ciprofloxacin
 (c) Co-trimoxazole
 (d) Crystalline penicillin (Pen. G)
226. Drug of choice for acute meningococcal pyogenic meningitis is: (Karnataka 2002)
 (a) Crystalline penicillin (Pen. G)
 (b) Sulphonamides
 (c) Chloramphenicol
 (d) Amoxycillin
227. Which of the following is not given in myasthenia gravis: (Jharkhand 2003)
 (a) Clofibrate
 (b) Polymixin B
 (c) Penicillin
 (d) All
228. Which of following drug's absorption is increased in gastric achlorhydria? (Jharkhand 2003)
 (a) Ketoconazole
 (b) Penicillin G
 (c) Chloramphenicol
 (d) Ciprofloxacin

RECENT QUESTIONS ASKED BY NATIONAL BOARD

1. Which does not cause pseudomembranous enterocolitis?
 - (a) Vancomycin
 - (b) Levofloxacin
 - (c) Clindamycin
 - (d) Ceftazidime
2. Single dose treatment for chlamydia is?
 - (a) Doxycycline
 - (b) Tetracycline
 - (c) Azithromycin
 - (d) Erythromycin
3. Mechanism of action of quinolones is by?
 - (a) Inhibiting DHFRase
 - (b) Inhibiting DNA gyrase
 - (c) Inhibiting protein synthesis
 - (d) Inhibiting cell wall synthesis
4. Longest acting sulphonamide is -
 - (a) Sulfadiazine
 - (b) Sulfadoxine
 - (c) Sulfamethoxazole
 - (d) Sulfamethiazole
5. Widest spectrum aminoglycoside is -
 - (a) Streptomycin
 - (b) Amikacin
 - (c) Framycetin
 - (d) Netilmicin
6. Penicillinase resistant penicillins include all of the following drugs except:
 - (a) Flucloxacillin
 - (b) Nafcillin
 - (c) Oxacillin
 - (d) Carbenicillin
7. Ampicillin is used in:
 - (a) Listeria
 - (b) Pertussis
 - (c) Atypical pneumonia
 - (d) Gonococci
8. Pseudomonas is resistant to:
 - (a) Vancomycin
 - (b) Aztreonam
 - (c) Ciprofloxacin
 - (d) Polymyxin B
9. Which of the following is contra-indicated in pregnancy?
 - (a) Tetracycline
 - (b) Erythromycin
 - (c) Ampicillin
 - (d) Chloroquine
10. Red man syndrome is due to:
 - (a) Vancomycin
 - (b) Polymyxin
 - (c) Rifampicin
 - (d) Teicoplanin
11. Drug of choice for syphilis is -
 - (a) Penicillin
 - (b) Rifampicin
 - (c) Tetracycline
 - (d) Erythromycin
12. Bleeding is a risk with the use of:
 - (a) Cefaloridine
 - (b) Cefazolin
 - (c) Moxalactam
 - (d) Ceftazidime
13. Sulphonamides act by:
 - (a) Competitive inhibition
 - (b) Non-competitive inhibition
 - (c) Allosteric inhibition
 - (d) None of these
14. All are true about ciprofloxacin except -
 - (a) Contra-indicated in pregnancy
 - (b) DNA inhibition
 - (c) Most potent first generation fluoroquinolone
 - (d) More active at acidic pH
15. Drug inhibiting bacterial protein synthesis are all except:
 - (a) Aminoglycosides
 - (b) Chloramphenicol
 - (c) Clindamycin
 - (d) Sulfonamides
16. Actinomycete is the source of which of the following anti microbials?
 - (a) Tetracycline
 - (b) Polyene
 - (c) Aztreonam
 - (d) Colistin
17. Drug that can cause hypertrophic pyloric stenosis is:
 - (a) Tetracycline
 - (b) Erythromycin
 - (c) Ampicillin
 - (d) Rifampicin
18. Drug that inhibits cell wall synthesis is?
 - (a) Tetracyclines
 - (b) Penicillins
 - (c) Aminoglycosides
 - (d) Chloramphenicol
19. Which of the following tetracycline can be used in renal failure without dose adjustment?
 - (a) Oxytetracycline
 - (b) Doxycycline
 - (c) Demeclocycline
 - (d) Tetracycline
20. Drug used in prophylaxis of meningococcal meningitis is:
 - (a) Ciprofloxacin
 - (b) Rifampicin
 - (c) Penicillin
 - (d) Gentamicin

21. Mechanism of action of quinolones is:
 - (a) DNA gyrase inhibitors
 - (b) Bind to 30 S unit of ribosomes and inhibit protein synthesis
 - (c) Bind to bacterial cell membrane
 - (d) Bind to tetra hydro folate reductase
22. Drug of choice in pregnant women with secondary syphilis is:
 - (a) Doxycycline
 - (b) Benzathine Penicillin
 - (c) Ceftriaxone
 - (d) Cotrimoxazole
23. True about imipenem is:
 - (a) It is narrow spectrum antibiotic
 - (b) It is easily broken by beta lactamases
 - (c) It should be used with cilastatin
 - (d) It is used with sulbactam
24. Which among the following is not a beta lactamase resistant Penicillin?
 - (a) Methicillin
 - (b) Carbenicillin
 - (c) Nafcillin
 - (d) Oxacillin
25. Drug of choice for Treponema pallidum is:
 - (a) Penicillin G
 - (b) Tetracycline
 - (c) Azithromycin
 - (d) Doxycycline
26. All are third generation Cephalosporins except:
 - (a) Ceftriaxone
 - (b) Ceftazidime
 - (c) Cefuroxime
 - (d) Cefoperazone
27. Treatment for clostridial myonecrosis is:
 - (a) Amikacin
 - (b) Penicillin
 - (c) Ampicillin
 - (d) Gentamicin
28. All of the following have beta lactam ring except:
 - (a) Penicillin
 - (b) Linezolid
 - (c) Cefotaxime
 - (d) Imipenem
29. Drug of choice for treatment of infections caused by MRSA is:
 - (a) Metronidazole
 - (b) Vancomycin
 - (c) Imipenem
 - (d) Clindamycin
30. The antibiotic causing pseudomembrane colitis is:
 - (a) Clindamycin
 - (b) Garamycin
 - (c) Erythromycin
 - (d) Vancomycin
31. An aminoglycoside that is resistant to majority of inactivating enzymes is:
 - (a) Gentamicin
 - (b) Amikacin
 - (c) Tobramycin
 - (d) Sisomicin
32. All of the following Beta-Lactam antibiotics possess antipseudomonal action, except:
 - (a) Piperacillin
 - (b) Ceftriaxone
 - (c) Ceftazidime
 - (d) Cefoperazone
33. All of the following are common antimicrobial agents used in treatment of typhoid fever except:
 - (a) Ceftriaxone
 - (b) Quinolones
 - (c) Clindamycin
 - (d) Azithromycin
34. The drug of choice in lymphogranuloma venereum is:
 - (a) Penicillin
 - (b) Ciprofloxacin
 - (c) Tetracycline
 - (d) Erythromycin
35. Antacid interfere with absorption of all of the following except:
 - (a) Ketoconazole
 - (b) Azithromycin
 - (c) Oxytetracycline
 - (d) Ofloxacin
36. All of the following are beta lactamase inhibitors except:
 - (a) Clavulanic acid
 - (b) Sulbactam
 - (c) Tazobactam
 - (d) Aztreonam
37. Which one of the following is true about the beta lactam antibiotics:
 - (a) All are based on the 6-amino-penicillanic acid structure
 - (b) Include amikacin
 - (c) Are safe in pregnancy
 - (d) Are uniformly ineffective against pseudomonas aeruginosa
38. Antibiotic which is effective as a single dose therapy for trachoma is:
 - (a) Doxycycline
 - (b) Clarithromycin
 - (c) Azithromycin
 - (d) Erythromycin
39. The prophylactic antibiotic indicated to prevent infection in lymphoedema is:
 - (a) Vancomycin
 - (b) Penicillin

- (c) Amikacin
(d) Quinolones
40. **Drug of choice in dermatitis herpetiformis is:**
(a) Corticosteroids
(b) Colchicine
(c) Dapsone
(d) Chloroquine
41. **The preferred treatment option for primary syphilis is:**
(a) Injection Benzathine penicillin 2.4 million units IM single dose
(b) Injection Benzathine penicillin 2.4 million units IM once a week for 3 weeks
(c) Cap. Doxycycline 100 mg orally twice a day for 2 weeks
(d) Tab. Azithromycin 2 gm single dose
42. **A diabetic patient developed cellulites due to *S. aureus*, which was found to be methicillin resistant on antibiotic sensitivity testing. All of the following antibiotics would be appropriate except:**
(a) Linezolid
(b) Vancomycin
(c) Teicoplanin
(d) Imipenem
43. **Which of the following antibacterial causes both ototoxicity and nephrotoxicity:**
(a) Methicillin
(b) Vancomycin
(c) Clindamycin
(d) Azithromycin
44. **Oral vancomycin can be used for treatment of:**
(a) Hepatic encephalopathy
(b) Pseudomembranous colitis
(c) Staphylococcal food poisoning
(d) None of the above
45. **Which of the following is responsible for antibiotic associated colitis:**
(a) *Clostridium botulinum*
(b) *Clostridium perfringens*
(c) *Clostridium difficile*
(d) *Actinomyces* species
46. **All of the following drugs can cause cholestatic jaundice except:**
(a) Ethambutol
(b) Chlorpromazine
(c) Erythromycin estolate
(d) Estrogens
47. **Which of the following antibiotics class is not safe in pregnancy:**
(a) Quinolones
(b) Cephalosporins
(c) Penicillins
(d) Macrolides
48. **Which of the following drugs is avoided in a patient with high serum creatinine (> 3 mg/dl)?**
(a) Gentamicin
(b) Azithromycin
(c) Moxifloxacin
(d) Amlodipine
49. **Which of the following is used in the prophylactic treatment of rheumatic heart disease:**
(a) Ampicillin
(b) Penicillin-G
(c) Benzathine penicillin
(d) Phenoxymethyl penicillin
50. **Which amongst the following antimicrobials exhibits a long post antibiotic effect:**
(a) Quinolones
(b) Macrolides
(c) Beta-lactams
(d) Oxazolidinones
51. **Which of the following is used as prophylaxis for meningococcal meningitis?**
(a) Gentamicin
(b) Erythromycin
(c) Rifampicin
(d) Chloramphenicol
52. **Which of the following drugs is most effective against an organism producing aminoglycoside inactivating enzymes?**
(a) Tobramycin
(b) Gentamicin
(c) Amikacin
(d) Streptomycin
53. **The persistent suppression of bacterial growth that may occur after limited exposure to some antimicrobial drug is called?**
(a) Time dependent killing
(b) Concentration dependent killing
(c) Post antibiotic effect
(d) Sequential blockade
54. **Prophylactic antibiotics to prevent surgical site infection are best administered:**
(a) After commencement of surgery
(b) 30 minutes before incision
(c) At the end of surgery
(d) With pre medication
55. **Which of the following antimicrobial agents act solely on the gram positive bacterial cell wall:**
(a) Ciprofloxacin
(b) Gentamicin
(c) Tetracycline
(d) Vancomycin

56. Sulfonamides inhibit bacterial synthesis of folic acid by:
 (a) Uncompetitive inhibition
 (b) Allosteric inhibition
 (c) Competitive inhibition
 (d) Non competitive inhibition
57. Which of the following drugs is an anti-pseudomonal penicillin?
 (a) Cephalexin
 (b) Dicloxacillin
 (c) Piperacillin
 (d) Cloxacillin
58. Which can be given safely in renal failure?
 (a) Tetracycline
 (b) Gentamicin
 (c) Amphotericin B
 (d) Doxycycline
59. Drug of choice in pneumonia caused by *P. carinii* is:
 (a) Penicillin
 (b) Cotrimoxazole
 (c) Kanamycin
 (d) Levofloxacin
60. Which of the following drugs is a 4th generation cephalosporin?
 (a) Cefixime
 (b) Ceftriaxone
 (c) Cefpirome
 (d) Cefazolin
61. Which of the following drugs should not be given in renal failure?
 (a) Clindamycin
 (b) Methicillin
 (c) Amoxicillin
 (d) Rifampicin
62. Beta lactam antibiotics are all except:
 (a) Amoxicillin
 (b) Aztreonam
 (c) Ceftriaxone
 (d) Vancomycin
63. All of the following drugs are administered orally except:
 (a) Ciprofloxacin
 (b) Cotrimoxazole
 (c) Gentamicin
 (d) Amoxicillin
64. Aplastic anemia is the adverse effect of:
 (a) Chloramphenicol
 (b) Ciprofloxacin
 (c) Penicillin
 (d) Gentamicin
65. Highest photosensitivity is seen with:
 (a) Pefloxacin
 (b) Gatifloxacin
 (c) Levofloxacin
 (d) Sparfloxacin
66. Drug most commonly implicated in causing pseudo membranous colitis is:
 (a) Clindamycin
 (b) Streptomycin
 (c) Amoxicillin
 (d) Metronidazole
67. Which of the following is a side effect of streptomycin?
 (a) Phototoxicity
 (b) Hepatotoxicity
 (c) Ototoxicity
 (d) All of the above
68. Not true about vancomycin is:
 (a) 95% oral bioavailability
 (b) Inhibits cell wall synthesis
 (c) Can be used parenterally as well as orally
 (d) Indicated for MRSA infections
69. Dosage of topical tobramycin eye drops:
 (a) 1 mg/ml
 (b) 2 mg/ml
 (c) 3 mg/ml
 (d) 4 mg/ml
70. Route of administration of vancomycin in pseudo-membranous colitis is:
 (a) i.m.
 (b) oral
 (c) i.v.
 (d) s.c.
71. Dosage of benzyl penicillin in treatment of primary syphilis is:
 (a) 1.2 MU single i.m.
 (b) 1.2 MU single i.v.
 (c) 2.4 MU single i.m.
 (d) 4.8 MU single i.m.
72. Treatment of non-specific urethritis is:
 (a) Erythromycin
 (b) Sulphonamides
 (c) Tetracycline
 (d) Ampicillin
73. Hemolysis in G-6 deficiency is precipitated by all of the following except:
 (a) Dapsone
 (b) Cotrimoxazole
 (c) Quinine
 (d) Penicillin

74. In treatment of Pseudomonas infections, carbenicillin is frequently combined with:

- (a) Penicillin
- (b) Gentamicin
- (c) Ciprofloxacin
- (d) Amoxycillin

75. All of the following are true regarding cephalosporins except:

- (a) Bactericidal agents
- (b) Active against only gram negative bacteria
- (c) IIIrd Generation are resistant to β -lactamases from gram negative bacteria
- (d) ceftriaxone is administered parenterally

76. Which antimalarial drug can be safely administered in baby with glucose-6-phosphagte dehydrogenase deficiency?

- (a) Chloroquine
- (b) Quinine
- (c) Mefloquine
- (d) Primaquine

77. Drug used in the treatment of resistant gonorrhoea is:

- (a) Penicillin
- (b) Cotrimoxazole
- (c) Spectinomycin
- (d) Erythromycin

78. Penicillinase resistant penicillin is:

- (a) Methicillin
- (b) Ampicillin
- (c) Carbenicillin
- (d) Ticarcillin

EXPLANATIONS

1. **Ans. (b) Beta lactam antibiotics** (Ref: *Katzung 12/e p907-908*)
 - Killing activity is shown by cidal drugs only. Beta lactams and fluoroquinolones are cidal among the options.
 - Time dependent killing (TDK) is shown by beta lactam antibiotics
 - Concentration dependent killing (CDK) is shown by aminoglycosides and fluoroquinolones
 - Daptomycin do not show TDK or CDK but the killing activity depends on AUC
 - All the drugs given in the option have long post-antibiotic effect against gram positive bacteria.
 - Clindamycin and erythromycin are bacteriostatic drugs and thus do not show TDK or CDK
2. **Ans. (b) Tigecycline** (Ref: *KK Sharma 2/e p733, 750*)

Tigecycline is a newer drug in the class 'Glycylcyclines.' Its mechanism of action and most properties are similar to tetracyclines. However, it is resistant to efflux pump (major mechanism of resistance against tetracyclines). Most protein synthesis inhibiting drugs (including tetracyclines and tigecycline) are bacteriostatic except aminoglycosides. Isoniazid, ciprofloxacin and daptomycin are bactericidal.
3. **Ans. (a) Plasmid** (Ref: *KDT 6/e p671*)

Plasmids contain extra-chromosomal DNAs that help in transferring the genes responsible for multiple drug resistance among bacteria. These are therefore involved in horizontal transfer of resistance. As it is not due to penicillinase, beta lactamase inhibitors like clavulanic acid cannot reverse this resistance.
4. **Ans (b) Occurs due to change in penicillin binding proteins** (Ref: *Katzung's 11/e p776*)

Methicillin resistance occurs due to altered PBPs, thus no penicillin, (infact no beta-lactam antibiotic) is useful against methicillin-resistant *Staphylococcus aureus* (MRSA) infections.
5. **Ans. (a) Aminoglycosides** (Ref: *KDT 6/e p720*)

Resistance to quinolones is due to altered DNA gyrase, to rifampicin is due to mutation in gene rpo B reducing its ability for the target and for glycopeptides like vancomycin due to reduced affinity for target site.
6. **Ans. (a) Cefepime** (Ref: *K.D.T. 6/e p669 & 5/e p628*)

Cefepime is a beta lactam antibiotic, which acts by inhibiting cell wall synthesis.
7. **Ans. (b) Doxycycline** (Ref: *Goodman & Gilman 11/e p1173; KDT 6/e p668-669*)
 - Doxycycline is a tetracycline that act by inhibiting protein synthesis
 - Cefotetan and oxacillin are β -lactam antibiotics that act by inhibiting cell wall synthesis.
 - Ciprofloxacin is a fluoroquinolone that acts by inhibiting DNA gyrase.
8. **Ans. (c) Streptomycin** (Ref: *Katzung 10/e p835 KDT 6/e p673*)

Streptomycin is an aminoglycoside and require dose adjustment in renal failure whereas doxycycline, rifampicin and cefoperazone are secreted in bile and do not require dose adjustment in renal failure.
9. **Ans. (d) Cefepime** (Ref: *KDT 6/e p668*)
10. **Ans. (d) Nitrofurantoin** (Ref: *KDT 6/e p668*)
11. **Ans. (c) Ampicillin and chloramphenicol** (See below) (Ref: *KDT 6/e p677*)

Combination of a bactericidal (ampicillin) and a bacteriostatic drug (chloramphenicol) is usually antagonistic in nature. This is because cidal drugs are usually acting on a fast multiplying organisms whereas static drugs decrease this multiplication.
12. **Ans. (b) Griseofulvin** (Ref: *KDT 6/e p760*)

It acts by affecting mitosis but exact mechanism is not known.
13. **Ans. (a) Cell wall** (Ref: *Katzung 10/e p741; KDT 6/e p668*)
 - Bacitracin acts by inhibiting the synthesis of cell wall.
 - Other polypeptide antibiotics like polymyxin B, colistin and tyrothricin act by affecting membranes.
14. **Ans. (a) Penicillin + streptomycin in SABE; (c) Sulfamethoxazole + trimethoprim in UTI; (d) Amphotericin B + flucytosine in cryptococcal meningitis** (Ref: *KDT 6/e p677*)

Antimicrobial drugs showing synergism are:

- Penicillin/ampicillin + streptomycin/gentamicin for enterococcal SABC
- Carbenicillin/ticarcillin + gentamicin for pseudomonas infection, specially neutropenic patients.
- Ceftazidime + ciprofloxacin for pseudomonas infected orthopedic prosthesis.
- Rifampicin + INH in tubercular infection.
- Flucytosine has supra additive action with amphotericin-B in cryptococcal meningitis.
- Sufamethoxazole + trimethoprim in UTI.

15. Ans. (d) Clindamycin (Ref: KDT 6/e p668)

Clindamycin acts by inhibiting the protein synthesis

16. Ans. (b) Post antibiotic effect (Ref: Katzung 10/e p756)

- Time dependent killing kinetics is shown by aminoglycosides. Here, the killing activity depends upon the length of time, plasma concentration is above MIC.
- Concentration dependent killing is shown by β lactam drugs. Here, killing activity depends upon the ratio of plasma concentration to MIC.
- Post antibiotic effect is the suppression of bacterial growth after limited exposure to antibiotic.

17. Ans. (c) Penicillin and tetracycline in bacterial meningitis (Ref: KDT 6/e p677)

Combination of a bacteriostatic and a bactericidal drug in most cases is antagonistic. Bactericidal drugs act on fast multiplying organisms whereas bacteriostatic drugs inhibit the growth. Here, penicillins are bactericidal whereas tetracyclines are bacteriostatic.

18. Ans. (d) Gentamicin (Ref: KDT 6/e p674)

Gentamicin is an aminoglycoside and is excreted via renal route.

19. Ans. (c) Conjugation (Ref: KDT 6/e p671)

Multiple drug resistance is transferred through plasmids, mostly by conjugation.

20. Ans. (b) Transduction (Ref: Goodman & Gilman 11/e p1098; KDT 6/e p671)

- Transduction is particularly important in transfer of resistance among staphylococci.
- Multidrug resistance is transferred by conjugation.

21. Ans. (a) Quinolones (Ref: KDT 6/e p688)

Resistance to fluoroquinolones is mediated by mutation in DNA gyrase.

22. Ans. (c) Transformation (Ref: KDT 6/e p671)

- Acquisition of antibiotic resistance by Transduction is common in Staphylococcal and that of by Transformation in Pneumococcus and Neisseria.
- Vancomycin resistance in enterococci and staphylococcus is mediated by conjugative plasmid.

23. Ans. (a) Neutropenia (Ref: Robbins 7th/640; KDT 6/e p686,806)

Bactericidal drugs kill the bacteria whereas bacteriostatic drugs only inhibits bacterial growth. Bacteriostatic activity is adequate for the treatment of most infections, **bactericidal activity may be necessary for cure in patients with altered immune systems like: neutropenias, HIV and other immunosuppressive conditions.**

24. Ans. (d) Penicillin (Ref: KDT 6/e p668)**25. Ans. (b) Cephalosporins (Ref: KDT 6/e p668)****26. Ans. (b) Transduction (Ref: Goodman & Gilman 11/e p1133)**

Beta lactamases are encoded by plasmids that can be transferred with the help of bacteriophage (transduction) in staphylococci and by transformation in Pneumococci.

27. Ans. (d) Cotrimoxazole (Ref: Katzung 11/e p817)**28. Ans. (b) Immunocompromised host (Ref: K.D. Tripathi 6/e p672)****29. Ans. (c) Tetracycline (Ref: KDT 6/e p711)****30. Ans. (a) Vancomycin (Ref: KDT 6/e p711)****31. Ans (c) Piperacillin-Tazobactam (Ref: Harrison 18th/1247)**

- Organisms producing ESBL like *Klebsiella* are resistant to most beta-lactams except carbapenems.
- ESBL can be inhibited by beta lactamase inhibitors.
- Amoxicillin is not effective against *Klebsiella* whereas piperacillin has wide spectrum including *Klebsiella*.

32. **Ans. (c) It can be used for treatment of rat bite fever** (Ref: *H-18/e p24, 3, Katzung 10/e p726-731; KDT 6/e p694-697*)
- It is **not effective orally** because of breakdown by acid in the stomach.
 - It has **short duration of action** due to its rapid excretion from kidney through tubular secretion. Probenecid decreases its tubular secretion, thus can be used **to prolong its action**.
 - It has **narrow spectrum** of activity covering mainly gram positive bacteria.

Penicillin G is first choice drug for

- Syphilis
- Meningococcal meningitis
- Actinomycosis
- Rat bite fever
- Yaws
- Leptospirosis
- Group A and B streptococcal infections
- Viridans streptococcal endocarditis

33. **Ans. (b) Carbapenems are sensitive to ESBL** (Ref: *Katzung 11/e p785-786, www.cdc.gov*)
ESBL producing bacteria are sensitive to carbapenems whereas these drugs are resistant to breakdown by ESBL.
34. **Ans. (a) Aztreonam** (Ref: *KDT 6/e p708*)
Aztreonam is the only beta lactam antibiotic that can be used in patients having severe allergy to penicillins or cephalosporins (as it is not cross allergenic).
35. **Ans. (c) These are target site of vancomycin** (Ref: *Harrison 17/e p854*)
Beta-lactam antibiotics act by inhibiting the cross-linking of peptidoglycan chains in bacterial cell wall. This action is carried out by transpeptidase enzyme. Transpeptidases and similar enzymes involved in cross-linking are called penicillin-binding proteins (PBPs). All beta-lactam antibiotics bind to PBPs and inhibit cell wall synthesis. The drugs in β -lactam category are:
- Penicillins
 - Cephalosporins
 - Carbapenems e.g. imipenem
 - Monobactam e.g. aztreonam
 - Mutation in PBPs is an important cause of methicillin resistance in *Staphylococcus aureus*.
 - Vancomycin does not bind to PBPs but act by inhibiting transglycosylase.
36. **Ans. (c) Cefoxitin has no activity against anaerobes** (Ref: *Katzung 11/e p780,783,784*)
 β -lactam antibiotics act by inhibiting cell wall synthesis. These include penicillins, cephalosporins, carbapenems and monobactam.

Anti-pseudomonal cephalosporins	Cephalosporins active against anaerobic bacteria	3rd Generation cephalosporins	
• Cefoperazone	• Cefoxitin	• Ceftazidime	• Cefditoren
• Ceftazidime	• Cefotetan	• Ceftriaxone	• Cefoperazone
• Cefepime	• Cefmetazole	• Ceftizoxime	• Cefpodoxime
• Cefpirome		• Ceftibuten	• Maxalactam
		• Cefotaxime	• Cefixime
		• Cefdinir	

37. **Ans. (b) Cefoperazone** (Ref: *Principles of Pharmacology, 1/e p749; KDT 6/e p706*)
Ceftriaxone and cefoperazone are excreted mainly in the **bile**, therefore do not require dose reduction in any grade of renal failure.
38. **Ans. (d) Carbapenems** (Ref: *Katzung 10/e p739*)
Carbapenems like imipenem are the only beta lactams reliably efficacious against ESBL producing bacteria.
39. **Ans. (b) It is never administered orally** (Ref: *Katzung 10/e p726-731; KDT 6/e p694-697*)
- Penicillins act by inhibiting bacterial cell wall synthesis via the inhibition of transpeptidation reaction.

- Penicillin G is drug of choice for:
 - Gram +ve bacteria (like Streptococcus, Pneumococcus, non-beta-lactamase producing Staphylococcus, Clostridium and other gram positive rods)
 - Gram negative bacteria (like Meningococci, Enterococci and non-β-lactamase producing gram negative anaerobic bacteria)
 - Actinomyces and Treponema pallidum (syphilis)
- Penicillin is rapidly excreted by kidney. 90% excretion is by tubular secretion whereas 10% is by glomerular filtration. Probenecid competes with tubular secretion and prolongs the duration of action.
- Penicillin G is less effective by oral route due to destruction by hydrochloric acid in stomach. Penicillin V is acid stable and thus can be given orally. Mostly penicillin G is administered parenterally (i.m. or i.v.) but it can be administered orally for mild infections. Katzung Pg. 742, in preparations available also shows the oral and parenteral preparations.
- Thus “penicillin is never administered orally” is not a true statement because it can be used orally but commonly used parenterally.

40. Ans. (b) Rickettsial infections (Ref: KDT 6/e p715)

Penicillins are used for:

- L - Listeria
- A - Actinomycosis
- S - Syphilis
- T - Tetanus
- M - Meningococcal meningitis
- AN - Anthrax

41. Ans. (c) Piperacillin (Ref: KDT 6/e p699, 702, 703)

42. Ans. (d) Cloxacillin (Ref: KDT 6/e p700)

- Methicillin, cloxacillin, oxacillin and nafcillin are penicillinase resistant penicillins.
- Piperacillin, ticarcillin, ampicillin, amoxycillin, carbenicillin etc. are broad spectrum penicillins but these are susceptible to penicillinase.

43. Ans. (d) Cefoperazone (Ref: KDT 6/e p706)

44. Ans. (c) Cefepime (Ref: KDT 6/e p707)

45. Ans. (a) Cephadroxil (Ref: KDT 6/e p706, 707)

First generation cephalosporins like cephadroxil are mainly effective against gram +ve organisms and possess little activity against *Pseudomonas*.

46. Ans. (a) It is a 4th generation cephalosporin; (c) It possess antipseudomonal action (Ref: KDT 6/e p707)

- Cefepime, a fourth generation cephalosporin is more stable against plasmid mediated β-lactamase. It is active against *Staph aureus* enterobacter and citrobacter. It possesses anti-pseudomonal activity comparable to that of ceftazidime and gram-positive activity similar to that of ceftriaxone.
- Cephalosporins except cefoperazone and ceftriaxone are eliminated primarily by kidney, thus dose adjustment required in renal insufficiency.
- Cefepime has a short $t_{1/2}$ (2 hrs) and needs to be given 8 hourly.

47. Ans. (c) Renal tubular reabsorption of beta-lactams is inhibited by probenecid (Ref: KDT 6/e p697)

- Probenecid inhibits renal tubular secretion of penicillins (not reabsorption)
- Beta lactams eliminated by biliary route are:
 - Ampicillin
 - Nafcillin
 - Ceftriaxone
 - Cefoperazone
- Penicillin G has to be given by i.m. route because it is broken down by gastric acid (decreases oral bioavailability).

48. Ans. (c) Inhibition of transpeptidation reaction (Ref: KDT 6/e p704)

49. Ans. (c) In renal dysfunction, dosage reductions are necessary to avoid seizures (Ref: KDT 6/e p708, 709)

- Imipenem is a broad spectrum β-lactam antibiotic.
- It is used in combination with cilastatin.

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- No beta lactam antibiotic is effective against MRSA.
- In high concentration, imipenem-cilastatin combination can result in seizures.

50. Ans. (c) They have acquired penicillin binding protein which has low affinity for β -lactam antibiotic

(Ref: KDT 6/e p700)

- Resistance to most penicillins is due to elaboration of beta-lactamase.
- Methicillin is most resistant penicillin to β -lactamase.
- *Staphylococcus aureus* develops resistance to methicillins by acquisition of altered penicillin binding proteins.

51. Ans. (a) Benzathine penicillin (Ref: KDT 6/e p697)

52. Ans. (a) Methicillin resistant *Staph aureus* (Ref: KDT 6/e p702, 703)

- *Staphylococcus aureus* develops resistance to methicillin by acquiring altered penicillin binding proteins that have low affinity. No β -lactam antibiotic is effective against MRSA.
- Clavulanic acid is an inhibitor of β -lactamase. It can restore the sensitivity of penicillins against the organisms who have developed penicillinases.

53. Ans. (b) It acts by inhibiting bacterial protein synthesis (Ref: KDT 6/e p732)

- Vancomycin is a glycopeptide that acts by inhibiting bacterial cell wall synthesis. It is a bactericidal drug (like other cell wall synthesis inhibitors).
- It is the drug of choice for MRSA and enterococci resistant to penicillins.
- Nephrotoxicity, ototoxicity and red man syndrome are prominent adverse effects of vancomycin.

54. Ans. (c) It is not susceptible to penicillinases (Ref: KDT 6/e p732)

- Vancomycin is a glycopeptide bactericidal antibiotic that is administered by parenteral route.
- It is penicillinase resistant, thus can be used in MRSA infections.
- It is also used for the treatment of pseudomembranous colitis.
- Vancomycin is ineffective against pseudomonas.

55. Ans. (c) Piperacillin (Ref: KDT 6/e p702)

- Piperacillin can be combined with beta-lactamase inhibitor, tazobactam.
- Vancomycin is NOT effective against pseudomonas.
- All β -lactams except aztreonam are contra-indicated if severe allergic reaction develops to any β -lactam antibiotic.

56. Ans. (b) Aztreonam (Ref: KDT 6/e p708)

In patient with severe sensitivity to penicillin, all beta lactams *except monobactams* are contraindicated. Both aztreonam and imipenem are effective for gram negative infections but because imipenem causes seizures as serious adverse effect, aztreonam is preferred in such a patient.

57. Ans. (d) Given twice daily orally (Ref: KDT 6/e p707)

- Cefepime is a 4th generation cephalosporin.
- Due to high potency and extended spectrum, it is effective in many serious infections like hospital acquired pneumonia, febrile neutropenia, bacteremia, septicemia etc.
- All β -lactam antibiotics act by inhibiting the enzyme transpeptidase.
- Cefepime is given by i.v. route as it is not effective orally.

58. Ans. (a) Cephalexin (Ref: KDT 6/e p704-705; Goodman & Gilman 10/e p1209)

Cephalexin is an orally effective first generation cephalosporin active against gram positive but not against gram negative organisms like pseudomonas.

59. Ans. (a) Imipenem (Ref: KDT 6/e p708)

60. Ans. (c) Ceftazidime (Ref: KDT 6/e p706)

61. Ans. (b) Benzathine penicillin is short acting penicillin (Ref: KDT 6/e p697, 699, 700)

Benzathine penicillin is the longest acting penicillin.

62. Ans. (a) Inhibition of cell wall synthesis (Ref: KDT 6/e p668)

63. Ans. (a) Effective in pseudomonas infection (Ref: KDT 6/e p702)

- Carbenicillin is a penicillin congener effective against pseudomonas and indole positive proteus which are not inhibited by penicillin G or ampicillin/amoxicillin.
- It is inactive orally and excreted rapidly in urine. It is sensitive to penicillinase and acid, so administered parenterally as sodium salt.

64. Ans. (b) Clavulanic acid (Ref: KDT 6/e p702)
65. Ans. (b) Third generation cephalosporin (Ref: KDT 6/e p704)
66. Ans. (a) Better bioavailability if taken with foods (Ref: KDT 6/e p701)
67. Ans. (a) Cell wall synthesis (Ref: Katzung 11/e p775)
68. Ans. (d) Treponema (Ref: KDT 6/e p696)
69. Ans. (d) IIIrd generation long acting cephalosporin (Ref: KDT 6/e p706)
70. Ans. (a) Methicillin (Ref: KDT 6/e p700)
71. Ans. (d) Cefaclor (Ref: KDT 6/e p704)
72. Ans. (d) Azithromycin (Ref: KDT 6/e p695)
73. Ans. (c) Cefaclor (Ref: KDT 6/e p705)
74. Ans. (a) Cefixime (Ref: KDT 6/e p704)
75. Ans. (b) Skin rash (Ref: KDT 6/e p701)
76. Ans. (c) Piperacillin (Ref: KDT 6/e p702)
77. Ans. (c) Cefaclor (Ref: KDT 6/e p704)
78. Ans. (a) Cell wall synthesis (Ref: KDT 6/e p668)
79. Ans. (c) Cefepime (Ref: KDT 6/e p704)
80. Ans. (a) Nafcillin (Ref: KDT 6/e p699-701)
81. Ans. (c) Cefoxitin (Ref: KDT 6/e p704)
82. Ans. (d) In renal dysfunction, dosage reduction are necessary to avoid seizures (Ref: KDT 6/e p708,709)
83. Ans. (b) Cefpirome (Ref: K.D. Tripathi 6/e p704)
84. Ans. (a) Direct hair cell toxicity (Ref: Goodman and Gilman 12/e p1513, CMDT 2012/87-88)
Aminoglycosides can lead to ototoxicity, nephrotoxicity and neuromuscular blockade.

- **Ototoxicity** involves progressive and irreversible damage to, and eventually **destruction of, the sensory cells in the cochlea and vestibular organ of the ear.**
- **Nephrotoxicity** consists of damage to the **proximal tubules**, and is **reversible.**
- A rare but serious toxic reaction is paralysis caused by **neuromuscular blockade**. This is usually seen only if the agents are given concurrently with neuromuscular-blocking agents. It results from **inhibition of the Ca^{2+} uptake necessary for the exocytotic release of acetylcholine.**

85. Ans. (a) Cholera (Ref: Katzung, 11/e p897, CMDT 2010, 1341)
Tetracyclines are used for prophylaxis of both cholera (Katzung) as well as leptospirosis (CMDT). However, if we have to choose one, we will go with cholera, as the table on pg 897 of Katzung clearly writes tetracycline for cholera prophylaxis whereas in CMDT reference, doxycycline is used for prophylaxis of leptospirosis.
86. Ans. (c) Platelet count (Ref: Katzung 11/e p804)
Principal toxicity of linezolid is hematological which is reversible and generally mild. Thrombocytopenia is the most frequent manifestation, particularly when the drug is administered for longer than 2 weeks.
87. Ans. (d) It binds to motilin receptor (Ref: Katzung 11/e p1078; KDT 6/e p728)
Macrolide antibiotics such as erythromycin directly stimulate motilin receptors on GI smooth muscle and promote the onset of a migratory motor complex. Intravenous erythromycin (3 mg/kg) is beneficial in some patients with gastroparesis. It may be used in patients with acute upper GI bleeding to promote gastric emptying of blood before endoscopy.
88. Ans. (a) Are bacteriostatic (Ref: KDT 6/e p718)

- The aminoglycosides are **bactericidal antibiotics.**
- They are more active at **alkaline pH.**
- They kill the bacteria by interfering with **protein synthesis.**

Contd...

Contd...

- They are distributed only extracellularly so the volume of distribution is nearly equal to the extracellular fluid volume.
- They are not metabolized, they are excreted unchanged in the urine.
- Glomerular filtration is the main route of excretion (tubular secretion and reabsorption are negligible).
- Accumulation of the drug occurs in conditions with **low G.F.R.** e.g. elderly, neonates, C.R.F.
- They have relatively **narrow margin of safety** and all of them exhibit **ototoxicity** and **nephrotoxicity**.
- Aminoglycosides should be avoided during pregnancy because these can cause fetal damage (teratogenic)

89. Ans. (a) It is not teratogenic (Ref: Goodman and Gilman 10/e p1174; KDT 6/e p714)

90. Ans. (d) Macrolides (Ref: Katzung 10/e p917; KDT 6/e p840)

Tacrolimus is also a macrolide in structure. Macrolides possess anti-inflammatory and immunosuppressant activity.

91. Ans. (c) Simultaneous use of penicillin (Ref: KDT 6/e p722)

Penicillins increase the bactericidal activity of aminoglycosides. Combination of penicillins/cephalosporins and aminoglycosides is the treatment of choice for pseudomonas infections.

Risk factors for nephrotoxicity due to aminoglycosides:

- Elderly patients
- Hypokalemia
- Concomitant nephrotoxic drugs
- Total amount used is high

92. Ans. (b) Binding to 30S subunit and inhibits the binding of amino acyl tRNA to A-site (Ref: KDT 6/e p711)

For details of mechanism of action, refer to text.

93. Ans. (c) Puromycin (Ref: Harper's 27/e p378)

Puromycin structurally resembles aminoacyl t-RNA and inhibits protein synthesis by causing premature termination. Tetracyclines inhibits the binding of aminoacyl-tRNA to the A site.

94. Ans. (a) Cisplatin; (b) Furosemide; (c) Vancomycin; (e) Erythromycin (Ref: Dhingra 2/e p39; KDT 6/e p722; Harrison 15/e p436)

Ototoxic drugs are:

D - Drugs causing deafness are

E - Ethacrynic acid

A - Aminoglycosides

F - Furosemide

N - Nitrogen mustards

E - Erythromycin

S - Salicylates

S - Smoking

Causing - Cisplatin

Vital - Vancomycin

Medicines - Malarial drugs eg. quinine

So, ototoxic effect of aminoglycoside is enhanced with concurrent use of the above mentioned drugs.

95. Ans. (c) It is more active than tetracycline against *H.pylori* (Ref: KDT 6/e p637, 710, 712, 713)

- Doxycycline is a bacteriostatic agent that acts by inhibiting protein synthesis.
- It is safe in renal failure as it is excreted mainly in feces.
- Doxycycline is useful in Lyme's disease.
- Tetracycline (and not doxycycline) is useful in *H.pylori* therapy.

96. Ans. (c) They induce formation of hepatic drug metabolizing enzymes (Ref: Katzung 10/e p753)

- Streptogramins like quinpristin and dalbapristin possess microsomal enzyme inhibitory property (NOT inducing).
- These are effective against MRSA and VRE infections.

97. Ans. (c) The spectrum of antimicrobial activity of aminoglycosides includes *Bacteroides fragilis*

(Ref: KDT 6/e p719, 720; Katzung 10/e p758)

Important points about aminoglycosides are:

- These are bactericidal inhibitors of protein synthesis.
- Due to formation of ionic molecules in GIT, these are ineffective orally.
- Combination of aminoglycosides with penicillins is synergistic and is used for pseudomonas and enterococcal infections.
- Aminoglycosides require O_2 for transport in the bacterial cell. These are therefore, not effective against anaerobic organisms like *Bacteroides fragilis*.

98. Ans. (b) Gentamicin continues to exert antibacterial effects even after plasma levels decrease below detectable range. (Ref: Katzung 10/e p756, 757)

- Aminoglycosides show concentration dependent killing and prolonged post antibiotic effect.
- For details, refer to text.

99. Ans. (a) Minocycline (Ref: KDT 6/e p713)

- Tetracycline causing maximum vestibular toxicity : Minocycline
- Most phototoxic tetracycline : Demeclocycline
- Tetracycline causing diabetes insipidus : Demeclocycline
- Tetracycline safe in renal failure : Doxycycline

100. Ans. (d) Doxycycline (Ref: KDT 6/e p713)

101. Ans. (b) Acquisition of a plasmid encoded for chloramphenicol acetyl transferase (Ref: KDT 6/e p716)

102. Ans. (b) Aminoglycosides (Ref: KDT 6/e p669)

Most protein synthesis inhibiting antibiotics are bacterostatic but aminoglycosides are bactericidal.

103. Ans. (c) Erythromycin estolate (Ref: KDT 6/e p728)

104. Ans. (a) Minocycline (Ref: KDT 6/e p753, 756)

105. Ans. (a) Amikacin (Ref: KDT 6/e p724)

Amikacin is most resistant to aminoglycoside inactivating enzymes.
Aminoglycosides are not effective against anaerobes.

106. Ans. (c) Blockade of binding of aminoacyl-tRNA to bacterial ribosomes (Ref: KDT 6/e p668)

107. Ans. (b) Clindamycin (Ref: KDT 6/e p731, 732)

Important points about clindamycin are:

- It acts by inhibiting protein synthesis (via. inhibition of translocation).
- It is effective against anaerobic organisms.
- Pseudomembranous colitis and hepatotoxicity are important adverse effects.
- It is secreted in bile, therefore can be used safely in patients with renal dysfunction.

108. Ans. (d) Streptomycin (Ref: KDT 6/e p719, 720)

109. Ans. (a) Trichomonas (Ref: KDT 6/e p715)

110. Ans. (a) Erythromycin (Ref: KDT 6/e p727)

111. Ans. (a) 50S ribosome (Ref: KDT 6/e p716)

112. Ans. (d) Topical in open wound (Ref: KDT 6/e p712)

113. Ans. (d) Azithromycin (Ref: KDT 6/e p727)

114. Ans. (d) Neomycin (Ref: KDT 6/e p721)

115. Ans. (d) Amikacin (Ref: KDT 6/e p721)

116. Ans. (a) Translocation of 50 S ribosome (Ref: KDT 6/e p727)

117. Ans. (c) Post antibiotic effect (Ref: Katzung 11/e p809)

118. Ans. (b) VRSA (Ref: KDT 6/e p733)

119. Ans. (d) All of the above (Ref: KDT 6/e p715)

- Doxycycline is drug of choice for rickettsial infections including Q fever and for borreliosis.
- It can also be used for leptospirosis for which the drug of choice is penicillin G

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120. Ans. (d) Moxifloxacin (Ref: KK Sharma 2/e p709-712)

Among the given options, the drug with longest half life is moxifloxacin (around 12 hours) but overall longest acting is sparfloxacin (20 hours)

121. Ans. (a) Chancroid (Ref: Katzung 11/e p818)

- Combination of trimethoprim-sulfamethoxazole is effective treatment for
 - P. jiroveci pneumonia
 - Shigellosis
 - Systemic salmonella infections
 - Upper respiratory tract infections
 - Community-acquired bacterial pneumonia.

Treatment of chancroid include azithromycin, doxycycline or ciprofloxacin.

122. Ans. (a) Acute Intermittent Porphyria (Ref: Harrison 17/e p2439)

It is a case of acute intermittent porphyria due to sulfonamide use.

Important Drugs Causing Precipitation of Porphyria

Barbiturates	Sulfonamides
Carbamazepine	Co-trimoxazole
Oral contraceptives	Phenobarbitone
Rifampicin	Phenytoin

123. Ans. (a) Sulfonamides; (b) Methotrexate; (d) Trimethoprim (Ref: CMDT 2010/440 446)

- Folic acid is formed by the action of folate synthase and dihydrofolic acid reductase enzymes.

Folate synthase inhibitors	DHFRase inhibitors	Other drugs which antagonise folic acid metabolism but mechanism is not fully understood
• Sulfonamides	• Methotrexate	• Triamterene (Reg. G.G. 11/e p759)
• Dapsone	• Pentamidine	• Phenytoin
• PAS	• Pyrimethamine	• Primidone
	• Proguanil	• Phenobarbitone

- N₂O inhalation causes the destruction of endogenous cobalamin. Fatal megaloblastic anaemia has been reported in patients treated with nitrous oxide continuously.

124. Ans. (b) Nalidixic acid; (c) Ciprofloxacin (Ref: KDT 6th Ed. Pg-687, 688)

- Cytarabine, 5-FU and 6-MP are anti-metabolites that inhibit DNA replication due to incorporation into DNA strands.
- Nalidixic acid and fluoroquinolones (like ciprofloxacin) inhibit DNA replication by inhibiting the enzyme DNA topoisomerase.)

125. Ans. (d) Sulfonamide (Ref: KDT 6/e p684)**126. Ans. (b) Sulfasalazine** (Ref: KDT 6/e p684)

- Sulphacetamide and mafenide are used topically in the eye.
- Silver sulfadiazine is used for preventing the infections in burn patients.
- Sulfasalazine is used orally for the treatment of ulcerative colitis.

127. Ans. (a) Sulfasalazine is absorbed well from GIT (Ref: Katzung 10/e p587; KDT 6/e p661-684)

- Sulfonamides can get precipitated in the urine resulting in crystalluria.
- These can displace bilirubin from plasma protein binding sites and result in elevated free bilirubin in the blood. In newborn baby blood brain barrier is not well developed and free bilirubin can enter the brain. It gets deposited in the basal ganglia resulting in kernicterus.
- Sulfonamides are very effective against nocardia species. Combination of sulphamethoxazole with trimethoprim (known as cotrimoxazole) is the treatment of choice for nocardiosis.
- Sulfasalazine is used for the treatment of ulcerative colitis. It is broken down in the colon to produce 5-aminosalicylic acid and sulfapyridine. 5-ASA acts locally in the colon to decrease the symptoms of ulcerative colitis. If used alone, 5-ASA is ineffective because it is absorbed in the small intestine and very little drug reaches the colon.

128. Ans. (b) Trovafloxacin (Goodman & Gilman 11/e p1121)

Fluoroquinolones safe in renal failure are:

- P – Pefloxacin
- M – Moxifloxacin
- T – Trovafloxacin

129. Ans. (a) Ventricular arrhythmia (Ref: KDT 6/e p692)

- Both sparfloxacin and astemizole blocks cardiac K⁺ channels in high concentration. This property may result in torsades de pointes (polymorphic ventricular tachycardia).
- Other drugs causing torsades de pointes are:
 - Terfenadine
 - Cisapride
 - Ziprasidone
 - Gepafloxacin

130. Ans. (a) Sulfonamides inhibit bacterial dihydrofolate reductase (Ref: KDT 6/e p685)

- Sulfonamides are antimetabolites that act by inhibiting the enzyme folate synthase. Dihydrofolate reductase is inhibited by methotrexate, trimethoprim and pyrimethamine.
- These can cause kernicterus in new born if used in late pregnancy.
- At acidic pH, these can get precipitated and result in crystalluria.

131. Ans. (c) A fluoroquinolone is the drug of choice for treatment of an uncomplicated urinary tract infection in a 7 year old child (Ref: KDT 6/e p689)

- Fluoroquinolones are contra-indicated in children (due to risk of cartilage damage) and pregnant female.
- Most common mode of resistance to fluoroquinolones is mutation in DNA gyrase.
- Dose of fluoroquinolones should be adjusted in renal failure (except moxifloxacin and trovafloxacin).
- These drugs act by inhibiting DNA gyrase.

132. Ans. (d) Skin reactions (Ref: KDT 6/e p684)

Rash is the most common adverse effect seen with the use of sulfonamides.

133. Ans. (b) Ofloxacin (Ref: KDT 6/e p756)

Single lesion single dose treatment of leprosy utilizes ROM therapy.

R: Rifampicin

O: Ofloxacin

M: Minocycline Nowdays, even single lesion leprosy is treated as paucibacillary leprosy

134. Ans. (b) Sparfloxacin (Ref: Principles of Pharmacology by KK Sharma and HL Sharma/734; KDT 6/e p692)

- Maximum phototoxic fluoroquinolone is sparfloxacin.
- Pefloxacin and Lomefloxacin are also phototoxic but less than sparfloxacin.

135. Ans. (c) Converted to formaldehyde at low pH (Ref: KDT 6/e p735)

Methanamine mandelate is used as an urinary antiseptic. It acts by conversion to formaldehyde at acidic urinary pH. Mandelic acid formed from this salt also serves the function of urinary acidifying agent. These are not effective against proteus because proteus results in the formation of ammonia which alkalinizes the urine.

136. Ans. (a) Epilepsy (Ref: KDT 6/e p689)

- Ciprofloxacin is contraindicated with NSAIDs because this combination results in increased risk of seizures.
- It is also contra-indicated with theophylline because it increases the risk of theophylline toxicity by inhibiting its metabolism.
- It is contra-indicated in pregnancy because it increases the risk of cartilage damage in newborn.

137. Ans. (c) Pneumocystis jiroveci (Ref: KDT 6/e p686, 687)

Cotrimoxazole is effective against Pneumocystis and toxoplasmosis.

138. Ans. (a) Ciprofloxacin inhibits theophylline metabolism (Ref: KDT 6/e p221)

Theophylline has a narrow margin of safety (low therapeutic index) Ciprofloxacin inhibits theophylline metabolism and increases its plasma level leading to toxicity. Thus, ciprofloxacin should not be given to an asthmatic using theophylline.

139. Ans. (c) Inhibits DNA gyrase (Ref: KDT 6/e p688)
140. Ans. (a) Sulfacetamide (Ref: KDT 6/e p684)
141. Ans. (d) Pefloxacin (Ref: KDT 6/e p691)
142. Ans (c) Clindamycin (Ref: Harrison 18/e p1013-1014)

Important points regarding pseudomembranous colitis:

- Most common organism implicated: Clostridium difficile
- Most common antimicrobial implicated: Cephalosporins > Clindamycin
- Drug of choice for treatment of mild to moderate PMC: Metronidazole
- Drug of choice for treatment of severe PMC: Vancomycin

143. (d) Cefotaxime + vancomycin (Ref: Harrison 18/e p3414)

Antibiotics Used in Empirical Therapy of Bacterial Meningitis and Focal CNS Infections

Indication	Antibiotic
Preterm infants to infants <1 month	Ampicillin + cefotaxime
Infants 1–3 month	Ampicillin + cefotaxime or ceftriaxone
Immunocompetent children >3 months and adults <55 years	Cefotaxime, ceftriaxone or cefepime + vancomycin
Adults >55 years and adults of any age with alcoholism or other debilitating illnesses	Ampicillin + cefotaxime, ceftriaxone or cefepime + vancomycin
Hospital-acquired meningitis, post-traumatic or post-neurosurgery meningitis, neutropenic patients, or patients with impaired cell-mediated immunity	Ampicillin + ceftazidime or meropenem + vancomycin

144. Ans. (b) Cefaclor (Ref: KK Sharma 2/e p727)

Cefaclor is a second generation cephalosporin and is not active against MRSA. Resistance in MRSA occurs due to altered PBP_s (transpeptidase). As the binding site is altered, therefore, no beta lactam can bind and thus all beta-lactams (penicillins, cephalosporins, carbapenems and monobactams) are ineffective against MRSA. However, recently fifth generation cephalosporins like ceftaroline and ceftobiprol have been formed, which are effective against MRSA.

145. Ans (a) Pencillin (Ref: CMDT 2012/1433)

The only acceptable treatment for syphilis in pregnancy is penicillin in dosage schedules appropriate for the stage of the disease.

Penicillin remains the preferred treatment for syphilis, since there have been no documented cases of penicillin resistant *T pallidum*. Although doxycycline is an alternative for some patients, pregnant women must be treated with penicillin (see below).

Recommended treatment of Syphilis

Stage of syphilis	Treatment	Alternative	Comment
Primary, secondary, or early latent	Benzathine penicillin G 2.4 million units IM once	Doxycycline 100 mg orally twice daily for 14 days or tetracycline 500 mg orally four times daily for 28 days or ceftriaxone 1g IM daily for 8–10 days	
Late			
Late latent or uncertain duration	Benzathine penicillin G 2.4 million units IM weekly for 3 weeks	Doxycycline 100 mg orally twice daily for 28 days or tetracycline 500 mg orally four times a day for 28 days	
Tertiary without neurosyphilis	Benzathine penicillin G 2.4 million units IM weekly for 3 weeks	Doxycycline 100 mg orally twice daily for 28 days or tetracycline 500 mg orally four times a day for 28 days	Cerebrospinal fluid evaluation recommended in all patients
Neurosyphilis	Aqueous penicillin G 18-24 million units IV daily, given every 3-4 hours or as continuous infusion for 10-14 days	Procaine penicillin, 2.4 million units IM daily with probenecid 500 mg orally four times a day for 10–14 days or ceftriaxone 2 g IM daily for 10–14 days	Follow treatment with benzathine penicillin G, 2.4 million units IM weekly for up to 3 weeks

contd...

Note: Penicillin is the only documented effective treatment in pregnancy, so pregnant patients with true allergy should be desensitized and treated with penicillin according to stage of disease as above.

146. **Ans. (d) Change over to imipenem** (Ref: *Katzung 11/e p786*)
Carbapenems like imipenem are the only reliable drugs against an organism producing ESBL (extended spectrum beta lactamases).
147. **Ans. (b) Metronidazole** (Ref: *CMDT 2010, 574*)
Metronidazole is drug of choice for pseudomembranous colitis. Vancomycin can also be used.
148. **Ans. (a) Ampicillin** (Ref: *Harrison 17/e p942*)
- *K. pneumoniae* and *K. oxytoca* are intrinsically resistant to ampicillin and ticarcillin.
 - Empirical treatment of serious or health care-associated Klebsiella infections should be done with amikacin, carbapenems, or tigecycline.
 - Polymyxin B can be considered for use against highly resistant strains but is an agent of last resort because of its potential toxicities.
149. **Ans. (c) Erythromycin** (Ref: *CMDT-2010/1328*)
- Drug of choice for chlamydial infections is doxycycline. However, it is contra-indicated in pregnancy.
 - DOC for chlamydial infections in pregnancy are macrolides like erythromycin and azithromycin.
150. **Ans. (c) Colistin** (Ref: *Katzung 10/e p1194; KDT 6/e p734*)
- Polypeptides like colistin and polymyxin B are effective against pseudomonas.
 - Carbenicillin, ticarcillin, piperacillin, azlocillin and mezlocillin are the penicillins effective against pseudomonas whereas cefoperazone, ceftazidime, cefepime and ceftazidime are cephalosporins effective against pseudomonas.
151. **Ans. (d) Glycopeptides** (Ref: *CMDT-2008, 1232; KDT 6/e p732*)
Vancomycin is a glycopeptide and is drug of choice for MRSA. Remember, no beta lactam is effective against MRSA.
152. **Ans. (d) Carbapenem** (Ref: *CMDT-2008, p1232; KDT 6/e p708*)
MRSA do not respond to any beta lactam antibiotic (penicillins, cephalosporins, carbapenems and monobactams) because it has altered penicillin binding sites.
153. **Ans. (b) Sulfonamides** (Ref: *Harrison 17/e p346*)
Sulfonamides are frequent cause of fixed drug eruptions.
154. **Ans. (a) Piperacillin** (Ref: *Katzung 10/e p733; KDT 6/e p702*)
155. **Ans. (b) Erythromycin** (Ref: *Katzung 10/e p840; KDT 6/e p729*)
Drug of choice for prophylaxis of diphtheria is penicillin or erythromycin.
156. **Ans. (d) Doxycycline** (Ref: *Principles of Pharmacology HL Sharma and KK Sharma 1/e p759, 769, 772, 803; KDT 6/e p673,721*)
- All aminoglycosides are nephrotoxic, ototoxic and produce curare type neuromuscular blockade.
 - Doxycycline with its longer half life and lack of nephrotoxicity (due to biliary excretion) is a popular choice for patients with pre-existing renal disease.
157. **Ans. (a) Amikacin** (Ref: *Harrison 17/e p900: Table 137-1; CMDT 2010, 1313; KDT 6/e p691-731*)
Antibiotic therapy for typhoid fever
- | | |
|--|-------------------------------------|
| • First line | <i>Ciprofloxacin or Ceftriaxone</i> |
| • Alternative (for Nalidixic acid Resistant S.typhi) | <i>Azithromycin</i> |
158. **Ans. (a) Ciprofloxacin** (Ref: *KDT 6/e p689*)
- Vancomycin is not effective against pseudomonas.

- **Drugs effective against pseudomonas are:**
 - *Penicillins:* Carbenicillin, ticarcillin, piperacillin, azlocillin and mezlocillin
 - *Cephalosporins:* Ceftazidime, cefoperazone, cefepime, ceftazidime
 - *Carbapenems:* Imipenem, meropenem
 - *Fluoroquinolones:* Ciprofloxacin, levofloxacin, pefloxacin
 - All aminoglycosides
 - Polymyxin B
 - Colistin

- Drug of choice for Pseudomonas is ceftazidime + aminoglycoside.

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159. **Ans. (a) Cefaclor** (Ref: KDT 6/e p690,685,732, CMDT 2010, 1294-1295)
MRSA is resistant to all the available beta-lactam antimicrobials except fifth-generation cephalosporins.
160. **Ans. (c) Brinzolamide** (Ref: KDT 6/e p147)
Brinzolamide is a carbonic anhydrase inhibitor that has a structure similar to sulfonamides.
161. **Ans. (b) Imipenem** (Ref: KDT 6/e p708, 709)
 - All beta lactam antibiotics are ineffective against MRSA. Therefore penicillins, cephalosporins, carbapenems (like imipenem) and monobactams (like aztreonam) are not appropriate for the treatment of MRSA infections.
 - Drug of choice for MRSA is vancomycin.
 - Other drugs used for MRSA are teicoplanin, streptogramins, linezolid and daptomycin.
162. **Ans. (c) Cefoperazone** (Ref: KDT 6/e p706)
Cefoperazone is not nephrotoxic. It causes disulfiram like reaction and hypoprothrombinemia.
163. **Ans. (a) Rifampicin** (Ref: KDT 6/e p742)
 - Rifampicin is drug of choice for prophylaxis of meningococcal meningitis.
 - Ciprofloxacin can also be used for the prophylaxis of meningococcal meningitis
164. **Ans. (a) Vancomycin** (Ref: KDT 6/e p732)
For drugs effective against *Pseudomonas aeruginosa*, refer to the table given in the text.
165. **Ans. (a) Neomycin** (Ref: KDT 6/e p725)
When administered by oral route, neomycin is not absorbed and kills intestinal bacteria. These bacteria are responsible for the generation of NH_3 . Excessive ammonia can result in hepatic encephalopathy. Neomycin decreases NH_3 by killing intestinal bacteria.
166. **Ans. (b) Tetracycline** (Ref: KDT 6/e p714)
167. **Ans. (d) Beclomethasone** (Ref: KDT 6/e p706, 799)
Drugs causing disulfiram like reaction are:
- Cefamandole
 - Procarbazine
 - Moxalactam
 - Cefoperazone
 - Metronidazole
 - Chlorpropamide
 - Griseofulvin
168. **Ans. (d) Azithromycin; (e) Doxycycline** (Ref: Harrison 17/e p1623-1624)
 - Macrolides (clarithromycin or azithromycin) or doxycycline are indicated for out patient treatment of community acquired pneumonia, if no cardiopulmonary disease is present and there is no risk factor of drug-resistant infection.
 - If cardiopulmonary disease is present or there is high risk of drug resistance, then out patient treatment of community acquired pneumonia should include fluoroquinolones (like levofloxacin, moxifloxacin or gatifloxacin) or β -lactams (cefepodoxime, cefuroxime, amoxicillin) plus macrolides/doxycycline/telithromycin.
 - Ceftriaxone and imipenem are indicated for in-hospital treatment of community acquired pneumonia.
 - Cefazolin is not indicated for community acquired pneumonia.
169. **Ans. (a) Quinupristin/dalfopristin; (b) Linezolid; (c) Teicoplanin** (Ref: KDT 6/e p733)
Drugs used in MRSA (Methicillin resistant *S. aureus*) treatment are:
- Vancomycin/Teicoplanin
 - Linezolid
 - Quinupristin/dalfopristin
 - Trimethoprim + sulfamethoxazole
 - Minocycline
- Beta-lactams are not effective against MRSA.
170. **Ans. (a) Ciprofloxacin; (b) Cycloserine; (c) Glucocorticoids** (Ref: KDT 6/e p278, 689-744)
Drugs and other substances that can cause seizure:

- Antimicrobials/anti virals
 - Procaine penicillin G, Imipenem-cilastatin
 - Quinolones, acyclovir, isoniazid, ganciclovir, **cycloserine**
- Anaesthetics and analgesics
 - Meperidine, tramadol, local anaesthetics, class IB anti-arrhythmic agents
- Immunomodulatory drugs
 - Cyclosporine, tacrolimus (FK-506), OKT3, interferons
- Antipsychotics, antidepressants, lithium, theophylline, alcohol, barbiturate, benzodiazepines.
- Drugs abuse like amphetamine, phencyclidine, methylphenidate, flumazenil etc.
- As these drugs causes seizure, so these drugs should better be avoided.
- High dose of glucocorticoids lowers the seizure threshold. So cautious use in epileptics is required.

171. Ans. (b) Ciprofloxacin; (c) Cefotaxime (Ref: Harrison 17/e p920)

Recommended Rx of Gonococcal infection (Penicillinase producing NG):

Diagnosis		Rx of choice	
•	Uncomplicated infection of urethra, cervix, rectum or pharynx	–	Ceftriaxone, cefixime
•	Alternative regimen	–	Spectinomycin, ceftizoxime, cefotaxim.
•	Pregnancy	–	Spectinomycin
•	Pediatric	–	Ceftriaxone
•	Allergic to β -lactam drugs ¹	–	Ciprofloxacin, Ofloxacin, Spectinomycin

172. Ans. (a) Metronidazole; (b) Imipenem and (e) vancomycin (Ref: Harrison 17/e p1005)

- Drugs effective against anaerobic organisms are:
 - Metronidazole
 - Ticarcillin/clavulanic acid
 - Meropenem
 - Clindamycin
 - Ampicillin/Sulbactam
 - Imipenem
 - Chloramphenicol
 - Vancomycin

173. Ans. (a) Cephalexin; (e) Doxycycline (Ref: KDT 6/e p673)

- The antibiotics which are safe in renal failure are:
 - Cephalexin
 - Cefoperazone
 - Chloramphenicol
 - Erythromycin
 - Azithromycin.
 - Cefaclor
 - Ceftriaxone
 - Clindamycin
 - Carbenicillin
- Most tetracyclines are primarily excreted in urine by glomerular filtration; dose has to be reduced in renal failure; doxycycline is an exception to this.
- The renal excretion of nitrofurantoin is reduced in azotemic patients; effective concentrations may not be reached in urine, while toxicity increases; so it is contraindicated in renal failure.

174. Ans. (e) Ciprofloxacin (Ref: KDT 6/e p690-691)

- Till recently chloramphenicol was drug of choice for typhoid fever. But due to emergence of resistant-strains of *S. typhi*, it is no longer used now a days.
- Due to emergence of MDR *S. typhi*— either quinolones or third-generation cephalosporins (e.g. ceftriaxone) are currently recommended for empirical antibiotic treatment.

175. Ans. (b) Vancomycin (Ref: KDT 6/e p732, 733; Katzung 11/e p787)

176. Ans. (a) Amikacin (Ref: KDT 6/e p721)

Aminoglycosides can cause nephrotoxicity, ototoxicity and neuromuscular block.

177. Ans. (c) Clindamycin (Ref: KDT 6/e p731, 732)

- Clindamycin is excreted by biliary route and therefore can be used safely in renal dysfunction.
- Other drugs excreted in bile are:
 - Ampicillin
 - Nafcillin
 - Chloramphenicol
 - Novobiocin
 - Rifampicin
 - Doxycycline

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178. Ans. (a) Tobramycin (Ref: KDT 6/e p719, 720)

Aminoglycosides require oxygen for transport in the bacterial cell. These are therefore ineffective against anaerobic organisms.

179. Ans. (c) Linezolid (Ref: KDT 6/e p733)

180. Ans. (d) Spectinomycin (Ref: Katzung 10/e p761, 762)

- Ceftriaxone is contraindicated in patients having severe allergy to penicillins.
- Tetracyclines are not effective against gonorrhoea.
- Although ciprofloxacin is effective as a single dose treatment of gonorrhoea but it is contraindicated in pregnancy.
- Spectinomycin can be given as single dose treatment of PPNG.

181. Ans. (a) Rifampicin (Ref: KDT 6/e p742)

Rifampicin and ciprofloxacin are used for the prophylaxis of meningococcal meningitis.

182. Ans. (b) Erythromycin (Ref: KDT 6/e p729)

Diagnosis is atypical pneumonia and DOC is erythromycin.

183. Ans. (d) Amikacin (Ref: KDT 6/e p719, 720)

- Drugs used to treat anaerobic organisms include:
- Metronidazole
- Moxifloxacin and Trovafloxacin
- Vancomycin
- Clindamycin
- Chloramphenicol

Aminoglycosides are ineffective against anaerobic organisms

184. Ans. (d) Vancomycin (Ref: KDT 6/e p732)

- Severe allergy to penicillins rule out the use of amoxicillin and cefazolin.
- Vancomycin is highly effective against MRSA and enterococcal infections.
- Drugs for VRSA and VRE (Vancomycin Resistant *Enterococcus faecalis*) include linezolid and daptomycin.

185. Ans. (b) Linezolid (Ref: KDT 6/e p733)

186. Ans. (c) Metronidazole (Ref: KDT 6/e p799, 800)

187. Ans. (b) Daptomycin (Ref: KDT 6/e p741)

Daptomycin is a newer antibiotic that acts by causing depolarization of bacterial cell membranes. It is effective in MRSA, VRSA and even streptogramin resistant SA infections as well as VRE infections. It can cause myopathy in patients taking statins.

188. Ans. (b) A drug effective against anaerobe should be included in the antibiotic regimen (Ref: KDT 6/e p679, 680)

Abdominal sepsis is a mixed type of infection caused by both aerobic and anaerobic organisms. Ampicillin and gentamicin will inhibit most of the aerobic organisms but these are not effective against anaerobic organisms. Therefore metronidazole or clindamycin should be included in the treatment regimen.

189. Ans. (b) Chloramphenicol (Ref: Katzung 11/e p803)

The patient's shows decreased erythrocytes, leukocytes, and platelets. This condition is called pancytopenia or aplastic anemia. It occurs due to suppression of stem cell function in the bone marrow. Chloramphenicol can cause both dose-dependent and dose-independent aplastic anemia. Dose-dependent aplastic anemia associated with chloramphenicol is reversible after the medication is withdrawn. Dose-independent anemia is usually severe and may be fatal.

190. Ans. (c) Vancomycin (Ref: KDT 6/e p732)

191. Ans. (d) Ethambutol (Ref: KDT 6/e p673)

Aminoglycosides, Amphotericin B, cephalosporins, vancomycin, flucytosine and ethambutol require dose reduction even in mild renal failure.

192. Ans. (c) Ciprofloxacin (Ref: KDT 6/e p689)

193. Ans. (b) Chloramphenicol (Ref: KDT 6/e p717; Satoskar Bhandarkar, 19/e p694)

194. Ans. (c) Pentamidine (Ref: Robbins 7/e p640; KDT 6/e p686,806)

- All of the options mentioned can cause folic acid deficiency resulting in megaloblastic anemia but pentamidine rarely causes this side effect.

- **Drugs causing macrocytic anaemia are:**
 - Co-trimoxazole
 - Folate antagonists like trimethoprim, pyrimethamine, methotrexate etc.
 - Nitrous oxide after repeated or prolonged exposure.
 - Oral contraceptives
 - Phenobarbital, phenytoin
 - Primidone
 - Triamterene

195. **Ans. (c) Clindamycin** (Ref: KDT 6/e p731)

Among the given options, the answer is clindamycin but presently, 3rd generation cephalosporins are the most common cause of pseudomembranous colitis.

196. **Ans. (c) Ampicillin** (Ref: KDT 6/e p721)

Aminoglycosides (tobramycin, gentamicin, kanamycin), vancomycin and amphotericin B are highly nephrotoxic agents.

197. **Ans. (c) Erythromycin** (Ref: KDT 6/e p728)

Erythromycin is secreted in bile and does not require dose adjustment in renal failure.

198. **Ans. (b) Penicillin** (Ref: KDT 6/e p698)

199. **Ans. (b) Aminoglycosides** (Ref: KDT 6/e p721)

200. **Ans. (a) Gentamicin** (Ref: KDT 6/e p721)

Gentamicin is an aminoglycoside. All aminoglycosides can cause nephrotoxicity.

201. **Ans. (c) Pyrimethamine** (Ref: KDT 6/e p790)

- INH causes B₆ deficiency resulting in sideroblastic anemia
- Chloramphenicol causes aplastic anemia.
- Pyrimethamine causes megaloblastic anemia.
- Methylidopa causes autoimmune hemolytic anemia (warm)

202. **Ans. (d) None** (Ref: KDT 6/e p674)

203. **Ans. (b) Penicillins** (Ref: CMDT 2010/1341-1342)

204. **Ans. (d) Oxacillin** (Ref: Katzung 11/e p780)

205. **Ans. (b) Chloramphenicol** (Ref: Katzung 11/e p803)

206. **Ans. (b) Ampicillin** (Ref: KDT 6/e p674)

207. **Ans. (b) Inj. Benzathine Penicillin** (Ref: KDT 6/e p699)

208. **Ans. (b) Tetracyclines** (Ref: KDT 6/e p715)

209. **Ans. (b) Chloramphenicol** (Ref: KDT 6/e p716)

210. **Ans. (d) Rifampicin** (Ref: KDT 6/e p742)

211. **Ans. (b) Doxycycline** (Ref: KDT 6th 713)

212. **Ans. (c) Both** (Ref: KDT 6/e p732-733)

213. **Ans. (c) Erythromycin** (Ref: KDT 6/e p729)

214. **Ans. (b) Gentamicin** (Ref: KDT 6/e p724)

215. **Ans. (d) Erythromycin** (Ref: KDT 6/e p729)

216. **Ans. (b) Ampicillin** (Ref: KDT 6/e p701)

217. **Ans. (b) Benzathine penicillin** (Ref: KDT 6/e p698)

218. **Ans. (c) Benzathine penicillin** (Ref: KDT 6/e p698)

219. **Ans. (d) INH** (Ref: Harrison 15/e p432)

220. **Ans. (d) Primaquine** (Ref: KDT 6/e p792)

221. **Ans. (c) Griseofulvin** (Ref: KDT 6/e p760)

222. **Ans. (a) Erythromycin** (Ref: KDT 6/e p728)

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- 223. (b) Cefuroxime (Ref: KDT 6/e p909)
- 224. Ans. (c) Azithromycin (Ref: KDT 6/e p730)
- 225. Ans. (d) Crystalline penicillin (Pen. G) (Ref: Katzung 11/e p798)
- 226. Ans. (a) Crystalline penicillin (Pen. G) (Ref: Katzung 11/e p778)
- 227. Ans. (b) Polymixin B (Ref: KDT 6th 734)
- 228. Ans. (b) Penicillin G (Ref: KDT 6th 697)

ANSWERS OF RECENT QUESTIONS ASKED BY NATIONAL BOARD

- 1. Ans (a) Vancomycin (Ref: KDT 7th/757)
- 2. Ans (c) Azithromycin (Ref: KDT 7th/755)
- 3. Ans (b) Inhibiting DNA gyrase (Ref: KDT 7th/709)
- 4. Ans (b) Sulfadoxine (Ref: KDT 7th/704)
- 5. Ans (b) Amikacin (Ref: KDT 7th/749)
- 6. Ans (d) Carbenicillin (Ref: KDT 7th/415)
- 7. Ans (a) Listeria (Ref: KDT 7th/722)
- 8. Ans (a) Vancomycin (Ref: KDT 7th/730, 711, 759)
- 9. Ans (a) Tetracycline (Ref: KDT 7th/736)
- 10. Ans (a) Vancomycin (Ref: KDT 7th/757)
- 11. Ans (a) Penicillin (Ref: KDT 7th/763)
- 12. Ans (c) Moxalactam (Ref: CMDT 2015/547)
- 13. Ans (a) Competitive inhibition (Ref: KDT 7th/704)
- 14. Ans (d) More active at acidic pH (Ref: KDT 7th/710)
- 15. Ans (d) Sulfonamides (Ref: KDT 7th/704)
- 16. Ans. (a) Tetracycline (Ref: KDT 7/e p733)
- 17. Ans. (b) Erythromycin (Ref: Internet)
- 18. Ans. (b) Penicillins (Ref: KDT 7/e p689)
- 19. Ans. (b) Doxycycline (Ref: KDT 7/e p735)
- 20. Ans. (b) Rifampicin (Ref: KDT 7/e p768)
- 21. Ans. (a) DNA gyrase inhibitors (Ref: KDT 7/e p709)
- 22. Ans. (b) Benzathine Penicillin (Ref: KDT 7/e p763)
- 23. Ans. (c) It should be used with cilastatin (Ref: KDT 7/e p731)
- 24. Ans. (b) Carbenicillin (Ref: KDT 7/e p721)
- 25. Ans. (a) Penicillin G (Ref: KDT 7/e p763)
- 26. Ans. (c) Cefuroxime (Ref: KDT 7/e p726)
- 27. Ans. (b) Penicillin (Ref: KDT 7/e p720)
- 28. Ans. (b) Linezolid (Ref: KDT 7/e p716)
- 29. Ans. (b) Vancomycin (Ref: KDT 7/e p757)
- 30. Ans. (a) Clindamycin (Ref: KDT 7/e p756)
- 31. Ans. (b) Amikacin (Ref: KDT 7/e p749)

32. Ans. (b) Ceftriaxone (Ref: KDT 7/e p724, 727-728)
33. Ans. (c) Clindamycin (Ref: KDT 7/e p712)
34. Ans. (c) Tetracycline (Ref: CMDT 2014/ p1415)
35. Ans. (b) Azithromycin (Ref: KDT 7/e p656)
36. Ans. (d) Aztreonam (Ref: KDT 7/e p724)
37. Ans. (c) Are safe in pregnancy (Ref: KDT 7/e 695)
38. Ans. (c) Azithromycin (Ref: CMDT 2014/ p162)
39. Ans. (a) Vancomycin (Ref: CMDT 2014/ p467, 1257)
40. Ans. (c) Dapsone (Ref: Goodman and Gilman 12/e p1823, CMDT 2014/ p119)
41. Ans. (a) Injection Benzathine penicillin 2.4 million units IM single dose (Ref: CMDT 2014/ p1258)
42. Ans. (d) Imipenem (Ref: KDT 7/e p731)
43. Ans. (b) Vancomycin (Ref: KDT 7/e p757)
44. Ans. (b) Pseudomembranous colitis (Ref: KDT 7/e p757)
45. Ans. (c) Clostridium difficile (Ref: KDT 7/e p694)
46. Ans. (a) Ethambutol (Ref: KDT 7/e p769)
47. Ans. (a) Quinolones (Ref: KDT 7/e p695)
48. Ans. (a) Gentamicin (Ref: KDT 7/e p746)
49. Ans. (c) Benzathine penicillin (Ref: KDT 7/e p720)
50. Ans. (a) Quinolones (Ref: KDT 7/e p697)
51. Ans. (c) Rifampin (Ref: KDT 7/e p768)
52. Ans. (c) Amikacin (Ref: KDT 7/e p749)
53. Ans. (c) Post antibiotic effect (Ref: KDT 7/e p697)
54. Ans. (b) 30 minutes before incision (Ref: KDT 7/e p702)
55. Ans. (d) Vancomycin (Ref: KDT 7/e p757)
56. Ans. (c) Competitive inhibition (Ref: KDT 7/e p704)
57. Ans. (c) Piperacillin (Ref: KDT 7/e p724)
58. Ans. (d) Doxycycline (Ref: KDT 7/e p735)
59. Ans. (b) Cotrimoxazole (Ref: KDT 7/e p708)
60. Ans. (c) Cefpirome (Ref: KDT 7/e p726)
61. Ans. (b) Methicillin (Ref: KDT 7/e p721)
62. Ans. (d) Vancomycin (Ref: KDT 7/e p721,726,730)
63. Ans. (c) Gentamicin (Ref: KDT 7/e p743)
64. Ans. (a) Chloramphenicol (Ref: KDT 7/e p740)
65. Ans. (d) Sparfloxacin (Ref: KDT 7/e p714)
66. Ans. (a) Clindamycin (Ref: KDT 7/e p756)
67. Ans. (c) Ototoxicity (Ref: KDT 7/e p745)
68. Ans. (a) 95% oral bioavailability (Ref: KDT 7/e p757)
69. Ans. (c) 3 mg/ml (Ref: KDT 7/e p749)
70. Ans. (b) oral (Ref: KDT 7/e p757)
71. Ans. (c) 2.4 MU single i.m. (Ref: KDT 7/e p763)
72. Ans. (c) Tetracycline (Ref: KDT 6/e p715)

- 73. Ans. (d) Penicillin (Ref: Harrison 15/e p432)
- 74. Ans. (b) Gentamicin (Ref: KDT 6/e p702)
- 75. Ans. (b) Active against only gram negative bacteria (Ref: KDT 6/e p705, 707)
- 76. Ans. (c) Mefloquine (Ref: Katzung 11/e p907)
- 77. Ans. (c) Spectinomycin (Ref: Katzung 11/e p813)
- 78. Ans. (a) Methicillin (Ref: KDT 6/e p699)

Chemotherapy B: Antimicrobials for Specific Conditions

ANTI-MYCOBACTERIAL ANTIBIOTICS

Mycobacterium causes tuberculosis and leprosy. Several atypical mycobacteria may also cause infection in humans especially in the immunocompromised patients.

Tuberculosis

It is caused by *Mycobacterium tuberculosis*. The drugs used for tuberculosis are

First line		Second line	
Essential	Supplementary		
Isoniazid (H)	Streptomycin (S)	Thiacetazone	
Rifampicin (R)	Rifabutin	Paraaminosalicylic acid	Ofloxacin
Pyrazinamide (Z)	Rifapentine	Ethionamide	Levofloxacin
Ethambutol (E)		Cycloserine	Moxifloxacin
		Kanamycin	Linezolid
		Capreomycin	Clarithromycin
		Amikacin	

Mycobacteria	Most effective drug
1. Rapidly growing (wall of cavitory lesion)	H
2. Slow growing (intracellular)	Z
3. Spurters (within caseous material)	R

Isoniazid (H)

- It is a **prodrug** activated by **catalase-peroxidase** (coded by *KatG*). Active metabolite *inhibits* the enzyme *ketoenylreductase* (coded by *inh A*), required for *mycolic acid synthesis*, an essential component of mycobacterial cell wall. It acts by O₂ dependent pathway such as catalase peroxidase reaction.
- It is the single most important drug used in tuberculosis. Mycobacterial strains are assumed to be susceptible to isoniazid, if the resistance is less than 4%.
- It is *bacteriostatic against resting* and *bactericidal against rapidly multiplying organisms*.
- It is effective against *intra- as well as extra-cellular* mycobacteria.
- Action is most marked against rapidly multiplying bacilli (*less effective against slow multipliers*).
- It is widely distributed in the body including CSF.
- It is effective orally and metabolized by **ACETYLATION** which is *genetically controlled*. Fast acetylators require high dose and slow acetylators are predisposed to toxicity (particularly peripheral neuritis).
- It is an essential component of multi-drug therapy of tuberculosis and is drug of choice (**used solely**) for **prophylaxis of tuberculosis** and for treatment of latent tuberculosis infection.
- Resistance occurs due to mutation in *Kat G* (gene for catalase-peroxidase) or *inhA*. Mutation in *kat G* is responsible for high level resistance whereas mutation in *inhA* confers cross resistance to ethionamide.
- It causes **peripheral neuritis** that can be *prevented and treated by pyridoxine*.
- It is also **hepatotoxic** and can cause *hemolysis in G-6 PD deficient patients*. Incidence of hepatotoxicity increases with age, daily alcohol consumption and in post partum (3 months) period.
- Isoniazid also *inhibits MAO-A; thus* can result in cheese reaction.
- Rash, fever, anemia, optic atrophy, seizures, lupus like syndrome, psychosis and gynaecomastia** has also been reported with this drug.

Isoniazid is metabolized by **ACETYLATION** which is genetically controlled. Slow acetylators are predisposed to toxicity particularly peripheral neuritis.

Drug	Action	Hepato-toxic	Bacteria Inhibited
H	CIDAL	Yes	Both
R	CIDAL	Yes	Both
Z	CIDAL	Yes	Intracellular
E	STATIC	No	Both
S	CIDAL	No	Extra cellular

Rifampicin (R)

- It is a derivative of rifamycin (other derivatives are *rifabutin* and *rifapentine*). It is **bactericidal** against both dividing and non-dividing mycobacterium and acts by *inhibiting DNA dependent RNA polymerase*.

Review of Pharmacology

Rifampicin is secreted in bile, so does not require dose adjustment in renal failure.

While penicillin is DOC for treatment of meningococcal meningitis, it is not indicated for prophylaxis where rifampicin (or ceftriaxone) is DOC because only rifampicin and 3rd generation cephalosporins can eliminate nasal carriers.

Rifampicin is the least toxic anti-tubercular drug and is also the safest drug in pregnancy.

Ethambutol is bacteriostatic

Pyrazinamide acts only on intracellular mycobacteria

Ethambutol and streptomycin are NOT hepatotoxic

- It undergoes *enterohepatic circulation* and is partly metabolized in the liver. Metabolites are coloured and can cause *orange discolouration of the urine* and secretions. It is **eliminated mainly in the feces** and can be used **safely in renal dysfunction**. Food interferes with absorption, therefore it must be given *empty stomach*.
- It *penetrates all membranes* including blood brain and placental barrier.
- It is equally effective against *intra- and extra-cellular* bacilli.
- It is the *only bactericidal drug active against dormant bacteria* in solid caseous lesions.
- Apart from tuberculosis, it is also used in leprosy (to delay resistance to dapsone). It is the **most effective and fastest acting drug in leprosy**. It can also be used as a *prophylactic drug for meningococcal and staphylococcal carrier states*.
- It can cause light chain proteinuria and may impair antibody responses. It is also *hepatotoxic* and may cause skin rash, flu like syndrome (*more prominent with intermittent regimen*) and anemia.
- Hepatotoxicity due to rifampicin is uncommon without pre-existing liver disease. It presents as *hyperbilirubinemia without SGPT elevations*.
- Rifampicin is an *inducer of drug metabolizing enzymes* and enhances the metabolism of many drugs like anticonvulsants, oral contraceptives, oral anticoagulants, antiretroviral drugs etc. **Rifabutin has little chances of drug interactions** and is equally effective, so it is *used in the treatment of tuberculosis in AIDS patients* (getting antiretroviral drugs).
- The female on oral contraceptives should either increase the dose of the pill or use an alternative method of contraception, when using rifampicin as a component of antitubercular treatment.
- PAS delays absorption, therefore concomitant administration should be avoided.
- Patient on *warfarin therapy* should be shifted to *unfractionated heparin or low molecular weight heparin*, if rifampicin is being used for the treatment of tuberculosis.

Ethambutol (E)

It is a **BACTERIOSTATIC** agent for mycobacterium and acts by inhibiting the synthesis of arabinogalactan (a component of cell wall) due to **inhibition of arabinosyl transferase**. It is distributed throughout the body except in the CSF. It causes dose dependent and reversible **visual disturbances like optic neuritis** (presents as *reduced visual acuity, central scotoma and loss of ability to see green, less commonly red*). It may be due to its effect on *amacrine and bipolar* cells of retina. Because children are unable to report early visual impairment, this drug is *contra-indicated in children*. It also causes *hyperuricemia and peripheral neuritis*. It requires dose adjustment in renal failure.

Pyrazinamide (Z)

This is a weakly **bactericidal** drug but is **more active against slowly replicating bacteria (than rapidly multiplying) and in the acidic media** (intracellular sites and at the sites of inflammation). It is effective **only against intracellular mycobacteria**. Its mechanism seems to be similar to isoniazid but the exact site is not known. Half life of this drug is prolonged in hepatic as well as *renal impairment*. In 40% of the patients it causes *non-gouty arthralgia*. **Hyperuricemia** also occurs commonly but is usually asymptomatic and it *should not be stopped* if hyperuricemia develops. It can also cause *hepatic dysfunction, porphyria and photosensitivity*.

Streptomycin (S)

This is a **tuberculocidal** aminoglycoside. It is *not absorbed orally* and must be administered by i.m injection. It is poorly plasma protein bound. Its half life is prolonged in renal failure. It is active **only against extra-cellular bacteria**. It is **NOT HEPATOTOXIC**. Other features are similar to aminoglycosides. Other aminoglycosides used for the treatment of tuberculosis are *amikacin, kanamycin and capreomycin*. Streptomycin is **contraindicated in PREGNANCY**.

Other Drugs

- *Thioacetazone* is a **tuberculostatic** drug. Major adverse effects include hepatitis, bone marrow suppression and Steven Johnson syndrome (*not used in HIV positive patients*)

due to risk of severe hypersensitivity reactions including exfoliative dermatitis). It is not used in intermittent regimens.

- Para amino salicylic acid (PAS) is related to sulfonamides, acts by similar mechanism and is bacteriostatic. It can cause kidney, liver and thyroid dysfunction.
- Ethionamide is another tuberculostatic drug that can cause hepatitis, optic neuritis and hypothyroidism. It can also be used in leprosy. It has mechanism similar to INH and bacteria resistant to INH are cross resistant to ethionamide also.
- Cycloserine is a cell wall synthesis inhibiting drug and can cause neuropsychiatric adverse effects.
- Kanamycin and amikacin are injectable aminoglycosides, which can be used in the treatment of MDR tuberculosis.
- Capreomycin is an injectable polypeptide. It can cause ototoxicity, nephrotoxicity, hypokalemia and hypomagnesemia.
- Fluoroquinolones used for this indication include ofloxacin, moxifloxacin and levofloxacin. These are also effective against mycobacterium avium complex in AIDS patients.
- Newer macrolides like azithromycin and clarithromycin are effective against non-tubercular atypical mycobacteria.
- Rifabutin is more effective than rifampicin against MAC. It has a longer $t_{1/2}$ (45 hrs) as compared to rifampicin (3-5 hours). Clarithromycin and fluconazole inhibit its hepatic metabolism and increase $t_{1/2}$. It has less potential than rifampicin to induce microsomal enzymes and thus preferred in patients on anti-HIV drugs (protease inhibitors or NNRTIs mainly nevirapine). It commonly causes gastrointestinal adverse effects. Rarely, it can cause anterior uveitis, hepatitis, clostridium difficile-associated diarrhea, diffuse polymyalgia syndrome, yellow skin discoloration (**Pseudo-jaundice**) and pancytopenia. Unlike rifampicin, it does not require dose adjustment in liver disease.
- **Rifapentine** is similar to rifampicin but is more lipophilic and longer acting. It is not approved for administration to patients with HIV disease because of higher rates of relapse. Its absorption increases with meals.

Rifabutin (as compared to rifampicin) is

- Less effective against TB
- More effective against MAC
- Longer acting
- Less potential to induce microsomal enzymes
- Do not require dose adjustment in liver disease

7

Bedaquiline is an inhibitor of mycobacterial ATP synthase. It is indicated as a part of MDT in adults with pulmonary MDR-TB. It can cause QT prolongation

TREATMENT OF TUBERCULOSIS (RNTCP 2010)

- Combination chemotherapy (short course chemotherapy) is used to prevent emergence of resistance to any one drug.
- For treatment purpose, previously patients were divided into three categories. **Under RNTCP 2010 guidelines, only two categories are distinguished. Category I** consists of new patients who have not been exposed to antitubercular agents earlier (Previous category I as well as III cases) and **category II** consisting of old cases who have been exposed to antitubercular drugs earlier (treatment defaulters and relapse cases).

	Tuberculosis	Treatment
1.	Latent TB Infection (Chemoprophylaxis)	: Daily INH for 9 months
2.	Category 1 (New or previously untreated cases)	: 2HRZE + 4HR
3.	Category 2 (Previously treated cases; relapses and treatment defaults)	: 2HRZES + 1 HRZE + 5HRE
4.	Treatment failure and special cases :	
	a. Resistance (or intolerance) to H	: 6 RZE + Q (for extensive disease)
	b. Resistance (or intolerance) to R	: 12 HZEQ + S (for ext. disease)
	c. Intolerance to Z	: 2 HRE + 7 HR
	d. MDR TB (resistance to H + R)	: See text
	e. Extensive drug resistance (XDR)	: See text

(Q: Fluoroquinolone, H: Isoniazid, R: Rifampicin, Z: Pyrazinamide, E: Ethambutol, S: Streptomycin)

Rifaximin is a rifampicin derivative indicated for Traveller's diarrhea (E.coli) and hepatic encephalopathy



H and Z have maximum CNS penetration whereas E and S do not cross BBB. R has moderate CNS entry.



MDR tuberculosis is defined as resistance to minimum H and R whereas XDR tuberculosis is defined as resistance to H and R, all fluoroquinolones and atleast one injectable agent.



Dapsone is the drug of choice for treatment of dermatitis herpetiformis.

For treatment of MDR and XDR tuberculosis, drugs are divided into 5 classes:

Class 1:	First line oral drugs	H, R, Z, E
Class 2:	Injectable agents	Streptomycin, kanamycin, amikacin, capreomycin
Class 3:	Fluoroquinolones	Levofloxacin, moxifloxacin
Class 4:	Oral bacteriostatic	PAS, cycloserine, ethionamide
Class 5:	Drugs with uncertain efficacy	Linezolid, clofazimine, amoxicillin + clavulanate, clarithromycin, imipenem, thioacetazone, high dose isoniazid

MDR tuberculosis is defined as resistance to minimum H and R whereas XDR tuberculosis is defined as resistance to H and R, all fluoroquinolones and atleast one injectable agent. Guidelines for treatment of MDR and XDR tuberculosis include:

- Use minimum 4 drugs (6 drugs in extensive phase)
- Follow the hierarchy of drugs from class 1 through class 5 as follows:
 - a. Use any first line oral agent that may be effective
 - b. Use a later generation fluoroquinolone.
 - c. Use injectable agent to which strain is susceptible
 - d. Use second-line oral drugs to which the patient is not exposed previously
 - e. Use drugs with unclear efficacy

For example, if bacteria is resistant to H and R only, the treatment will be:

- 6 ZE + Q + One Injectable + PAS + Cycloserine in the extensive phase
- 18 E + Q + PAS + Cycloserine in the continuation phase
- Injectable drugs and Z is removed and rest 4 drugs are continued for minimum 18 months in continuation phase.

Note:

- Ethambutol and streptomycin do not cross blood brain barrier.
- Ethambutol and streptomycin are not hepatotoxic among the first line drugs.
- Ethambutol and pyrazinamide can cause hyperuricemia.
- Rifampicin is the safest drug in renal failure.
- Streptomycin is contra-indicated in pregnancy.

Atypical Mycobacterial Infections

Clarithromycin or azithromycin is recommended for prophylaxis of *Mycobacterium avium* complex (MAC) in patients with CD₄ count less than 50 μ l. **Treatment of MAC requires REC regimen** (rifabutin + ethambutol + clarithromycin/azithromycin). Due to its long $t_{1/2}$, azithromycin can be used as once weekly dose in place of once daily dose of clarithromycin for prophylaxis of MAC. Other drugs effective against atypical mycobacteria are quinolones (ciprofloxacin, levofloxacin, moxifloxacin and gatifloxacin) and amikacin.

Leprosy

The drugs used for treatment of leprosy include rifampicin, dapsone, clofazimine, ethionamide, ofloxacin, minocycline and clarithromycin.

Dapsone

It is a **leprostatic** drug related to sulfonamides with similar mechanism of action. It is metabolized by **ACETYLATION** and undergoes enterohepatic circulation. It can cause gastrointestinal irritation, fever, skin rash, methemoglobinemia and hemolysis in G-6-PD deficient patients. Hemolytic anemia is the most common adverse effect of dapsone. It can also cause sulfone (DDS) syndrome that is also called infectious mononucleosis like syndrome. **Acedapsone** is a *repository form* of dapsone whose single intramuscular injection maintains inhibitory levels of dapsone in tissues for up to 3 months. Dapsone is also an *alternative drug* for the treatment of *Pneumocystis jiroveci* infection in AIDS patients. It is the **drug of choice for treatment of dermatitis herpetiformis**.

Clofazimine

It is a dye with **leprostatic and anti-inflammatory** activity. It interferes with the template function of DNA. It can cause *gastrointestinal irritation, ichthyosis of skin and discolouration of skin and secretions*. Due to its anti-inflammatory action it can be *used for lepra reaction*.

Rifampicin

It is the **bactericidal** and **most effective** drug used in leprosy. It *prevents development of resistance to dapsone*.

Other Drugs

Ethionamide has antileprotic activity but causes hepatotoxicity in 10% patients. *Ofloxacin, pefloxacin and sparflaxacin* are effective drugs for leprosy **but ciprofloxacin is not active** against *Mycobacterium leprae*. *Minocycline and clarithromycin* can also be used in leprosy.

TREATMENT OF LEPROSY

Pauci-bacillary leprosy: It is the form of leprosy in which *five or less skin lesions* are present and includes TT, BT and indeterminate leprosy. The treatment is *600mg once monthly supervised dose of rifampicin and 100mg daily dose of dapsone* **for 6 months**.

Multi-bacillary leprosy: It includes leprosy with *more than five skin lesions or smear positive cases even if the lesions are less than five*. BB, BL and LL leprosy are multi bacillary. The treatment is *600mg rifampicin + 300mg clofazimine (once monthly supervised dose) and 100mg dapsone and 50mg clofazimine once daily* **for one year**.

Another regimen called **single lesion single dose therapy** utilizes *600mg rifampicin + 400mg ofloxacin + 100mg minocycline (ROM therapy)* as a single dose. This therapy has been discarded now and even single skin lesion of leprosy is now treated as pauci-bacillary leprosy.

TREATMENT OF LEPROSY

Multibacillary		Paucibacillary
– Rifampicin (600mg) once monthly supervised – Clofazimine 300mg once monthly supervised – Dapsone 100 mg OD – Clofazimine 50mg OD	× 12 months	- Rifampicin 600 mg once monthly supervised - Dapsone 100 mg OD
		× 6 months



Drug of choice for Type 1 as well as Type 2 lepra reaction is corticosteroids.

ANTI-FUNGAL AGENTS

According to the mechanism of action these can be classified as

- **Drugs altering membrane permeability**
 - *Azoles*
 - Triazoles e.g. Fluconazole, itraconazole, voriconazole, terconazole, posaconazole.
 - Imidazoles e.g. Ketoconazole, miconazole, clotrimazole, econazole, butoconazole, oxiconazole, sertaconazole, sulconazole.
 - *Terbinafine, butenafine, naftifine.*
 - *Polyenes* e.g. Amphotericin B, nystatin, hamycin
- **Drugs blocking nucleic acid synthesis** e.g. Flucytosine
- **Drugs disrupting microtubule function** e.g. Griseofulvin
- **Drugs inhibiting cell wall synthesis** e.g. Caspofungin, nikkomycin.

Drugs used for the Treatment of Systemic Fungal Infections

These include amphotericin B, flucytosine, triazoles, ketoconazole and echinocandins.

MC adverse effect of AMB is infusion-related reactions whereas MC dose-dependent adverse effect of AMB is nephrotoxicity.

Dose limiting toxicity of AMB is nephrotoxicity manifested by renal tubular acidosis, hypokalemia and hypomagnesemia.

Infusion of normal saline before giving AMB decreases nephrotoxicity but solution of AMB should not be made in normal saline (It is made in dextrose.)

Amphotericin B

It is a **polyene** antibiotic similar to nystatin. It is *not absorbed orally* so administered by slow i.v. infusion. It is *widely distributed except in the CNS*. It binds to ergosterol and causes the *formation of artificial pores in fungal cell membrane*. Amphotericin B has the *widest antifungal spectrum [except Pseudoallescheria boydii (also called Scedosporium apiospermum) and Fusarium]* and is the *drug of choice or co-drug of choice for most systemic fungal infections*. It can be used intrathecally in fungal meningitis and locally for corneal ulcers and keratitis. **Infusion related reactions** are seen frequently with this drug and require premedication with antihistaminics or glucocorticoids. **Dose limiting toxicity is nephrotoxicity** manifested by *renal tubular acidosis, hypokalemia and hypomagnesemia*. Infusion of normal saline before giving AMB decreases nephrotoxicity but solution of AMB should not be made in normal saline (It is made in dextrose.) Saline loading (IL of normal saline infusion before therapy) may decrease nephrotoxicity. It may also result in **anemia** (due to decreased erythropoietin). Intrathecal administration may cause seizures and neurological damage. **Liposomal AMB**, colloidal dispersion (ABCD) and lipid complex (ABLC) are **lipid preparations** of amphotericin B (*costlier* than conventional preparations). These formulations result in *decreased accumulation* of the drug in tissues like kidney, thus *nephrotoxicity is decreased*. Some formulations also show decreased incidence of infusion related reactions. However, these new preparations have *similar efficacy and antifungal spectrum as possessed by conventional preparations*.

Flucytosine

This is a pyrimidine analogue and is administered orally. It is converted by cytosine deaminase to 5-FU, an inhibitor of thymidylate synthase. It has *synergistic activity with amphotericin B*. Spectrum of 5-flucytosine is narrow and includes cryptococcus and candida. Major toxicities include bone marrow suppression, alopecia and liver dysfunction.

Azoles

Ketoconazole, fluconazole, voriconazole, itraconazole, posaconazole and rabuconazole are the azoles used for *systemic fungal infections*. These drugs *act by inhibiting 14 α demethylase*, which is responsible for the conversion of lanosterol to ergosterol. Due to opposite mechanism of action of AMB and azoles, the combination of these drugs is antagonistic [azoles inhibit formation of ergosterol where AMB binds to produce action].

- **Ketoconazole** has *narrow antifungal spectrum* and due to severe and frequent adverse reactions, is now *rarely used*. Ketoconazole *inhibits cytochrome P450 enzymes* (also inhibited by *fluconazole, itraconazole and voriconazole*) and increases plasma concentrations of cyclosporine, warfarin and theophylline etc. Inhibition of CYP enzymes result in decreased formation of adrenal and gonadal steroids and may lead to *gynaecomastia, menstrual irregularities and infertility*.
- **Fluconazole** has *maximum oral bioavailability and CNS penetration* among this group of drugs. It is excreted by kidney as compared to other azoles which are mainly metabolized by liver. It is the **drug of choice for candidiasis, coccidioid and cryptococcal meningitis (co-drug of choice with AMB)**.
- **Itraconazole** is the *drug of choice for blastomycosis (non-meningeal), histoplasmosis, coccidioidomycosis, paracoccidioidomycosis and sporotrichosis* (previously KI was used for sporotrichosis) infections. Its entry in the CNS is limited, therefore *not used for CNS fungal infections*. Fluconazole is antifungal DOC for prophylaxis of febrile neutropenia whereas voriconazole is DOC for treatment.
- **Voriconazole** has the *widest spectrum among azoles (except Mucor and Sporotrichosis)* and is the *drug of choice for invasive aspergillosis, Fusarium and Scedosporium*. Adverse reactions of azoles include diarrhea, rash and hepatotoxicity in preexisting liver dysfunction. It is also implicated in *prolonging QT interval*. Voriconazole causes *visual disturbances* like blurred vision, altered colour perception and photophobia. Long-term use is associated with multistep phototoxic process followed by actinic keratosis, then **squamous cell carcinoma**.
- **Posaconazole** is the only azole active against *mucormycosis*.
- **Isavuconazole** is an orphan drug for treatment of aspergillosis and mucormycosis.

Fluconazole is the drug of choice for

- Candidiasis
- Cryptococcus (not meningitis)
- Coccidioidomycosis

Fluconazole is antifungal DOC for prophylaxis whereas voriconazole is DOC for treatment of febrile neutropenia

Voriconazole has very wide spectrum anti-fungal action but not effective against mucormycosis

Echinocandins

This is a new group of antifungal drugs that include **caspofungin**, **micafungin** and **anidulafungin**. These are used *intravenously* and act by *inhibiting the synthesis of $\beta_1, 3$ glycan*, a component of fungal cell wall. Caspofungin is *approved only for invasive aspergillosis not responding to AMB or voriconazole*. It is quite nontoxic and causes only mild infusion related reactions.



CASP ofungin
↓
Aspergillosis
↓
Candida

Nikkomycins

These are new antifungal drugs that *act by inhibiting chitin synthesis*, which is an important component of fungal cell wall.

Systemic Drugs for Superficial Fungal Infections

1. Griseofulvin

It is used orally and its oral *absorption is increased by fatty meal*. It gets distributed to stratum corneum and *acts by interfering with microtubule function* in dematophytes. It may also inhibit synthesis and polymerization of nucleic acids. It is used for dematophytoses of skin and hair (tinea infections) because it **gets concentrated in keratin**. It causes gastrointestinal disturbances, photosensitivity and liver dysfunction. It can also cause *disulfiram like reaction* with alcohol. Its metabolism is induced by phenobarbitone.

2. Allylamines

The drugs in this group include **terbinafine**, **naftifine** and **butenafine**. These are **fungicidal** agents that act by *inhibiting squalene epoxidase* resulting in the decreased ergosterol synthesis. Inhibition of this enzyme can lead to accumulation of squalene that is toxic to the fungus. Main adverse effect of terbinafine is rash and gastrointestinal upset. Allylamines like terbinafine are oral fungicidal drugs.



Allylamines like terbinafine are oral fungicidal drugs.

3. Azoles

Ketoconazole, fluconazole and itraconazole can be used orally for superficial fungal infections but **voriconazole is not used for this purpose**.



Drug of choice for cryptococcal meningitis is amphotericin B whereas for other cryptococcal infections, it is fluconazole.

Topical Drugs for Superficial Fungal Infections

These include:

- **Polyenes** e.g. *nystatin* (used topically for local candida infections and orally for gastrointestinal fungi)
- **Imidazoles** e.g. *miconazole, econazole, clotrimazole, luliconazole, efinaconazole, ketoconazole, terconazole, butaconazole, tioconazole, oxiconazole, sertaconazole*.
- **Allylamines** e.g. *terbinafine, butenafine, naftifine*
- **Oxaboroles** e.g. *tavaborole*
- **Ciclopirox olamine**
- **Benzoic acid with salicylic acid** (Whitfield's ointment)
- **Tolnaftate**
- **Undecylenic acid**
- **Haloprogin**.

ANTI VIRAL AGENTS

- Antiviral drugs can act at any step of viral replication. Viral replication involves fusion of the virus to host cell membrane and penetration inside the cell. Then uncoating occurs and early proteins (like DNA polymerase) are synthesized. The nucleic acids (DNA or RNA) are then synthesized and after that late proteins (final functional proteins) are synthesized and processed. After packaging and assembly,

viral particles are released (with the help of neuraminidase) and cause infection of other cells. Drugs can act at any of these steps to inhibit viral replication.

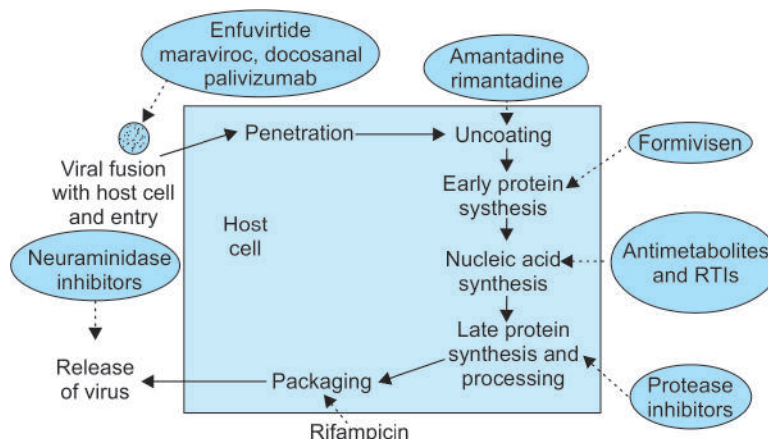


Fig. 14.1: Mechanism of action of anti-viral drugs

Anti Herpes Drugs

Most of these drugs are antimetabolites and inhibit viral DNA polymerase after bioactivation by kinases.

Acyclovir and its Congeners

It is a *guanosine analogue* active **against herpes simplex virus** (HSV-1 and 2) and **varicella zoster virus** (VZV). Acyclovir is *not active against CMV* infections. It is *activated first by a virus specific kinase (thymidine kinase) to form acyclovir monophosphate* (virus develops resistance due to mutation of this kinase) and then by host kinases to form acyclovir triphosphate. This product *competitively inhibits the action of DNA polymerase* (by competing with GTP) and also gets incorporated into the DNA and causes chain termination. It can be used *topically, orally or intravenously*. It has **very short $t_{1/2}$** and requires multiple daily dosing. It is primarily excreted by kidneys. It is used for the treatment of *mucocutaneous and genital herpes* and also for the prophylaxis of herpes infections in AIDS and immunocompromised patients. **Parenteral** administration for serious herpes infections cause *nephrotoxicity and neurotoxicity* (altered sensorium, tremor, myoclonus, delirium, seizures etc.) as principal dose limiting toxicities but *it does not cause bone marrow suppression*. Mycophenolate (immunosuppressant) potentiates antiherpes activity of acyclovir and related drugs by depleting intracellular GTP. It is essential to maintain hydration while the patient is on acyclovir therapy because *dehydration increases its nephrotoxic potential*. **Valacyclovir has a long half life** and gets converted to acyclovir by hepatic metabolism. **Famciclovir is a prodrug** that gets converted to *peniciclovir* (also developed as a separate drug) and acts via similar mechanism.

Ganciclovir

It is active against *CMV and HSV* and acts by inhibiting DNA polymerase. First phosphorylation step in this case also is virus specific. **Ganciclovir is used only intravenously** whereas **valganciclovir has good oral absorption**. Ganciclovir is the **drug of choice for CMV** infections including retinitis. Dose limiting adverse effect is **myelosuppression**. Its bone marrow suppressive action is additive to other myelosuppressive drugs like zidovudine. *CNS side effects* (headache to convulsions) also occur quite commonly.

Cidofovir

It is *activated exclusively by host cell kinases* and is active against HSV, CMV, adenovirus and papilloma virus. Its diphosphate product has prolonged $t_{1/2}$. Dose limiting toxicity is **nephrotoxicity**. Probenecid and i.v. saline can decrease nephrotoxicity. Ocular toxicity including **uveitis and iritis** is another complication. It is considered as a potential human carcinogen.

Acyclovir is drug of choice for H. Simplex encephalitis

Ganciclovir is the drug of choice for CMV infections including retinitis.

Cidofovir has wide-spectrum antiviral activities against:

- HSV
- CMV
- Papilloma virus
- Polyomavirus
- Pox virus
- Adeno virus

Foscarnet

It is not an antimetabolite and **does not require intracellular activation by viral or cellular kinases**. It is used *i.v* for CMV infections. Nephrotoxicity (30% incidence), symptomatic hypomagnesemia and hypocalcemia (increased by concomitant pentamidine) and CNS problems are the major adverse effects.

Other Drugs

- Vidarabine, idoxuridine, trifluridine, fomivirsen and docosanol (alcohol exclusively found in breast milk) are other drugs that can be used for herpes infections.
- **Fomivirsen is the first antisense oligonucleotide** and is active against CMV retinitis (by intravitreal route) resistant to other drugs. It can cause iritis, vitritis and changes in intraocular pressure.
- Idoxuridine is used only topically for keratoconjunctivitis by HSV.
- Docosanol is a long chain saturated alcohol that can be used topically (as a cream) for herpes labialis. It prevents the entry of the virus in cell by inhibiting the fusion of the virus envelope with the host cell membrane.

Anti Influenza Drugs

These include amantadine, rimantadine, oseltamivir and zanamavir.

Amantadine and Rimantadine

These drugs prevent uncoating of influenza A virus (not influenza B). These drugs decrease the duration of symptoms of influenza if used prophylactically. **Rimantadine is longer acting** than amantadine. Most common adverse effects of these drugs are gastrointestinal complaints and minor CNS effects. Amantadine is also effective for the treatment of Parkinsonism.

Oseltamivir and Zanamavir

These drugs act as **neuraminidase inhibitors** and prevent the virion release by causing clumping of mature virions. These drugs are effective against **both influenza A and influenza B**. **Oseltamivir is an oral prodrug** (can cause nausea and vomiting) whereas **zanamavir is administered by inhalational route** (bronchospasm is an important adverse effect). **Neuropsychiatric disorders** including suicidal tendency have been associated with oseltamivir and zanamavir. These can be used prophylactically to prevent influenza during epidemics. **Oseltamivir is drug of choice for bird flu** (currently strain causing pandemic is H5N1) as well as swine flu (by H1N1). **Peramivir** is a newer drug in this category that can be administered intravenously. **Laninamivir** is a long-acting inhaled neuraminidase inhibitor effective even against oseltamivir resistant virus.

Anti Hepatitis Drugs

Drugs active against hepatitis B (HBV) and hepatitis C virus (HCV) are interferon α (IFN- α), lamivudine, ribavirin, entecavir, adefovir and telbivudine. **Goal of therapy in chronic HBV is to sustain suppression of HBV replication whereas in HCV, it is viral eradication.**

IFN- α

It acts by JAK-STAT pathway to increase antiviral proteins and also promotes formation of natural killer (NK) cells. It is used in chronic HBV infections. It can also be used with ribavirin in acute HCV infections and prevent its progression to chronic disease. **Pegylated IFN- α 2a and 2b are superior to conventional IFN α 2a and 2b**. Intravesicular IFNs are useful for verruca vulgaris and condyloma acuminata (imiquimod; an immunomodulator is also effective).

Lamivudine

It is a nucleoside reverse transcriptase inhibitor used in the treatment of HIV infections. Low dose of this drug can be used alone or in combination with IFN- α for chronic HBV infections (because it has longer intracellular $t_{1/2}$ in HBV than in HIV).

Ribavirin

It has a **wide antiviral spectrum** and can be given orally. It is used with IFN- α in chronic HCV infection. Although it affords no benefit in respiratory syncytial virus (RSV) infections, however, some authorities still recommend its use in immunocompromised children for this purpose. It can cause **dose dependent hemolytic anemia** and is a known human **teratogen**.

Oseltamivir is drug of choice for bird flu (currently strain causing pandemic is H5N1) as well as swine flu (by H1N1).

Simeprevir is a protease inhibitor and sofosbuvir is a polymerase inhibitor approved for chronic hepatitis C

DOC for chronic HBV is entecavir whereas for HCV (both acute and chronic), DOC is Peg-IFN- α plus ribavirin.

Entecavir

It is the newer HBV viral DNA polymerase inhibitor. It is effective *against HBV resistant to lamivudine* and has become first line drug for chronic HBV infection. It should be given in empty stomach.

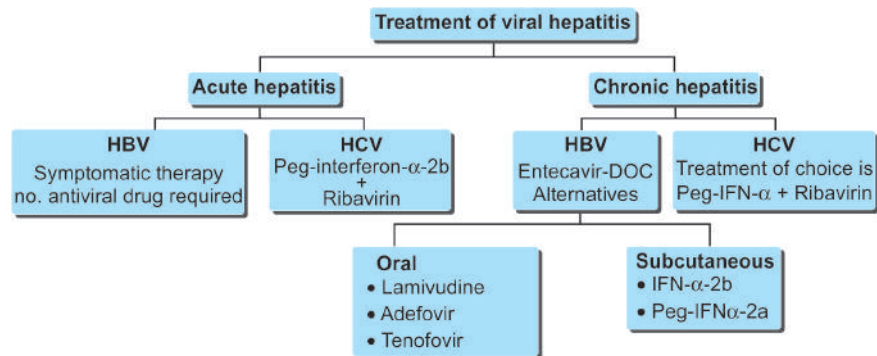
Adefovir

It acts as an antimetabolite for HBV but nephrotoxicity is dose limiting adverse effect. It can also cause lactic acidosis with hepatomegaly and steatosis.

DOC for chronic HBV is entecavir whereas for HCV (both acute and chronic), DOC is Peg-IFN- α plus ribavirin.

New Drugs for Hepatitis C Virus

- **Boceprevir** and **Telaprevir** are **protease inhibitors** of HCV. These act by binding to NS-3 active site and inhibit NS3/4A serine protease of HCV. These are used along with Peg-interferon and ribavirin and are approved for **HCV genotype 1 only**. These are administered orally with food. Anemia and rash are common adverse effects. These are also inhibitors of CYP 3A4.
- **Sofosbuvir** is a nucleotide analog that act by inhibiting RNA polymerase (NS-5B protein). It can be given without interferons. Combination with ribavirin is approved for HCV genotypes 2 and 3.
- **Ledipasvir** (NS 5A inhibitor) is approved in combination with sofosbuvir for HCV.



Anti HIV Drugs

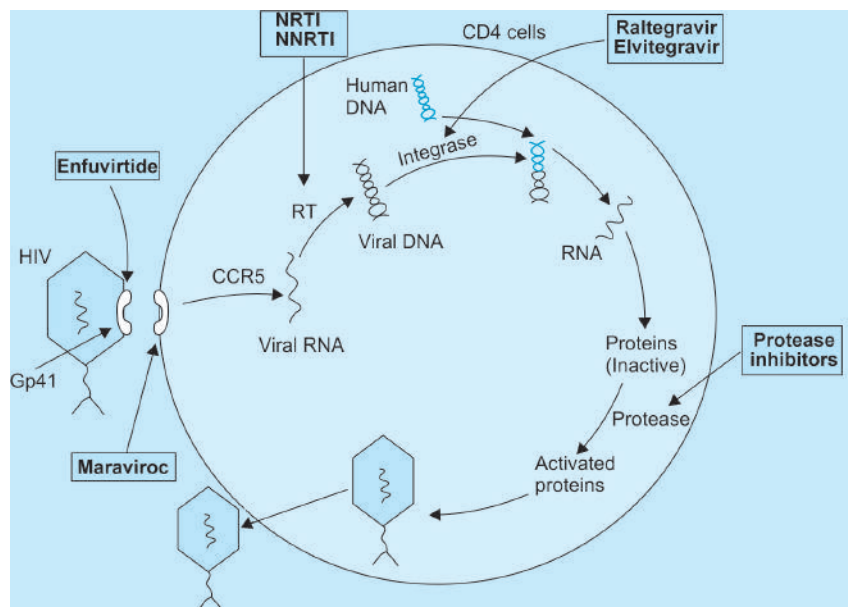
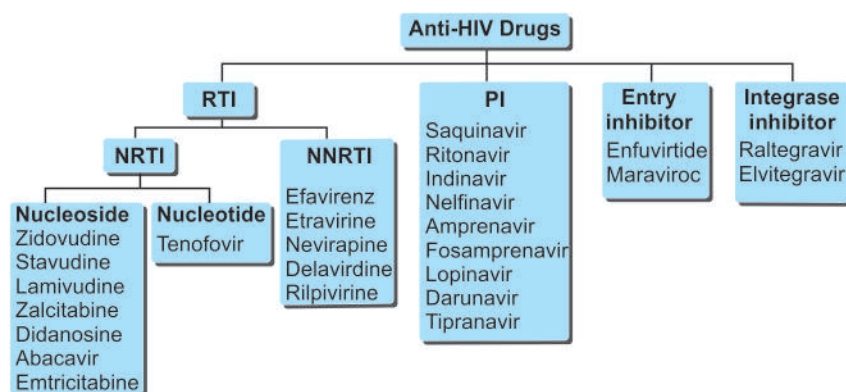


Fig. 14.2: Pathogenesis of HIV and target of various drugs

Human Immunodeficiency Virus (HIV) enters the CD4 cells after fusion of viral Gp41 with CCR5 or CXCR4 receptors on human cells. After entry, viral RNA is converted to DNA with the help of reverse transcriptase (RNA dependent DNA polymerase). This viral DNA integrates with human DNA to form provirus with the help of enzyme, integrase. This proviral DNA can replicate and transcript to form RNA which forms proteins via translation. The proteins formed initially are inactive and require protease enzyme for activation. Complete virus is generated from these components, which leaves the CD4 cells to infect other cells. Various drugs can target these steps and are described ahead.



REVERSE TRANSCRIPTASE INHIBITORS

HIV is a retrovirus that forms its DNA from RNA with the help of the enzyme RNA dependent DNA polymerase (reverse transcriptase). Drugs may inhibit this enzyme either competitively (anti-metabolites) or non-competitively. The competitive inhibitors may be nucleoside reverse transcriptase inhibitors (NRTIs) or nucleotide reverse transcriptase inhibitors (e.g. tenofovir). The non- competitive inhibitors are also known as non-nucleoside/non-nucleotide reverse transcriptase inhibitors (NNRTIs).

a. NRTIs

These are *prodrugs* and are activated by host cell kinases to form *triphosphates*. These drugs *competitively inhibit reverse transcriptase* and also act as chain terminators by incorporation into the DNA chain (because these lack 3' hydroxyl group on ribose ring, attachment of next nucleotide is not possible). Resistance to these drugs emerges rapidly if used alone.

- **Zidovudine** is frequently used NRTI in the treatment of HIV infections. It *can also be used for the prophylaxis* of needle stick injury patients and for the *prevention of vertical transmission of HIV* from mother to fetus. Major adverse effect of zidovudine is **bone marrow suppression** leading to megaloblastic anemia, neutropenia and thrombocytopenia (*ganciclovir should not be combined*). It is contra-indicated in patient with Hb < 8g%. It can also cause *myopathy*. Rifampicin increases the clearance of this drug. Chronic administration is associated with *lipodystrophy syndrome, nail hyperpigmentation and lipoatrophy*.
- **Didanosine** is another NRTI. Its *oral bioavailability is reduced by food*. It can lead to dose limiting *pancreatitis (maximum chances)*, *hyperuricemia*, *optic neuritis* and also *painful sensory peripheral neuropathy*. Diarrhea is more common than with other NRTIs. It may cause *neutropenia (not anemia)* and fulminant hepatic failure and electrolyte abnormalities
- **Stavudine** causes dose limiting *peripheral neuropathy*. It has maximum chances of causing *lactic acidosis (mitochondrial toxicity)*. It can also result in *pancreatitis*. It is *most strongly associated with lipodystrophy syndrome among all NRTIs and protease inhibitors*.
- **Lamivudine and emtricitabine** are *best tolerated NRTIs*. These are **not** associated with *peripheral neuropathy or pancreatitis*. Both are effective against hepatitis B. Emtricitabine is once a day alternative to lamivudine.

Maximum risk of:

- **Pancreatitis:** Didanosine
- **Peripheral neuropathy:** Stavudine
- **Lipodystrophy Syndrome:** Stavudine



Abacavir increases the risk of myocardial infarction particularly in patients having HLA B*5701 allele. Testing of this allele should be done before starting abacavir.



Drugs having activity against both HIV and HBV

L – Lamivudine
E – Emtricitabine
T – Tenofovir

- **Zalcitabine** has unique toxicity to cause oral ulceration and stomatitis. It is least effective NRTI. It also results in peripheral neuropathy and pancreatitis.
- **Abacavir** increases the **risk of myocardial infarction**. It may cause severe hypersensitivity reaction particularly in patients having HLA B*5701 allele. Testing of this allele should be done before starting abacavir.
- **All NRTIs are excreted by the kidney** (require dose adjustment in renal failure) except **abacavir** which gets metabolized by alcohol dehydrogenase. **Hypersensitivity** is the major adverse reaction of abacavir (should not be restarted).
- All NRTIs may cause **lactic acidosis, hepatomegaly and steatosis** by inhibiting mammalian mitochondrial DNA polymerase. Risk factors are obesity and pre-existing liver dysfunction.

b. Nucleotide RTI

Tenofovir is a nucleotide and does not require bioactivation by kinases. It is excreted mainly by the kidney and renal impairment including a Fanconi like syndrome with hypophosphatemia may occur. *Oral bioavailability of tenofovir increases with meals* (decreased for other NRTIs). It is well tolerated and flatulence is only significant side effect. *It is also effective against hepatitis B.*

Note:

- Lamivudine, emtricitabine and tenofovir have activity against hepatitis B virus.
- Thymidine analog NRTIs (zidovudine and stavudine) and protease inhibitors are associated with lipodystrophy syndrome characterized by hyperlipidemia, hypercholesterolemia, glucose intolerance and fat re-distribution.
- Strains of HIV resistant to lamivudine (due to M184V substitution) appear to have enhanced sensitivity to other NRTIs.
- Zidovudine is most likely to cause anemia whereas zidovudine and didanosine are most likely to cause neutropenia.
- Stavudine (followed by zidovudine) are most likely to cause lipodystrophy.
- Zidovudine and didanosine are most likely to cause peripheral neuropathy. Didanosine has maximum risk of causing pancreatitis.

c. NNRTIs

These drugs inhibit reverse transcriptase by acting at a site (**allosteric site**) different from that of NRTIs. These are **selective for HIV-1** and have no activity against HIV-2. *Resistance to these drugs develops very rapidly.* Drugs in this group are **efavirenz, nevirapine, etravirine and delavirdine**. *Skin rash* is an adverse effect of all of these drugs and *nevirapine can cause Steven Johnson syndrome* and toxic epidermal necrolysis. *Delavirdine and efavirenz should be avoided in first trimester of pregnancy.* **Nevirapine is used in pregnancy to prevent vertical transmission (single oral dose of 200 mg to mother during labour and single 2 mg/kg oral dose to neonate within 3 days after birth).** *It decreases transmission to 13% as compared to 21.5% by zidovudine.* However because of *hepatotoxicity* and less effectiveness of nevirapine, it is *not preferred* for this indication. **Efavirenz** is *neurotoxic* and side effects may range from lack of concentration to vivid dreams to delusions and mania.

- **Etravirine** is a recently approved NNRTI. This **second generation NNRTI** is effective against HIV resistant to first generation NNRTI (Efavirenz, nevirapine and delavirdine). Another recently approved second generation NNRTI is **rilpivirine**.

Note:

- NNRTI do not cause lipodystrophy
- Nevirapine and efavirenz are CYP 450 enzyme inducers whereas delavirdine is enzyme inhibitor.

PROTEASE INHIBITORS

Protease helps in the maturation of infectious virions and inhibitors of this enzyme can be used in the treatment of HIV infections (by *inhibiting the post-translational modification of viral proteins*).

- Oral bioavailability of **indinavir** is decreased by food. It can cause *crystalluria and kidney stones*. To prevent renal damage, good hydration must be maintained. It can also cause **asymptomatic hyperbilirubinemia**.

- This group of drugs inhibits the metabolism of several drugs by inhibiting CYP3A4. *Ritonavir in low doses can be used with other protease inhibitors to increase their plasma concentration. Current guidelines recommend that all protease-inhibitor containing regimens use ritonavir boosting if possible. Only Nelfinavir and Atazanavir can be used safely without ritonavir boosting. Nelfinavir is the only protease inhibitor for which ritonavir boosting is not recommended.*
- Concentration of **amprenavir** and **fosamprenavir** (a long-acting prodrug of amprenavir) decrease when co-administered with **ethinyl estradiol**.
- **Tipranavir** is the **only nonpeptidic protease inhibitor**. It is effective against HIV resistant to other protease inhibitors. It can cause *hepatotoxicity and intra-cranial hemorrhage*.
- **Atazanavir** frequently cause *asymptomatic unconjugated hyperbilirubinemia* (like indinavir) and *increase in PR interval in ECG*. It requires acidic pH to remain in solution, therefore should not be given with proton pump inhibitors. *Both tenofovir and efavirenz lower the serum concentration of atazanavir, therefore when used with these drugs, it must be boosted by ritonavir.*
- Amprenavir can cause Steven Johnson syndrome.
- All protease inhibitors are metabolized by liver and all can cause **metabolic abnormalities** including *hypercholesterolemia, diabetes mellitus, hyperlipidemia, insulin resistance and altered fat distribution* (collectively called lipodystrophy syndrome). **Atazanavir** is devoid of this adverse effect. **Tesamorelin** is a synthetic analogue of growth hormone releasing factor indicated to **reduce excess abdominal fat in HIV-infected patients with lipodystrophy**.

Nelfinavir is the only protease inhibitor for which ritonavir boosting is not recommended.

All protease inhibitors can cause lipodystrophy syndrome. Atazanavir is devoid of this adverse effect.

Tesamorelin is a synthetic analogue of growth hormone releasing factor indicated to reduce excess abdominal fat in HIV-infected patients with lipodystrophy.

ENTRY INHIBITORS

- **Enfuvirtide** is a drug that **binds to Gp 41 subunit of HIV envelope protein** and *inhibits the fusion of viral and host cell membranes*. This prevents the entry of the virus in the host cells. It is *used subcutaneously* and can cause *injection site reactions, hypersensitivity and pneumonia*. It is not effective against HIV-2
- **Maraviroc** is the **first CCR5 co-receptor antagonist** to be approved for use. It is only active against "CCR-5-tropic virus" and thus, a co-receptor tropism assay should be performed before starting maraviroc. This type of HIV-1 virus tends to predominate early in infection. It can be *given orally*.

Cobicistat is a new drug that inhibits the metabolism of elvitegravir. It is approved as a booster for this drug.

INTEGRASE INHIBITORS

Raltegravir, elvitegravir and **dolutegravir** are the *oral drugs* approved by FDA that act by inhibiting the integrase enzyme. **Cobicistat** is used to boost the effect of elvitegravir. Recently, cobicistat has been approved to boost the effect of darunavir and atazanavir also.

Mnemonic

1. **EN FU VIR TIDE**
 Bind to **Envelope protein (Gp41)** and inhibits **Fusion of virus to T-cells**
2. **RAL TEGRA VIR**
 integrase inhibitor
3. All protease inhibitors end with **NAVIR**
4. **Tenovir** is only **nucleoTide RTI**

Antimicrobial prophylaxis in HIV

Organism	CD4 count
1. <i>P. jiroveci</i>	< 200
2. MAC	< 75-100
3. <i>Toxoplasma</i>	< 100
4. CMV	< 50

Note: Anti-HIV drug combinations that should NOT be used are:

- Zidovudine + Stavudine : Pharmacological antagonism (compete for intracellular phosphorylation)
- Atazanavir + Indinavir : Additive unconjugated hyperbilirubinemia.
- Didanosine/stavudine + Zalcitabine : Additive peripheral neuropathy.
- Lamivudine + Zalcitabine : In vitro antagonism.

Post exposure prophylaxis (PEP) for HIV is given for 4 weeks

Anti-Retroviral Therapy (ART)

Highly active anti-retroviral therapy (HAART) also known as combination ART (cART) is recommended with the primary goal of complete suppression of viral replication (viral load <50 copies/mL).

WHEN TO START

WHO (2010) and NACO (India) 2011 Guidelines	US-Guidelines [as in Harrison's and CMDT]
1. HIV-infected adults, adolescents and pregnant - All patients in WHO-stage III and IV irrespective of CD4 count - Patients in WHO-clinical stage I and II if CD4 <350 cells/mm³	1. All symptomatic patient with HIV-infection
2. All patients with HIV-infection and Tuberculosis irrespective of CD4 count.	2. HIV + asymptomatic patients who have - CD4 < 500 cells/mm³ - Rapidly dropping CD4 count (>100 cells/mm³/year)
3. HIV-infection with hepatitis B/C infection All patients with chronic active hepatitis	- High viral loads (> 100,000/mm³) - Active hepatitis B or C
Patients without chronic active hepatitis but CD4 < 350 cells/mm³	- High risk factors for cardiac disease - Renal impairment due to HIV
	- Pregnancy - Risk factors for non-AIDS related cancers

WHAT TO START

	WHO (2010)	NACO (2011)	US
First Line	2 NRTI+INNRTI [Z/T + L/Em + Ef/N]	2NRTI + 1NNRTI [Z/S + L + Ef/N]	2NRTI + 1NNRTI/PI [T + Em + Ef × At/R]
Preferred to start	T + L + Ef	Z + L + N	T + Em + Ef
2nd Line	T + L/Em + At/Lo	T+L+At/Lo	3 drugs from at least 2 groups to which the patient is not resistant

National AIDS Control Organization (NACO) 2011 Guidelines for Management of HIV/AIDS

ART should be started as given in table above. Zidovudine, lamivudine and nevirapine should be started as first line. If Hb is < 8 g%, zidovudine should be replaced by stavudine [S+L+N]. If co-existing TB is present, replace nevirapine with efavirenz because of additive hepatotoxicity of nevirapine with ATT.

Drugs	Drugs	Comment
Regimen I	Z + L + N	Preferred
Regimen I (a)	S + L + N	If Hb < 8 g%
Regimen II	Z + L + E	If co-existing TB
Regimen II (a)	S + L + E	Both TB and Hb < 8 g%
Regimen III	T + L + N	Intolerant to both Z and S
Regimen III (a)	T + L + E	Intolerant to both Z and S and Hb < 8g%
Regimen IV	Z + L + At	Intolerant to both N and E
Regimen V	T + L + At	Both first line NRTI not tolerated

If both zidovudine and stavudine are not tolerated, tenofovir is recommended. combination of atazanavir with ritonavir is used if both efavirenz and nevirapine cannot be used.

POST-EXPOSURE PROPHYLAXIS

It is considered for health care workers and others who get accidental exposure to HIV infection. Aim is to suppress local viral replication prior to dissemination, so that the infection is aborted.

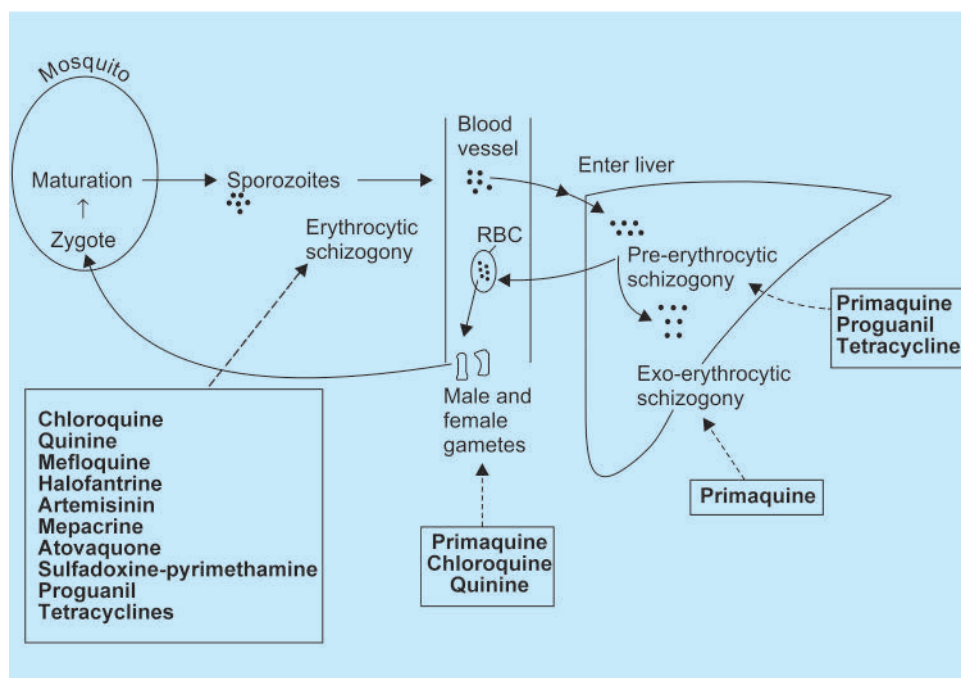
Z: Zidovudine,
T: Tenofovir,
L: Lamivudine,
Em: Emtricitabine,
Ef: Efavirenz,
N: Nevirapine,
S: Stavudine,
At: Atazanavir + ritonavir,
Lo: Lopinavir + ritonavir,
R: Raltegravir

Risk	Drugs for PEP	Duration	Start within
1. Low	Basic Regimen : Z + L	4 Weeks	Within 72 hours
2. High	Expanded Regimen: Z + L + PI	4 Weeks	Within 72 hours

ANTIMALARIAL DRUGS

Malarial parasite (plasmodium) undergoes a primary developmental stage in liver (pre erythrocytic stage; responsible for the cause of malaria) and then it enters the RBCs (erythrocytic stage; responsible for symptoms). Symptoms of malaria (fever, chills and rigors) correspond to the erythrocytic stage. Plasmodium may give rise to gametes in the blood which can be taken up by the female anopheles (responsible for transmission of malaria). Some schizonts remain dormant in liver and this dormant hepatic stage (exo-erythrocytic) is responsible for relapse of malaria. **Exo-erythrocytic stage is absent in *P. falciparum*, so relapses do not occur.** The drugs used for the treatment or prevention of malaria may be classified (on the basis of the stage in the life cycle of the parasite at which these act) as:

Exo-erythrocytic stage is absent in *P. falciparum*, so relapses do not occur.



Stage	Clinical Use
Pre-Erythrocytic	Causal prophylaxis
Erythrocytic	– Clinical cure – Suppressive prophylaxis
Exo-Erythrocytic	– Radical cure
Gametocytic	– Prevention of transmission

Fig. 14.3: Life cycle of malarial parasite with target of drugs

- **Primary tissue schizonticides:** These are the drugs that kill schizonts in the liver (pre-erythrocytic stage) e.g. *proguanil*, *primaquine* and *pyrimethamine*. These drugs are used for **causal prophylaxis**.
- **Erythrocytic schizonticides:** These drugs kill schizonts in the blood and can be used for the **treatment of acute attacks as well as suppressive prophylaxis** of malaria. All of these drugs are used for treatment of malaria but not for prophylaxis. Artemisinin derivatives are very short acting whereas quinine and sulfadoxine are toxic on long term administration, therefore are not suitable for prophylaxis. Erythrocytic schizonticides may be fast acting or slow acting:
 - **Fast acting:** *Chloroquine*, *mepacrine*, *quinine*, *mefloquine*, *halofantrine*, *atovaquone* and *artemisinin* derivatives
 - **Slow acting:** *Proguanil*, *pyrimethamine*, *sulfonamides*, *tetracyclines*
- **Exo-erythrocytic schizonticides:** These drugs kill the exo-erythrocytic forms and are thus used for **radical cure** e.g. *primaquine*.
- **Sporonticides or gametocides:** These drugs kill the gametes and thus **prevent transmission** of malaria. Chloroquine, mepacrine and quinine kill the gametes of *P. vivax* only whereas *proguanil*, *pyrimethamine*, *primaquine* and *artemisinin* kill gametes of both *P. vivax* as well as *P. falciparum*.

P. falciparum do not form hypnozoites (exo-erythrocytic stage). Therefore, it does not show relapse.

Chloroquine

It is the drug possessing **largest volume of distribution** (>1300 L). It accumulates in the food vacuole of the plasmodium. Thus, it is selectively concentrated in the parasitized erythrocytes. It *prevents polymerization of heme to hemozoin* resulting in accumulation of heme that is toxic for the parasite. It is the *drug of choice for treatment and prophylaxis of non-falciparum malaria and chloroquine sensitive P. falciparum malaria*. It is an erythrocytic schizonticide and has no effect on exo-erythrocytic stages. It is also used for other indications that are

- Rheumatoid arthritis
- Extraintestinal amoebiasis
- Discoid lupus erythematosus
- Lepa reaction
- Infectious mononucleosis
- Photogenic reactions
- Malaria
- Giardiasis

Note: This can be remembered from the mnemonic: **RED LIP** Mahatma Gandhi

Adverse effects of chloroquine include skin rashes (lichenoid eruptions), peripheral neuropathy, hypotension, myocardial depression (T wave changes in ECG), auditory impairment and toxic psychosis. **Prolonged use of high doses can result in blindness due to retinal damage** (Bull's eye maculopathy). It can also precipitate porphyria and cause discolouration of nails and mucous membranes. Chloroquine is the drug of choice for treatment of malaria in pregnant women.

Quinine

Its mechanism of action is not clear and may be similar to chloroquine. Its major use is treatment of *P. falciparum* infections resistant to chloroquine (drug of choice). It is often used with doxycycline or clindamycin to decrease the duration of therapy and limit toxicity. To delay emergence of resistance, it is not advocated for chemoprophylaxis. It is 70% bound to plasma proteins especially α_1 acid glycoprotein, such binding increases in acute attacks of malaria, so that patients of malaria can tolerate much higher doses of quinine than other subjects. Its d-isomer, quinidine can be used i.v. for severe *P. falciparum* infections. It can cause hypoglycemia manifested by palpitations, sweating and tachycardia. To prevent hypoglycemia, i.v. infusion of quinine should always be given in 5% dextrose solution (instead of normal saline). At toxic doses, cinchonism can occur which manifests as symptoms of gastrointestinal distress, vertigo, blurred vision, headache and tinnitus. It can also cause cardiac conduction abnormalities and hemolysis in G-6-PD deficient patients. According to WHO guidelines, quinine is safe in pregnancy and can be used for severe or chloroquine resistant malaria.

Mefloquine

It can be used for chloroquine resistant *P. falciparum* infections, both for treatment as well as prophylaxis. It can cause **cardiac conduction disturbances, psychosis and seizures**. Administration with *halofantrine* or *quinine* is **contraindicated** because it can cause prolongation of QT interval. It is effective as a **single dose treatment** of malaria.

Primaquine

It acts by forming redox compounds that act as cellular antioxidants. It is a tissue (pre as well as exo-erythrocytic) schizonticide and gametocide. It is always used along with blood schizonticides for **radical cure** of malaria. It can cause *methemoglobinemia* and *hemolysis* in G-6-PD deficient patients. It is **contra-indicated in pregnancy**. It has **no role (for radical cure) in P. falciparum malaria** because this organism has no exo-erythrocytic stage.

DOC for radical cure of *P. vivax* malaria is primaquine

Prolonged use of high doses of chloroquine can result in blindness due to retinal damage (Bull's eye maculopathy).

Primaquine is contra-indicated in G-6-PD deficiency

Mefloquine is effective as a single dose treatment of malaria.

Proguanil potentiates the action of atovaquone

Antifolate Drugs

These include *pyrimethamine*, *proguanil*, *sulfadoxine* and *dapsone*. **Proguanil** is a prodrug and is activated to form *cycloguanil*. **Pyrimethamine and cycloguanil act by inhibiting DHFRase**. Pyrimethamine plus sulfadoxine act through sequential blockade. These are *slow acting blood schizonticides* that are active against chloroquine resistant *P. falciparum* infections. Proguanil plus atovaquone can be used for treatment as well as chemoprophylaxis of chloroquine resistant malaria.

Atovaquone

It is a rapidly acting blood schizonticide that acts by collapsing the parasite's membrane. Proguanil potentiates its antimalarial action. It can also be used for *Pneumocystis jiroveci* pneumonia and *Toxoplasma gondii* infections.

Artemisinin Derivatives

Artemisinin, dihydroartemisinin, artesunate, artemether and arteether are the compounds obtained from a Chinese herb *Artemisia annua*. Artemisinin is a prodrug and is activated in the body to dihydroartemisinin. These drugs generate highly active free radicals that damage parasite membranes. These drugs are the fastest acting drugs against malaria. Artesunate has a very short half life and can be given i.v. These can be used for the treatment of multidrug resistant malaria as well as serious forms like cerebral malaria. Artemisinin derivatives are not indicated for chemoprophylaxis of malaria. It can rarely cause QT prolongation.

Halofantrine and Lumefantrine

Halofantrine has erratic oral bioavailability and can cause potentially serious cardiotoxicity (even more if combined with mefloquine). Due to these reasons, it is not recommended for chemoprophylaxis of malaria. Use of this drug is reserved for treatment of multidrug resistant malaria. Lumefantrine is a new drug similar to halofantrine and is always used along with artemether. *Its absorption markedly increases with fatty food.*

Other drugs

Other antimalarial drugs include *doxycycline*, *amodiaquine*, *mepacrine* and *pyronaridine* etc. **Mepacrine is most concentrated in collagen.**



Fast acting Erythrocytic schizonticidal drugs

- M** – Mefloquine
- A** – Atovaquone
- C** – Chloroquine (and amodiaquine and piperazine)
- H** – Halofantrine (and lumefantrine)
- A** – Artemisinins
- R** – Res-Q (Quinine)



Artemisinins are the fastest acting drugs against malaria.

	Males and Non-pregnant Females	Pregnancy 1st trimester	Pregnancy 2nd and 3rd trimester	Remarks
Treatment of Uncomplicated Malaria				
<i>P. vivax</i>	Chloroquine (3 days) + Primaquine (14 days)	Chloroquine (3 days)	Chloroquine (3 days)	Primaquine is contra-indicated in pregnancy, infants and patients with G-6-PD deficiency
<i>P. falciparum</i>	Artesunate (3 days) + Primaquine (single dose)	Quinine	Artesunate (3 days) + Sulfadoxine/Pyrimethamine (1 day)	Primaquine is used for killing the gametes here
Mixed (<i>P. vivax</i> + <i>P. falciparum</i>)	Artesunate (3 days) + Sulfadoxine/Pyrimethamine (1 day) + Primaquine (14 days)	Quinine	Artesunate (3 days) + Sulfadoxine/Pyrimethamine (1 day)	Primaquine is given for 14 days to prevent relapse (for radical cure)
Suspected malaria but parasitological diagnosis is not possible	Full course of chloroquine, till the results of microscopy are received. Once the parasitological diagnosis is available, appropriate treatment as per the species (as given above)			
Treatment of Severe or complicated malaria	Parenteral artemisinin derivative (minimum 24 hours) followed by Oral ACT (3 days)	Parenteral quinine (minimum 24 hours) + oral quinine + clindamycin (for 7 days)	Parenteral artemisinin derivative (minimum 24 hours) followed by Oral ACT (3 days)	Artemisinin derivatives include: • Artesunate (i.v. or i.m.) • Artemether (i.m.) • Arteether (i.m.) – Arteether is not recommended for children – Doxycycline is contraindicated in pregnant women and children under 8 years of age

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Table Contd...

			– The parenteral treatment in severe malaria cases should be given for minimum of 24 hours once started (irrespective of the patient's ability to tolerate oral medication earlier than 24 hours)
Short term chemoprophylaxis (up to 6 weeks)	Doxycycline (should be started 2 days before travel and continued for 4 weeks after leaving the malarious area)		Doxycycline is not recommended for pregnant women and children less than 8 years.
Chemoprophylaxis for longer stay (more than 6 weeks)	Mefloquine (should be administered two weeks before, during and four weeks after exposure)		Mefloquine is contraindicated in individuals with history of convulsions, neuropsychiatric problems and cardiac conditions.

Treatment and Prophylaxis of Malaria (National guidelines according to NBVDCP)

THE WHO RECOMMENDED ACTs INCLUDE

• Artemether-Lumefantrine	• Artesunate-Amodiaquine
• Artesunate-Mefloquine	• Artesunate-Sulfadoxine-Pyrimethamine
• Dihydroartemisinin-Piperaquine	

DRUGS FOR AMOEBIASIS

The drugs effective against infections of *Entamoeba histolytica* can be classified as:

- Tissue (extra-intestinal) amoebicides only e.g. Chloroquine.
- Both intestinal (luminal) and extra-intestinal amoebicides e.g. nitroimidazoles (metronidazole, tinidazole, secnidazole, ornidazole), emetine and dehydroemetine.
- Luminal amoebicides only e.g. diloxanide furoate, paromomycin, iodoquinol, quiniodochlor and tetracyclines.

Nitroimidazoles

This group includes metronidazole and related drugs. These are effective orally as well as i.v. and eliminated by hepatic metabolism. Nitro group of these drugs gets bioactivated (by reduction) to form reactive cytotoxic products that damage DNA.

- **Metronidazole is the drug of choice for intestinal wall disease and amoebic liver abscess.** It is usually combined with a luminal amoebicide for these indications. It is **not a very good drug for luminal amoebiasis** because it is almost completely absorbed in the proximal intestine and very little amount reaches the colon.
- Metronidazole is also the **drug of choice for the treatment of trichomoniasis, giardiasis, bacterial vaginosis and pseudomembranous colitis by *C. difficile*.**
- It is also used for the treatment of infections caused by **anaerobic bacteria** like bacteroides and clostridium, and in combination therapy *H. pylori*.

Nausea, metallic taste and abdominal cramps are the most common adverse effects. It can also cause discolouration of urine, leucopenia and dizziness. Seizures can occur with the use of high dose. Opportunistic fungal infections can occur in a patient on metronidazole. It can cause **disulfiram like reaction** if used in patients taking alcohol. Metronidazole can potentiate the anticoagulant effect of coumarins. **Tinidazole, secnidazole, ornidazole and satranidazole** have similar potency and efficacy as metronidazole but are **long acting (secnidazole has longest half life)**. Satranidazole is devoid of metallic taste, neurological adverse effects as well as disulfiram like reaction.

Diloxanide Furoate

It is the **drug of choice for asymptomatic intestinal amoebiasis** and is used with tissue amoebicides for extra-intestinal infections. It is also the **drug of choice for carriers**. It can cause *flatulence as adverse effect*.

M

Metronidazole is the drug of choice for

- G – Giardiasis**
Gardnerella vaginalis (Bacterial vaginosis)
- U – Ulcer** (Peptic ulcer)
(In combination therapy for *H. pylori*)
- P – Pseudomembranous colitis**
by *C. difficile*
- T – Trichomoniasis**
- A – Amebiasis**
(Anaerobic bacteria like bacteroides and clostridium)



Diloxanide furoate is the drug of choice for asymptomatic intestinal amoebiasis

Emetine

Emetine and dehydroemetine act by *inhibiting protein synthesis* and can be used parenterally in severe hepatic amoebiasis. Toxicity of these drugs includes **emesis, muscle weakness and cardiotoxicity** (arrhythmias and congestive heart failure). It is rarely used now.



Satranidazole does not cause disulfiram-like reaction

Iodoquinol and Quinidochlor

Iodoquinol is a *luminal amoebicide* and in large doses can lead to thyroid enlargement and peripheral neuropathy. **Quinidochlor and other 8-hydroxyiodoquinolines** in high dose can cause eye defects (Subacute Myelo Optic Neuropathy or SMON).

Paromomycin

It is an **aminoglycoside** that can be used as luminal amoebicide. It has some activity against cryptosporidiosis in AIDS patients. **Recently it has been approved for the treatment of kala-azar.**



8-hydroxyquinolines like quinidochlor can cause SMON

Nitazoxanide

It is a **prodrug** and is converted to tizoxanide. Latter *inhibits* the enzyme **pyruvate ferredoxin oxidoreductase** (PFOR) which is essential for energy metabolism in anaerobic organisms. It has good activity against *cryptosporidium parvum*. It has some activity against *Entamoeba histolytica*, *T. Vaginalis*, *Ascaris*, *H. Nana* and metronidazole resistant *Giardia* but is approved only for the treatment of giardiasis and cryptosporidiosis.

DRUGS FOR TRYPANOSOMIASIS

Trypanosomiasis may be African or South American. African trypanosomiasis (sleeping sickness) is caused by *T. gambiense* and *T. rhodesiense*. It has an early haemolymphatic stage and in later stage CNS is involved. South American trypanosomiasis (Chagas' disease) is caused by *T. cruzi*.

Pentamidine

Its mechanism of action is not clear but it may act by interference with nucleic acid metabolism. It is *effective against early haemolymphatic stage of sleeping sickness*. It does not cross blood brain barrier, therefore is not effective against late CNS stages. It is **also used for the prophylaxis (aerosol) and treatment (i.v) of *Pneumocystis jiroveci* pneumonia and in the treatment of kala-azar**. It can cause *respiratory abnormalities, hypotension, hyperglycemia (as well as hypoglycemia) neutropenia and pancreatitis*.



Liposomal amphotericin B is the treatment of choice for visceral leishmaniasis.

Melarsoprol

It is an *organic arsenical* and is the **drug of choice for late stages of African trypanosomiasis**.

Other Drugs

Benznidazole is the **drug of choice for Chagas disease**.

Suramin is the *drug of choice for early haemolymphatic stages* of African trypanosomiasis. It is also used as an *alternative to ivermectin in onchocerciasis*.

Eflornithine is also effective in some cases of trypanosomiasis. It is also used *topically* in women to *dealy regrowth of facial hair* following depilation.



Miltefosine and sitamaquine can be administered orally for kala-azar.

Trypanosomiasis	Drug of Choice
East African sleeping sickness	
Early haemo lymphatic stage	Suramin
Late CNS stage	Melarsoprol
South-American (Chagas disease)	Benznidazole (alternative is nifurtimox)

DRUGS FOR LEISHMANIASIS

- Leishmaniasis can be visceral (kala-azar), mucocutaneous or cutaneous. Liposomal amphotericin B is the treatment of choice for visceral leishmaniasis. Sodium stibogluconate (pentavalent antimonial compound) is the most commonly used treatment for all forms of the disease. But it must be administered parenterally and is a cardiotoxic (cause QT prolongation) drug. The alternative agents for visceral leishmaniasis are pentamidine, miltefosine and sitamaquine. Last two drugs can be administered orally. Paromomycin has recently been approved for the treatment of kala-azar.
- Fluconazole or metronidazole can be used for cutaneous lesions and amphotericin B can be used for mucocutaneous lesions. However, sodium stibogluconate remains the first line therapy.
- Other drugs effective against leishmaniasis are ketoconazole, mepacrine and allopurinol.

Drug of Choice for Some Protozoal Infections

Organism	Drug of choice
Babesia	Clindamycin + Quinine
Balantidium coli	Tetracyclines
Cryptosporidium	Nitazoxanide/Paromomycin
Cyclospora	Cotrimoxazole
Isospora	Cotrimoxazole
Pneumocystis jiroveci	Cotrimoxazole
Leishmania donovani	Liposomal amphotericin B
Giardia lamblia	Metronidazole
Trichomonas vaginalis	Metronidazole
Toxoplasma gondii	Pyrimethamine + Sulfadiazine + Folinic acid
T. gondii in pregnancy	Spiramycin
Early African trypanosomiasis	Suramin
Late (CNS) African trypanosomiasis	Melasoprol
Chagas disease	Benznidazole

Note:

- DOC for Kala-azar – Liposomal amphotericin-B [CMDT 2012/1447]
- DOC for cutaneous Leishmaniasis – Sodium stibogluconate
- Most commonly used drug for Leishmania – Sodium stibogluconate

ANTI- HELMINTHIC DRUGS

Various helminthes causing human infestation are

1. NEMATODES

- Round worm (*Ascaris lumbricoides*)
- Hook worm (*Necator americanus* and *Ancylostoma duodenale*)
- Pinworm (*Enterobius vermicularis*)
- Threadworm (*Strongyloides stercoralis*)
- Filarial worm (*Wuchereria bancrofti* and *Brugia malayi*, *Onchocerca volvulus*)
- Whip worm (*Trichuris trichiura*)
- Trichinea worm (*Trichinella spiralis*)
- Guinea worm (*Dracunculus medinensis*)

2. TREMATODES

- Blood fluke (*Schistosoma haematobium*, *mansoni* and *japonicum*)
- Lung fluke (*Paragonimus westermani*)
- Liver fluke (*Fasciola hepatica*)

3. CESTODES

- Pork tapeworm (*Taenia solium*)
- Beef tapeworm (*Taenia saginata*)
- Fish tapeworm (*Diphyllobothrium latum*)
- Dog tapeworm (*Echinococcus granulosus*)
- Dwarf tapeworm (*Hymenolepis nana*)

Classification

Based on mechanism of action, these drugs may be classified as:

- Drugs inhibiting polymerization of beta tubulin: Albendazole, mebendazole, thiabendazole, triclabendazole
- Drugs causing spastic paralysis (NN receptor agonist): Pyrantel pamoate, levamisole
- Drugs causing flaccid paralysis (GABAA agonist): Piperazine, ivermectin
- Drugs altering microfilarial membrane and increasing phagocytosis: Diethylcarbamazine (DEC)
- Drugs causing uncoupling of oxidative phosphorylation: Bithionol, niclosamide
- Drugs causing influx of calcium: Praziquantal.

Important Points

- Albendazole, mebendazole and pyrantel pamoate have wide antihelminthic spectrum.
- Albendazole is the drug of choice for the treatment of all nematode infestations including cutaneous larva migrans (creeping eruption), visceral larva migrans (toxocariasis) and neurocysticercosis except enterobius (mebendazole), wuchereria and brugia (DEC), onchocerca and strongyloides (ivermectin) and dracunculus (Metronidazole).
- Praziquantal is the drug of choice for all trematode and cestode infestations except *Fasciola hepatica* (triclabendazole) and hydatid disease (albendazole).
- High dose albendazole if used for greater than 3 months (as for hydatid disease) may cause hepatotoxicity.
- DEC acts on both microfilaria and adult whereas ivermectin acts only on microfilaria.
- Onchocerciasis is also known as river blindness and is treated by ivermectin.
- Ivermectin should be avoided in children below 5 years old.
- Niclosamide is used for most cestodes. However it has been superseded by praziquantal for this indication.

Albendazole is the drug of choice for the treatment of all nematode infestations including cutaneous larva migrans (creeping eruption), visceral larva migrans (toxocariasis) and neurocysticercosis except enterobius (mebendazole), wuchereria and brugia (DEC), onchocerca and strongyloides (ivermectin) and dracunculus (Metronidazole).

Praziquantal is the drug of choice for all trematode and cestode infestations except *Fasciola hepatica* (triclabendazole) and hydatid disease (albendazole).

Ivermectin has recently been approved for topical treatment of inflammatory lesions of rosacea.

DRUG OF CHOICE	
Conditions	Drug of choice
Mycobacterial diseases	
• Tuberculosis	See text
• Leprosy	See text
- Type 1 Lepra reaction	Corticosteroids
- Type 2 Lepra reaction	Corticosteroids
• M. avium intracellulare	Azithromycin + Ethambutol ± Rifabutin
• M. kansasii	Isoniazid + Rifampicin ± Ethambutol
• M. fortuitum chelonae	Cefoxitin + clarithromycin
Fungal diseases	
• Candida albicans	Fluconazole
• Candida glabrata	Caspofungin
• Candida krusei	Caspofungin
• Candida endocarditis	Amphotericin B (AMB)
• Histoplasmosis	
- Meningeal	AMB
- Non-meningeal	Itraconazole
• Coccidioidomycosis	AMB
• Para-coccidioidomycosis	Itraconazole ¹
• Sporotrichosis	Itraconazole
• Blastomycosis	
- Mild and Non-CNS	Itraconazole
- Severe or CNS	AMB
• Penicillium marneffeii	Itraconazole ¹
• Chromoblastomycosis	Itraconazole
• Mycetoma	
- Eumycetoma	Itraconazole
- Actinomycetoma	Itraconazole
• Cryptococcal meningitis	
- Induction	AMB (for 2 weeks)
- Maintenance	Fluconazole (for further 8 weeks)
• Aspergillosis	
- Invasive	Voriconazole
- Allergic broncho-pulmonary (AMBA)	Prednisolone + Itraconazole/Voriconazole
• Mucormycosis	AMB ²
• Pseudoallescheria boydii	Voriconazole
• Fusarium	Voriconazole
• Exserohilum	AMB
• Febrile neutropenia	
- Treatment	Voriconazole
- Prophylaxis	Fluconazole

Contd...

DRUG OF CHOICE	
Conditions	Drug of choice
Viral diseases	
• Herpes simplex	
- Keratitis	Topical vidarabine/Trifluridine
- Neonatal	Acyclovir
- Encephalitis	Acyclovir
- Disseminated	Acyclovir
- Esophagitis	Acyclovir
- Genital	Acyclovir
- Bell's Palsy	Prednisolone
• Varicella	Acyclovir
• Herpes zoster	
- Acute	Valacyclovir
- Post herpetic neuralgia	Gabapentin
• Epstein Barr virus	Symptomatic (no antiviral)
• Cytomegalo virus	
- Retinitis	Ganciclovir
- Post-transplant	
* Mild	Valganciclovir
* Severe	Ganciclovir
• Measels	Ribavirin ³
• Prion disease	Flupirtine ⁴
• Viral hemorrhagic fever	
- Lassa virus	Ribavirin
- Rift Valley fever	Ribavirin
- Congo crimean hemorrhage fever	Ribavirin
- Hantaan virus	Ribavirin
• Respiratory syncytial virus	
- High risk patient, acute	Ribavirin (aerosolized)
- Prophylaxis (infants)	Palivizumab
• Influenza virus	
- Seasonal influenza	Oseltamivir
- Avian influenza (including bird flu)	Oseltamivir
- Oseltamivir-resistant influenza	Zanamivir
• Human immunodeficiency virus (HIV)	
- Treatment	Zidovudine + Lamivudine + Nevirapine
- Post-exposure prophylaxis	Zidovudine + Lamivudine ± Atazanavir
Protozoal diseases⁵	
• Ameobiasis	
- Asymptomatic intestinal	Diloxanide furoate
- Mild, moderate and severe intestinal	Metronidazole + diloxanide
- Extra-intestinal (hepatic abscess)	Metronidazole + diloxanide

Contd...

Contd...

DRUG OF CHOICE	
Conditions	Drug of choice
- Primary amebic meningo-encephalitis (<i>Naegleria fowleri</i>)	AMB
- Acanthameoba keratitis	Topical propamidine isethionate
• Coccidiosis	
- Cryptosporidiosis	Nitazoxanide/Paromomycin
- Isoporiasis	Cotrimoxazole
- Cyclosporiasis	Cotrimoxazole
- Microsporidiosis	Albendazole ⁶
- Sacrocytosis	No treatment ⁷
Helminthic diseases	
• Flukes	
- Schistosoma	Praziquantal
- Clonorchis	Praziquantal
- Opisthorchis	Praziquantal
- Paragonimus	Praziquantal
- Fasciolopsis	Praziquantal
- Fasciola	Triclabendazole
• Tapeworms	
- Taenia solium	Praziquantal
- T. saginata	Praziquantal
- D. latum	Praziquantal
- H. nana	Praziquantal
- Echinococcus	Albendazole
- Neurocysticercosis	Albendazole
• Nematodes	
- Ascaris	Albendazole
- Trichuris	Albendazole
- Ancylostoma	Albendazole
- Necator	Albendazole
- Enterobius	Albendazole
- Trichinella	Albendazole
- Cutaneous larva migrans	Albendazole
- Visceral lara migrans	Albendazole
- Dracunculus (Guinea worm)	Metronidazole
• Filarial worm	
- W. bancrofti	Di Ethyl Carbamezine (DEC)
- B. malayi	DEC
- B. timori	DEC
- Loa loa	DEC
- Onchocerca volvolus	Ivermectin
• Strongyloides stercoralis	Ivermectin

Note:

1. For severe cases, AMB is drug of choice
2. Posaconazole should be given after disease has stabilized
3. Indicated only when severe pneumonitis is present
4. Decreases cognitive decline but does not stop mortality
5. For other protozoa, see text
6. Fumagillin topically should be added for ocular disease
7. Sulfadiazine may clear cysts

MULTIPLE CHOICE QUESTIONS

ANTI-MYCOBACTERIAL DRUGS

1. A middle aged man with chronic renal failure is diagnosed to have sputum-positive pulmonary tuberculosis. His creatinine clearance is 25 ml/min. All of the following drugs need modification in doses EXCEPT:
 - (a) Isoniazid (AIIMS May, 2003)
 - (b) Streptomycin (AIIMS Nov, 2001) (DPG 2001)
 - (c) Rifampicin
 - (d) Ethambutol
2. Which of the following drugs is most likely to be effective against multidrug-resistant strains of *M. tuberculosis*, including those resistant to streptomycin?
 - (a) Amikacin (AIIMS May, 2012)
 - (b) Clarithromycin
 - (c) Gentamicin
 - (d) Spectinomycin
3. Slow acetylators of isoniazid are more prone to develop:
 - (a) Failure of therapy (AI 2012)
 - (b) Peripheral neuropathy
 - (c) Hepatotoxicity
 - (d) Allergic reactions
4. Prolonged treatment with INH leads to deficiency of?
 - (a) Pyridoxine (AI 2011)
 - (b) Thiamine
 - (c) Pantothenic acid
 - (d) Niacin
5. Pseudojaundice is an adverse effect of: (DPG - 2011)
 - (a) Phenytoin
 - (b) Rifabutin
 - (c) Omeprazole
 - (d) Chlorpromazine
6. Commonest side effect of Dapsone is: (DPG - 2011)
 - (a) Hemolytic anemia
 - (b) Thrombocytopenia
 - (c) Cyanosis
 - (d) Bone marrow depression
7. Cross resistance of isoniazid is seen with:
 - (a) Rifampicin (AIIMS May 2008)
 - (b) Ethionamide
 - (c) Cycloserine
 - (d) Ethambutol
8. Ethambutol causes: (DPG 2009)
 - (a) Retrobulbar neuritis
 - (b) Deafness
 - (c) Red urine
 - (d) Peripheral neuritis
9. Which of the following antitubercular drugs is safe in hepatitis? (DPG 2009)
 - (a) Isoniazid
 - (b) Rifampicin
 - (c) Pyrazinamide
 - (d) Ethambutol
10. A 30 year old pregnant woman develops tuberculosis. Which of the following antitubercular drugs should not be used? (AI 2004)
 - (a) INH
 - (b) Rifampicin
 - (c) Streptomycin
 - (d) Ethambutol
11. Patients suffering from multidrug resistant tuberculosis can be treated with all the following drugs EXCEPT: (AI 2004)
 - (a) Tobramycin
 - (b) Amikacin
 - (c) Ciprofloxacin
 - (d) Clarithromycin
12. Which anti-tubercular drug is implicated in the causation of transient memory loss? (AIIMS Nov 2006)
 - (a) Ethionamide
 - (b) Isoniazid
 - (c) Ethambutol
 - (d) Pyrazinamide
13. All of the following are true about the therapy of tuberculosis EXCEPT: (AIIMS Nov, 2004)
 - (a) Flu like syndrome is usually seen with rifampicin being taken on daily basis
 - (b) Ethambutol accumulates in renal failure
 - (c) Hyperuricemia is a recognized side effect of pyrazinamide
 - (d) Red green color impairment is an early sign of ethambutol induced optic neuritis
14. In leprosy, the best bactericidal agent is:
 - (a) Clofazimine (AI 2003, AIIMS May, 2002)
 - (b) Dapsone
 - (c) Rifampicin
 - (d) Ethionamide
15. A patient suffering from AIDS is on zidovudine, lamivudine and indinavir therapy. He develops pulmonary tuberculosis for which treatment is started. Which of the following should be avoided in him?
 - (a) INH (AIIMS Nov, 2001 and May, 2003)
 - (b) Ethambutol
 - (c) Pyrazinamide
 - (d) Rifampicin

16. **Bactericidal drugs in ATT are:** (PGI Dec. 2005) (PGI June 2004)
 (a) Pyrazinamide
 (b) Ethambutol
 (c) PAS
 (d) Rifampicin
 (e) Isoniazid
17. **Side effects of dapsone apart from hemolytic anaemia are:** (PGI June, 2003)
 (a) G-6-PD deficiency
 (b) Infectious mononucleosis like syndrome
 (c) Agranulocytosis
 (d) Lichenoid eruption
 (e) Skin pigmentation
18. **The primary reason for the use of drug combination in the treatment of tuberculosis is to:**
 (a) Ensure patient compliance with the drug regimen
 (b) Enhance activity against metabolically inactive mycobacteria
 (c) Delay or prevent the emergence of resistance
 (d) Provide prophylaxis against other bacterial infections
19. **Which of the following statements regarding drugs used in leprosy is FALSE?**
 (a) Single intramuscular injections of acedapsone maintain inhibitory levels of dapsone in tissues for upto 3 months
 (b) Monthly doses of rifampicin delay the emergence of resistance to dapsone
 (c) Clofazimine should not be given to patients who are intolerant to dapsone or who fail to improve during treatment with dapsone
 (d) Clofazimine may cause changes in the skin colour
20. **Which of the following statements regarding pyrazinamide is FALSE?**
 (a) One should discontinue treatment if hyperuricemia occurs
 (b) There is minimal cross resistance with INH
 (c) Polyarthralgia is a common side effect
 (d) It can cause hepatotoxicity
21. **Occurrence of the following adverse reaction absolutely contraindicates further use of rifampicin in the treatment of tuberculosis:**
 (a) Respiratory syndrome
 (b) Cutaneous syndrome
 (c) Flu like syndrome
 (d) Abdominal syndrome
22. **Corticosteroids are absolutely contraindicated in the following type of tuberculosis:**
 (a) Miliary
 (b) Meningeal
 (c) Intestinal
 (d) Renal
23. **Once weekly administration of which of the following antibiotics has prophylactic activity against bacteremia caused by *M. avium* complex in AIDS patients?**
 (a) Azithromycin
 (b) Clarithromycin
 (c) Isoniazid
 (d) Rifabutin
24. **Most effective drug against extracellular mycobacteria is:** (DPG 2008)
 (a) Isoniazid
 (b) Rifampicin
 (c) Pyrazinamide
 (d) Ethambutol
25. **Hypothyroidism is caused by which of the following anti-tubercular drug?** (DPG 2008)
 (a) Streptomycin
 (b) Ethionamide
 (c) Thioacetazone
 (d) Ethambutol
26. **ATT causing orange coloured urine is:** (DPG 2007) (DNB 2002, 2005)
 (a) Rifampicin
 (b) Isoniazid
 (c) Streptomycin
 (d) Pyrazinamide
27. **Which of the following antitubercular drug is not hepatotoxic:** (DPG 2006)
 (a) Isoniazid
 (b) Rifampicin
 (c) Ethionamide
 (d) Streptomycin
28. **Which of the following is active against atypical mycobacteria?** (DPG 2006)
 (a) Clarithromycin
 (b) Rifabutin
 (c) Ciprofloxacin
 (d) All of the above
29. **ATT most commonly implicated in causing peripheral neuropathy is:** (RJ 2002) (DPG 2006)
 (a) Rifampicin
 (b) Pyrazinamide
 (c) INH
 (d) Ethambutol
30. **Arthralgia is commonly caused by which ATT drug?** (DPG 2004)
 (a) INH
 (b) Rifampicin
 (c) Pyrazinamide
 (d) Ethambutol
31. **Which of the following antitubercular drugs can be safely used in severe renal failure:** (DPG 2003) (RJ 2003)
 (a) Streptomycin
 (b) Ethambutol
 (c) Capreomycin
 (d) Rifampicin

32. A patient of multidrug resistant tuberculosis is on antitubercular drugs. After a few months he develops an inability to distinguish between red and green color. Most likely drug causing these symptoms is:
(DPG 2002, RJ 2004, DPG 2000, DPG 2007, MH 2000)
- Rifampicin
 - Ethambutol
 - Cycloserine
 - Ethionamide
33. Which of the following drugs is useful in the treatment of infection by *Mycobacterium avium* complex?
(DPG 2000)
- Isoniazid
 - Clarithromycin
 - Cycloserine
 - Rifampicin
34. Which of the following antitubercular drugs can cause psychosis?
(DPG 2000)
- Ofloxacin
 - Cycloserine
 - Capreomycin
 - Rifampicin
35. INH induced peripheral neuropathy results from deficiency of vitamin:
(DPG 1999)
- B₁
 - B₂
 - B₆
 - B₁₂
36. Antitubercular drug which DOES NOT cross blood brain barrier is:
(DPG 1998)
- Streptomycin
 - INH
 - Rifampicin
 - Pyrazinamide
37. Which of the following antitubercular drugs can be used in patients with hepatic dysfunction?
(DPG 1997)
- Streptomycin
 - INH
 - Pyrazinamide
 - Rifampicin
38. INH can be used safely in the presence of:
(MPPG 2003)
- Jaundice
 - Chronic renal failure
 - Epilepsy
 - Coronary artery disease
39. Which of the following antitubercular drug is preferred in severe liver disease?
(UP 2008)
(RJ 2001)
- Streptomycin + Isoniazid
 - Streptomycin + Ethambutol
 - Isoniazid + Rifampicin
 - Rifampicin + Ethambutol
40. Which of the following ATT has maximum CSF penetration?
(UP 2005)
- Streptomycin
 - INH
 - Rifampicin
 - Ethambutol
41. Common dose dependant side effects of ethambutol is:
(UP 2005)
- Red-urine
 - Optic neuritis
 - Nephropathy
 - Peripheral neuropathy
42. Most common drug used in Leprosy is:
(UP 2006)
- Dapsone
 - Clofazimine
 - Ethionamide
 - Ofloxacin
43. The bacterial drug resistance in tuberculosis results from:
(UP 2006)
(Jharkhand 2006)
(Karnataka 2006)
- Transduction
 - Transformation
 - Plasmid mediated
 - Mutation
44. INH and pyridoxine are given together in antituberculous chemotherapy:
(TN 2003)
- To prevent peripheral neuritis
 - To prevent emergence of INH resistance
 - As a nutrient supplement
 - As a synergistic combination
45. Bacteriostatic antitubercular drug among the following is:
(TN 2004, RJ 2004)
- Isoniazid
 - Rifampin
 - Streptomycin
 - Ethambutol
46. Dapsone is used in all except:
(RJ 2002)
- Dermatitis herpetiformis
 - Leprosy
 - Pneumocystis jiroveci pneumonia
 - Tuberculosis
47. In Lepra reaction, the drug useful is:
(MH 2000)
- Pencillins
 - Clofazimine
 - Dapsone
 - Rifampicin
48. Antitubercular drug that can cause hyperuricemia is:
(MH 2002)
- Rifampicin
 - INH
 - Pyrazinamide
 - Streptomycin
49. Treatment of lepromatous leprosy is:
(MH 2003)
- Rifampicin + Dapsone
 - Rifampicin + Clofazimine
 - Rifampicin + Dapsone + Clofazimine
 - Rifampicin + Ofloxacin + Minocycline

50. Ethambutol should be used very cautiously in childhood tuberculosis due to which of its side effect? (MH 2005)
- Ocular toxicity
 - Renal damage
 - Hepatotoxicity
 - Neurotoxicity
51. Which of the following drugs can produce dramatic improvement in patients with Type II lepra reaction? (MH 2005)
- Thalidomide
 - Steroids
 - Dapsone
 - Clofazimine
52. Mechanism of action of rifampicin is? (MH 2008)
- Inhibition of mycolic acid synthesis
 - DNA dependent RNA polymerase inhibition
 - Protein synthesis inhibition
 - Inhibits synthesis of arabinogalactone
53. Drug that crosses placenta is: (Jharkhand 2005)
- Isoniazid
 - Rifampicin
 - Pyrazinamide
 - All
54. Treatment of Mycobacteria avium complex include all except: (AP 2006)
- Ciprofloxacin
 - Clarithromycin
 - Rifabutin
 - Pyrazinamide
55. Which one of the following drugs is not used in the treatment of mycobacterium avium intercellulare infection? (Karnataka 2006)
- Clarithromycin
 - Eflornithine
 - Ethambutol
 - Rifabutin
56. Most important side effect of ethambutol is: (Karnataka 2005)
- Hepatotoxicity
 - Renal toxicity
 - Peripheral neuropathy
 - Retro bulbar neuritis
57. The following drugs are useful in the treatment of isoniazid poisoning: (Karnataka 2004)
- Pyridoxine
 - Diazepam
 - Bicarbonate
 - All of the above
58. Treatment of lepra reaction includes: (Karnataka 2002)
- Chloroquine
 - Corticosteroids
 - Stoppage of drug
 - All of above
59. Leprosy treatment includes following drugs except: (Karnataka 2002)
- Dapsone
 - Rifampicin
 - Penicillin
 - Clofazimine

ANTI-FUNGAL AND ANTIVIRAL (EXCEPT HIV) DRUGS

60. A diabetic patient presents with fungal infection of sinuses and peri-orbital region with significant visual impairment. The best drug for treatment of this patient is:
- Amphotericin B
 - Itraconazole
 - Ketoconazole
 - Broad spectrum antibiotics
61. Amphotericin B causes deficiency of? (AI 2011) (AP 2005)
- Sodium
 - Calcium
 - Potassium
 - Chloride
62. Amphotericin B toxicity can be reduced by? (AI 2010)
- Incorporating it in liposomal complex
 - Combining with fluconazole
 - Combining with flucytosine
 - Injecting the drug with dextrose
63. Voriconazole is not effective against: (AIIMS Nov 2009)
- Candida albicans
 - Mucormycosis
 - Candida tropicalis
 - Aspergillosis
64. Which drug would treat both dermatophytosis and candidal infections? (AIIMS May 2008)
- Ketoconazole
 - Griseofulvin
 - Nystatin
 - Tolnaftate
65. Liposomal amphotericin B has the following advantage over conventional amphotericin B: (DPG 2009)
- Lesser nephrotoxicity
 - Lesser cost
 - Absence of infusional toxicity
 - Once a week administration
66. Which of the following is not an antifungal drug? (AI-2008)
- Ketoconazole
 - Undecylenic acid
 - Ciclopirox
 - Clofazimine
67. Which of the following is caused by amphotericin B? (AIIMS May, 2004)
- Hypokalemia
 - Hyperkalemia
 - Hypermagnesemia
 - Hyponatremia

68. The antimicrobial agent which inhibits the ergosterol biosynthesis is: (AIIMS Nov, 2003)
- Ketoconazole
 - Amphotericin B
 - 5-Flucytosine
 - Griseofulvin
69. Which of the following is the treatment of choice for cryptococcal meningitis? (AP 2003) (AIIMS Nov, 2002)
- Fluconazole
 - Itraconazole
 - Flucytosine
 - Amphotericin B
70. Which of the following statements about fluconazole is most accurate?
- It is highly effective in the treatment of aspergillosis
 - It does not penetrate the blood-brain barrier
 - Its oral bioavailability is less than that of ketoconazole
 - It inhibits demethylation of lanosterol
71. If amphotericin B is administered, the patient should be premedicated with:
- Diphenhydramine
 - Ibuprofen
 - Prednisone
 - Any of the above
72. Which of the following statements about terbinafine is FALSE?
- Its activity is restricted to dermatophytes
 - It is effective in onychomycosis
 - It inhibits squalene epoxidase
 - It is used topically only
73. Fluconazole differs from ketoconazole in that:
- It is not active by the oral route
 - It is a more potent inhibitor of drug metabolism
 - It is not effective in cryptococcal meningitis
 - It is unlikely to produce anti-androgenic side effects
74. Fluconazole is more effective than itraconazole in the following systemic fungal disease:
- Pulmonary histoplasmosis
 - Cryptococcal meningitis
 - Non-meningeal blastomycosis
 - Disseminated sporotrichosis
75. Ganciclovir is preferred over acyclovir in the following condition:
- Herpes simplex keratitis
 - Herpes zoster
 - Chickenpox
 - Cytomegalovirus retinitis in AIDS patients
76. Resistance to acyclovir is most commonly due to mutation in a viral gene that encodes a protein that:
- Converts viral RNA into DNA
 - Phosphorylates acyclovir
 - Transports acyclovir into the cell
 - Transports acyclovir out of the cell
77. A fungicidal drug that can be used orally for the treatment of onychomycosis is:
- Griseofulvin
 - Amphotericin B
 - Clotrimazole
 - Terbinafine
78. Dose limiting toxicity of amphotericin B is:
- Infusion related reaction
 - Renal tubular acidosis
 - Myelosuppression
 - Hypotension
79. All of the following antifungal drugs inhibit ergosterol biosynthesis EXCEPT:
- Ketoconazole
 - Fluconazole
 - Amphotericin B
 - None of these
80. Regarding the lipid or liposomal formulations of amphotericin B, which of the following statements is accurate?
- They are less expensive to use than conventional amphotericin B
 - They are more effective in fungal infections than conventional preparations because they increase tissue uptake of amphotericin B
 - They may decrease the nephrotoxicity of amphotericin B
 - They have wider spectrum of antifungal activity than conventional formulations of amphotericin B
81. Griseofulvin is not useful in one of the following:
- Tinea capitis (DPG 2010)
 - Tinea cruris (DPG 2009, 2008)
 - Tinea versicolor
 - Tinea pedis
82. Avian influenza is treated by: (DPG 2007)
- Amantadine
 - Ribavarin
 - Cidofovir
 - Oseltamivir
83. Amphotericin-B is obtained from: (DPG 2006)
- Streptomyces nodosus
 - Streptomyces pimprina
 - Streptomyces nousseri
 - Streptomyces fragilis
84. Which of the following is NOT true about anti-fungal drugs? (DPG 97)
- Amphotericin B is given only parenterally
 - Griseofulvin is effective orally
 - Ciclopirox olamine is effective in systemic mycoses
 - Fluconazole is effective orally as well as i.v.

85. Topically used antifungal agent is: (MPPG 2003)
 (a) Ketoconazole
 (b) Clotrimazole
 (c) Amphotericin B
 (d) Physostigmine
86. Which of the following is a broad spectrum systemic antifungal agent? (UP 2007)
 (a) Econazole
 (b) Miconazole
 (c) Ketoconazole
 (d) Clotrimazole
87. Which of the following anti-metabolites act as an antifungal agent? (UP 2005)
 (a) Paclitaxel
 (b) 5-Flucytosine (5 FC)
 (c) Chlorambucil
 (d) Decarbazine
88. Drug of choice for herpes simplex virus infection is: (TN 2005)
 (a) Acyclovir
 (b) Zidovudine
 (c) Indinavir
 (d) Ribavirin
89. All can be used for systematic fungal infections except: (RJ 2002)
 (a) Ketoconazole
 (b) Fluconazole
 (c) Amphotericin B
 (d) Griseofulvin
90. Drug of choice for chronic hepatitis -B is (RJ 2006)
 (a) Lamivudine
 (b) IFN- α
 (c) Ribavirin
 (d) Zidovudine
91. All are effective against Tinea versicolor except: (All India 2002) (MH 2000)
 (a) Fluconazole
 (b) Clotrimazole
 (c) Ketoconazole
 (d) Griseofulvin
92. Drugs that can be used to treat candida infection are all except: (MH 2002)
 (a) Ketoconazole
 (b) Nystatin
 (c) Amphotericin
 (d) Griseofulvin
93. Which of the following anti-fungal drugs has only topical action? (MH 2003)
 (a) Fluconazole
 (b) Ketoconazole
 (c) Itraconazole
 (d) Clotrimazole
94. Drug that can cause complete histopathological resolution in patients with hepatitis B is: (MH 2005)
 (a) Cyclosporin
 (b) Ribavirin
 (c) Entercavir
 (d) None of the above
95. Mechanism of action of terbinafine is? (MH 2008)
 (a) Binds to ergosterol
 (b) Prevents formation of purine
 (c) Inhibition of microtubule formation
 (d) Inhibition of ergosterol synthesis
96. In dermatophytosis, which antifungal drug is not indicated: (Bihar 2006)
 (a) Fluconazole
 (b) Terbinafine
 (c) Griseofulvin
 (d) Amphotericin B
97. Treatment of choice for coccidioidomycosis is: (Jharkhand 2005)
 (a) Amphotericin
 (b) Fluconazole
 (c) Flucytosine
 (d) Griseofulvin
98. Acyclovir is indicated in: (AFMC 2000) (AI 2000) (AP 2000)
 (a) Candida
 (b) Herpes simplex
 (c) Mycoplasma
 (d) Pneumocystis
99. Most serious adverse effect of ketoconazole is: (Kolkata 2008)
 (a) Adrenal insufficiency
 (b) Pellagra like skin lesion
 (c) Liver injury
 (d) Prostate cancer
100. Induction of treatment in serious fungal infections is mostly done by: (Kolkata 2009)
 (a) IV amphotericin B
 (b) Ketoconazole
 (c) 5 - Flucytosine
 (d) Fluconazole
101. Which one of the statements is false regarding adefovir dipivoxil? (Karnataka 2006)
 (a) Acyclic nucleotide analogue
 (b) Well tolerated orally
 (c) Used in chronic hepatitis B infection
 (d) Used in anti-retroviral therapy
102. Drug of choice for Herpes simplex encephalitis is: (Karnataka 2005, 2004)
 (a) 5-Hydroxy deoxyuridine (5-HU)
 (b) Acyclovir
 (c) Gancyclovir
 (d) None of the above

ANTI-HIV DRUGS

103. All of the following are common adverse effects of HAART therapy except:
 (a) Steatosis
 (b) Lipodystrophy
 (c) Optic neuritis
 (d) Increased cholesterol
104. A person is being treated for Human Immunodeficiency Virus-1. He developed hypertriglyceridemia and hypercholesterolemia. Most likely drug implicated for these adverse effects is: (AI 2012)
 (a) Ritonavir
 (b) Raltegravir
 (c) Didanosine
 (d) Efavirenz
105. Efavirenz is used for treatment of HIV infections. It acts
 (a) As protease inhibitor (AIIMS Nov. 2011)
 (b) As reverse transcriptase inhibitor
 (c) As integrase inhibitor
 (d) By inhibiting the HIV entry into the cell
106. Which of the following drugs is used to prevent HIV transmission from an HIV positive pregnant mother to child? (AIIMS Nov. 2011)
 (a) Lamivudine
 (b) Stavudine
 (c) Nevirapine
 (d) Didanosine
107. Which is the integrase inhibitor used in treatment of HIV? (AI 2011)
 (a) Raltegravir
 (b) Indinavir
 (c) Lopinavir
 (d) Fosamprenavir
108. All of the following cause inhibition of CYP3A except: (AIIMS May 2010)
 (a) Saquinavir
 (b) Ritonavir
 (c) Itraconazole
 (d) Erythromycin
109. Which of the following drug is a reverse transcriptase inhibitor? (DPG - 2011)
 (a) Indinavir
 (b) Ritonavir
 (c) Nelfinavir
 (d) Abacavir
110. Maximum risk of pancreatitis is present with: (AI 2010)
 (a) Didanosine
 (b) Lamivudine
 (c) Zidovudine
 (d) Abacavir
111. The basis of combining ritonavir with lopinavir:
 (a) Pharmaceutical compatibility (DPG 2009)
 (b) CYP3A4 inhibition by ritonavir
 (c) Long elimination half life of ritonavir
 (d) Ability to counteract side-effects of lopinavir
112. Nevirapine is: (AI 2007, 2006, 2005)
 (a) Non-nucleoside reverse transcriptase inhibitor (NNRTI) (AIIMS May 2004, RJ 2008)
 (b) Nucleoside reverse transcriptase inhibitor (NRTI)
 (c) Protease inhibitor
 (d) Fusion inhibitor
113. Drug causing maximum peripheral neuropathy is: (AI 2007)
 (a) Zidovudine
 (b) Lamivudine
 (c) Stavudine
 (d) Didanosine
114. All of the following drugs are protease inhibitors EXCEPT: (AI 2006)
 (a) Nelfinavir
 (b) Saquinavir
 (c) Abacavir
 (d) Ritonavir
115. Which of the following anti-retroviral drugs does not cause peripheral neuropathy? (AI 2000)
 (a) Lamivudine
 (b) Stavudine
 (c) Didanosine
 (d) Zalcitabine
116. True about protease inhibitors are all EXCEPT: (AIIMS Nov., 2007)
 (a) Acts as a substrate for P-glycoprotein (P-gp) and action is mediated by mdr-1 gene
 (b) Undergo hepatic oxidative metabolism
 (c) Protease inhibitors interfere with metabolism of several drugs
 (d) Saquinavir causes maximum induction of CYP3A4
117. Resistance to zidovudine develops due to: (AIIMS May, 2005)
 (a) Mutation at reverse transcriptase
 (b) Increased efflux of the drug from inside the cell
 (c) Increased metabolism of the drug
 (d) Decreased zidovudine 5 triphosphate formation
118. Complications of zidovudine therapy are: (PGI June, 2006)
 (a) Nausea and vomiting
 (b) Anemia
 (c) Steatosis
 (d) Nephrotoxicity
 (e) Cardiotoxicity
119. Nucleoside reverse transcriptase inhibitors are: (PGI June, 2004)
 (a) Zalcitabine
 (b) Delavirdine
 (c) Nevirapine
 (d) Stavudine
 (e) Ritonavir

120. Regarding ritonavir use in AIDS patient, which of the following is/are true? (PGI Dec. 2004)
- Interacts with terfenadine
 - G.I. symptoms are seen
 - Contraindicated in renal failure
 - It is NNRTI
 - Should not be used in AIDS patient with bleeding disorder
121. Bone marrow depressive drugs in the treatment of AIDS patient are: (PGI June, 2003)
- Didanosine
 - Zalcitabine
 - Zidovudine
 - Cotrimoxazole
 - Ganciclovir
122. Drugs used for treatment of chorioretinitis in AIDS patients are: (PGI June, 2003)
- Valacyclovir
 - Ganciclovir
 - Rivabirin
 - Amantadine
 - Cidofovir
123. Protease inhibitors are: (PGI Dec. 2002)
- Saquinavir
 - Nevirapine
 - Nelfinavir
 - Abacavir
 - Efavirenz
124. Which of the following statements about stavudine is accurate?
- Bone marrow suppression is dose limiting
 - It causes marked neurotoxicity
 - It inhibits HIV protease
 - It is a non-nucleoside reverse transcriptase inhibitor
125. Select the drug that is active against both HIV and hepatitis B virus:
- Lamivudine
 - Indinavir
 - Didanosine
 - Efavirenz
126. Efavirenz limits HIV infection by:
- Binding to active site of HIV reverse transcriptase
 - Impairing the binding of HIV virion to CD4 receptors on T- cells
 - Inhibiting the HIV protease
 - Serving as an allosteric inhibitor of HIV reverse transcriptase
127. Which of the following drugs inhibits post translational modification of viral proteins?
- Indinavir
 - Enfuvirtide
 - Lamivudine
 - Zalcitabine
128. Which of the following binds to viral envelope glycoprotein preventing the conformational changes required for the fusion of viral and cellular membranes?
- Abacavir
 - Indinavir
 - Enfuvirtide
 - Oseltamivir
129. A patient with AIDS and a CD4 cell count of 100/ μ L, has a persistent fever and a weight loss associated with invasive pulmonary disease due to *M avium* complex. Optimal management of this case requires:
- Select an antibiotic regimen based on drug susceptibility of the cultured organism
 - Start treatment with isoniazid and rifampicin
 - Treat the patient with clarithromycin, ethambutol and rifabutin
 - Treat with trimethoprim sulfamethoxazole
130. In an accidental needle stick, an unknown quantity of blood from an AIDS patient is injected into a nurse. The most recent laboratory report on the AIDS patient shows a CD4 count of 20/ μ L and a viral RNA load of greater than 10^7 copies/mL. The most appropriate course of action regarding treatment of the nurse is to:
- Monitor the nurse's blood to determine whether HIV transmission has occurred
 - Treat with full doses of zidovudine for 2 weeks
 - Add acyclovir to the 4-weeks zidovudine regimen
 - Administer zidovudine with lamivudine for 4 weeks
131. Which of the following drugs is most likely to cause additive anemia and neutropenia if administered to an AIDS patient taking zidovudine?
- Acyclovir
 - Amantadine
 - Ganciclovir
 - Stavudine
132. Zidovudine and didanosine used in HAART act by: (UP 2008)
- Inhibitory effects on viral DNA
 - Nucleoside reverse transcriptase inhibition
 - Inhibit the synthesis of gp41
 - Protease inhibition
133. Zidovudine causes: (UP 2005)
- Neurotoxicity
 - Nephrotoxicity
 - Neutropenia
 - Ototoxicity
134. Antiviral drug having dual antiviral activity against HIV and HBV is: (RJ 2008)
- Enfuvirtide
 - Emtricitabine
 - Abacavir
 - Entecavir

- 135. Which of the following statements about lamivudine is FALSE:** (RJ 2008)
- Possess Anti-HIV and anti-HBV activity
 - Dose lower for blocking HIV replication than HBV replication
 - Should not be used as monotherapy in HBV/HIV infected patients
 - Anti-HBe seroconversion occurs in minority of patients
- 136. Which of the following is most common side effect of zidovudine?** (MH 2003)
- Anemia
 - Peripheral neuropathy
 - Lactic acidosis
 - All
- 137. A laboratory technician was accidentally exposed to a HIV serum positive sample, which of the following shall be the role of zidovudine in treatment of this patient?** (MH 2003)
- Protects against acquiring the HIV infection
 - Makes the patient seronegative
 - Delays the progression of disease
 - None
- 138. Prophylactic therapy should be started against Pneumocystis carinii pneumonia in AIDS patients with CD4 counts below:** (Karnataka 2003) (MH 2005)
- < 50/microL
 - < 150/microL
 - < 200/microL
 - < 400/microL
- 139. Which of the following anti-HIV drug should never be given as rechallange once history of producing allergic reaction with drug is known?** (MH 2006)
- Lamivudine
 - Abacavir
 - Zidovudine
 - Nelfinavir
- 140. All are protease inhibitor EXCEPT:** (Bihar 2005)
- Ritonavir
 - Amprenavir
 - Tenofovir
 - Nelfinavir
- 141. Which protease inhibitor has boosting effect?** (Bihar 2005)
- Amprenavir
 - Tenovir
 - Nelfinavir
 - Ritonavir
- 142. Which of the following is a protease inhibitor?** (AP 2004)
- Lamivudine
 - Saquinavir
 - Delavirdine
 - Zidovudine
- 143. Following drugs act against HIV-2 Except:** (MP 2009)
- Ritonavir
 - Tenofovir
 - Efavirenz
 - Zalcitabine
- 144. Enfuvirtide belongs to the class of:** (MP 2009)
- Fusion inhibitors
 - Protease inhibitors
 - Gp 120 inhibitors
 - Nucleotide reverse transcriptase inhibitors
- 145. Drug which produces Steven Johnson's syndrome in HIV infected individuals is:** (MP 2009)
- Paraaminosalicylate
 - Cycloserine
 - Thioacetazone
 - Rifampicin
- 146. In anti retroviral therapy, Zidovudine should not be combined with:** (MP 2009)
- Lamivudine
 - Nevirapine
 - Didanosine
 - Stavudine
- 147. The HIV fusion inhibitor, enfuvirtide, acts at the site of:** (MP 2009)
- Gp 120
 - Gp 41
 - P24
 - CXCR4
- 148. Viral HIV integrase inhibitor is:** (Kolkata 2009)
- Zidovudine
 - Maroviroc
 - Raltegravir
 - Enfuvirtide
- 149. All the following antiretroviral drugs produce dyslipidemia except:** (Karnataka 2006)
- Atazanavir
 - Saquinavir
 - Amprenavir
 - Nelfinavir

ANTI-MALARIAL DRUGS

- 150. All of the following are criteria for high risk of developing chloroquine retinopathy except:** (AIIMS Nov. 2011)
- Duration of use > 5 years
 - Seen at a dose of >250mg/d or >3mg/kg
 - >480g total dose
 - Presence of renal failure
- 151. The development of resistance to conventional treatment has led WHO to recommend the use of combination therapies containing artemisinin derivative (artemisinin-based combination therapies also known as**

- ACTs). All of the following combination therapies are recommended if such resistance is suspected, except:
- Artemether plus lumefantrine (DPG - 2011)
 - Artesunate plus quinine
 - Artesunate plus pyrimethamine-sulfadoxine
 - Artesunate plus mefloquine
- Drug of choice in a patient with severe complicated falciparum malaria is:** (AI 2009)
 - Chloroquine
 - Quinine
 - Artesunate
 - Artemether
 - Chloroquine is used in the treatment of:** (DPG 2009)
 - DLE
 - Pemphigus
 - Psoriasis
 - Nummular eczema
 - Which of the following drugs can be used for the treatment of chloroquine resistant malaria in children?** (AI-2008)
 - Chloroquine
 - Doxycycline
 - Tetracycline
 - Clindamycin
 - Which of the following is best associated with lumefantrine?** (AI 2005)
 - Antimycobacterial
 - Antifungal
 - Antimalarial
 - Antiamoebic
 - Which of the following antimalarial drugs is a slow acting schizonticide?** (AIIMS May, 2004)
 - Artemether
 - Mefloquine
 - Pyrimethamine
 - Quinine
 - Bull's eye lesion in the macula is seen in:** (PGI Dec. 2007)
 - Chloroquine
 - Hydroxychloroquine
 - Quinine
 - Sulfamethoxazole
 - Primaquine
 - If a drug is active against the pre-erythrocytic stage of the malarial parasite it will be useful as a:**
 - Suppressive prophylactic
 - Causal prophylactic
 - Clinical curative
 - Radical curative
 - The fastest acting schizontocidal drug among the following is:**
 - Artemether
 - Mefloquine
 - Chloroquine
 - Proguanil
 - Drug of choice for treatment of malaria due to *P. vivax* in a 25 year old pregnant female is:** (AI 2000)
 - Chloroquine
 - Primaquine
 - Sulfadoxine-pyrimethamine
 - Quinine
 - Choose the drug whose single oral dose affords clinical cure of uncomplicated malaria caused by chloroquine sensitive/resistant *P. falciparum* as well as *P. vivax*:**
 - Quinine
 - Mefloquine
 - Artesunate
 - Proguanil
 - Chloroquine is useful in:** (DPG 1997)
 - Discoid lupus erythematosus
 - Rheumatoid arthritis
 - Infectious mononucleosis
 - All of the above
 - Drug of choice for treatment of chloroquine resistant falciparum malaria is:** (Bihar 2003, MPPG 2003, 2007 DPG 1998)
 - Quinine
 - Chloroquine
 - Pyrimethamine
 - Primaquine
 - Tissue schizonticide which prevents relapse of vivax malaria is:** (MPPG 2001)
 - Quinine
 - Primaquine
 - Pyrimethamine
 - Chloroquine
 - Chloroquine is given in high loading dose because of:** (RJ 2005)
 - High volume of distribution
 - Poor GIT absorption
 - High first pass metabolism
 - All
 - Which of the following can cause hypoglycemia in a patient of severe cerebral malaria on treatment?** (MH 2002)
 - Quinine
 - Chloroquine
 - Halofantrine
 - Mefloquine
 - Radical cure is required for malaria caused by:** (MH 2002)
 - P. falciparum* and *P. vivax*
 - P. falciparum* and *P. malariae*
 - P. vivax* and *P. malariae*
 - P. vivax* and *P. ovale*
 - Which antimalarial drug is known to cause neuropsychiatric adverse reaction?** (MH 2007)
 - Artesunate
 - Artimisnin
 - Quinine
 - Mefloquine

169. Drawback of artesunate is: (MH 2007)
- Poor bioavailability
 - Rapid recrudescence of malaria
 - Hypoglycemia
 - Hemolysis
170. Absorption of which of the following anti-malarial drug increases with food intake? (MH 2008)
- Mefloquine
 - Lumefantrine
 - Chloroquine
 - Amodiaquine
171. Patient is being administered i.v. quinine following which he developed restlessness and sweating, the most likely cause is: (AP 2002)
- Hypoglycaemia
 - Cinchonism
 - Arrhythmias
 - Sweating
172. Which one of the following antimalarial drugs is safe for use in pregnancy? (MP 2008)
- Atovaquone
 - Tetracycline
 - Proguanil
 - Primaquine
173. Chloroquine is given as 600 mg loading dose because: (Kolkata 2005)
- It is rapidly absorbed
 - It is rapidly metabolized
 - It has increased tissue binding
 - It is rapidly eliminated
174. Drug of choice for chloroquine resistant malaria in pregnancy is: (Kolkata 2007)
- Quinine
 - Mefloquine
 - Artemisinin
 - Sulphadoxine+ pyrimethamine
175. Radical cure of Plasmodium vivax is by: (Karnataka 2007, UP 2006)
- Chloroquine
 - Tetracycline
 - Primaquine
 - Artesunate
176. Volume of distribution for chloroquine is: (Karnataka 2001)
- 5–8 L
 - 9–15 L
 - 100–650 L
 - Above 1300 L
177. A patient was being treated with a drug that interferes with the activity of enzyme pyruvate ferredoxin oxidoreductase. Which of the following is the most likely organism causing infection in this patient?
- Beef tapeworm
 - Whipworm
 - Cryptosporidium
 - Trypanosoma
178. All the following are administered under supervision in India except: (AIIMS Nov 2009)
- Dapsone
 - Clofazimine
 - Pyrazinamide
 - Rifampicin
179. All of these are used in the treatment of visceral leishmaniasis except: (AIIMS Nov 2009)
- Sitamaquine
 - Paromomycin
 - Miltefosine
 - Hydroxychloroquine
180. Potassium iodide is useful in the treatment of: (DPG 2009)
- Sporotrichosis
 - Impetigo
 - Viral warts
 - Dermatitis herpetiformis
181. Pyronaridine is: (AIIMS Nov, 2003)
- Antimalarial
 - Anti-HIV
 - Antifungal
 - Antibacterial
182. The drug most likely to be responsible for acute pancreatitis is:
- Didanosine
 - Ketoconazole
 - Saquinavir
 - Zidovudine
183. Which of the following statements about amoebicides is LEAST accurate?
- Diloxanide furoate is a luminal amoebicide
 - Emetine is contra-indicated in pregnancy and in patients with cardiac disease
 - Metronidazole has little activity in the gut lumen
 - Paromomycin is effective in extraintestinal amoebiasis
184. Choose the most effective drug for mild intestinal amoebiasis and asymptomatic cyst passers:
- Metronidazole
 - Emetine
 - Quiniodochlor
 - Diloxanide furoate
185. Prolonged use of the following drug has been implicated in the causation of subacute myelo-optic neuropathy (SMON):
- Diloxanide furoate
 - Quiniodochlor
 - Emetine
 - Furazolidone

ANTI-PROTOZOAL, ANTI-HELMINTHIC AND MISCELLANEOUS DRUGS

186. The drug of choice for Kala azar is:
 (a) Pentamidine
 (b) Amphotericin B
 (c) Sodium stibogluconate
 (d) Ketoconazole
187. What is true of ivermectin?
 (a) It is the most effective drug for strongyloidosis
 (b) It is the drug of choice for onchocerciasis
 (c) It can be used to treat scabies
 (d) All of the above
188. Metronidazole is LEAST likely to be effective in the treatment of:
 (a) Hepatic amoebiasis
 (b) Infection caused by *Bacteroides fragilis*
 (c) Pseudomembranous colitis
 (d) Pneumocystosis
189. Which of the following drugs is LEAST effective luminal amoebicide?
 (a) Metronidazole
 (b) Diloxanide furoate
 (c) Iodoquinol
 (d) Paromomycin
190. This drug can clear trypanosomes from blood and lymph nodes and is active in late CNS stages of African sleeping sickness. It is:
 (a) Emetine
 (b) Melarsoprol
 (c) Nifurtimox
 (d) Suramin
191. An antihelmenthic drug that is effective against blood fluke, liver fluke, lung fluke and cysticercus is:
 (a) Albendazole
 (b) Praziquantal
 (c) Ivermectin
 (d) Thiabendazole
192. Drug of choice for treatment of infestation due to *Onchocerca volvulus* is:
 (a) Albendazole
 (b) Ivermectin
 (c) Praziquantal
 (d) Suramin
193. Which of the following antimalarial agents is most commonly associated with acute hemolytic reaction in patients with glucose-6-phosphate dehydrogenase deficiency?
 (a) Chloroquine
 (b) Clindamycin
 (c) Mefloquine
 (d) Primaquine
194. Sudha, a 20 year old female developed antibiotic associated pseudomembranous colitis caused by *Clostridium difficile*. Which of the following drugs is most likely to be effective in the treatment of this disease?
 (a) Ampicillin
 (b) Clindamycin
 (c) Metronidazole
 (d) Chloramphenicol
195. More than 90% of this drug is excreted in the urine in intact form. Because its urinary solubility is low, patients should be well hydrated to prevent nephrotoxicity. The drug is:
 (a) Indinavir
 (b) Zidovudine
 (c) Acyclovir
 (d) Amantadine
196. A 25 year old male was hospitalized with liver cyst due to *Echinococcus granulosus*. He refused to undergo surgery for removal of cyst. Therefore, albendazole was used at high dose for 3 months. This patient should be monitored for the toxicity to:
 (a) Gonads
 (b) Kidney
 (c) Liver
 (d) Peripheral nerves
197. A 26-year-old male, Vikas presents to OPD complaining of hair loss and itching on scalp. Physical examination reveals moderate patchy hair loss from the central portion of scalp and the lesions have ring like configuration with central clearing. Which of the following drugs can be used to treat this patient's condition?
 (a) Local glucocorticoids
 (b) Progesterone
 (c) Finasteride
 (d) Terbinafine
198. Bull's eye retinopathy is seen in: (DPG 2010)
 (a) Chloroquine
 (b) Methanol
 (c) Ethambutol
 (d) Steroids
199. The drug of choice for schistosomiasis is: (Karnataka 2009)
 (a) Albendazole
 (b) Metronidazole
 (c) Praziquantel
 (d) Triclabendazole
200. Hepatotoxic drugs are all EXCEPT: (DPG 2008)
 (a) Methotrexate
 (b) Isoniazid
 (c) Cycloserine
 (d) Ethionamide
201. Drug of choice for neurocysticercosis is: (DPG 2006) (MPPG 2005)
 (a) Praziquantel
 (b) Albendazole
 (c) Levamisole
 (d) Piperazine

202. Which of the following drug causes flaccid paralysis of ascaris? (DPG 2006)
- Albendazole
 - Pyrantel pamoate
 - Piperazine
 - Ivermectin
203. Which of the following is TRUE about drugs useful in amoebiasis? (DPG 1997)
- Diloxanide furoate is useful in intestinal and extra-intestinal amoebiasis
 - Emetine is well tolerated orally
 - Chloroquine is effective only in hepatic amoebiasis
 - Mepacrine is useful in chronic cyst passers
204. DEC (Di-ethyl-carbamazine) is used for the treatment of: (MPPG 2007) (MPPG 2004)
- Filariasis
 - Dracunculiasis
 - Schistosomiasis
 - Taeniasis
205. Which of the following drug is deposited in the retina? (UP 2007)
- Isoniazid
 - Chloroquine
 - Rifampicin
 - Pyrizinamide
206. Round worm infection is best treated with: (UP 2007)
- Metronidazole
 - Mebendazole
 - Albendazole
 - Pyrantel pamoate
207. Drug of choice for bacterial vaginosis is: (TN 2005)
- Metronidazole
 - Ampicillin
 - Ciprofloxacin
 - Fluconazole
208. Mebendazole cannot be used for: (RJ 2001, RJ 2002)
- Ascariasis
 - Enterobius vermicularis
 - Onchocercosis
 - Hydatid cyst disease
209. Drug of choice for medical treatment of hydatid cyst of liver is: (MH 2002)
- Praziquantel
 - Thiabendazole
 - Ivermectin
 - Albendazole
210. What is the dose of niclosamide used in treatment of Taenia saginata infection in children? (MH 2005)
- 40 mg/kg single dose
 - 40 mg/kg/day for 3 days
 - 40 mg/kg/day for 7 days
 - 40 mg/kg/day for 21 days
211. Drug commonly used in the treatment of echinococcosis is: (MH 2006)
- Albendazole
 - Ivermectin
 - Pyrental prremeated
 - Metronidazole
212. Ivermectin is used for the treatment of: (Bihar 2003)
- Filariasis
 - Ascariasis
 - Teniasis
 - Hookworm infestation
213. Drug amphotericin B is used for treatment of: (Jharkhand 2004)
- Sleeping sickness
 - Kala azar
 - Malaria
 - Filaria
214. Drug that is not used in renal failure is: (Jharkhand 2005)
- Ethambutol
 - Rifampicin
 - Isoniazid
 - Streptomycin
215. The antiretroviral drug which is also effective in chronic active hepatitis-B infection is: (Karnataka 2004)
- Zidovudine
 - Nelfinavir
 - Efavirenz
 - Lamivudine
216. Drug of choice for hookworm infestation is: (Karnataka 2002)
- Piperazine citrate
 - Bephenium hydroxynaphthoate
 - Mebendazole
 - Albendazole
217. Drug of choice for ascariasis is: (Karnataka 2002)
- Piperazine citrate
 - Bephenium hydroxynaphthoate
 - Mebendazole
 - Albendazole
218. Drugs of choice for the treatment of neurocysticercosis are: (Karnataka 2002)
- Hydroquinone and metronidazole
 - Metronidazole and pyrental palmoate
 - Albendazole and praziquantel
 - Cyclophosphamide

RECENT QUESTIONS ASKED BY NATIONAL BOARD

- Oral contraceptive (OCP) failure by rifampicin is due to:**
 - Decreased absorption of OCPs
 - Increased binding of OCPs by rifampicin and reduced free drug concentration
 - Increased metabolism of OCPs
 - Increased chances of ovulation due to rifampicin
- Which of the following is not used as treatment for lymphatic filariasis?**
 - Ivermectin
 - Diethyl carbamezine
 - Praziquantal
 - Albendazole
- Oseltamivir dose is**
 - 75 mg BD x 5 days orally
 - 75 mg BD x 5 days i. v.
 - 200 mg BD x 5 days orally
 - 200 mg BD x 5 days i.v.
- Acyclovir is used in:**
 - Herpes keratitis
 - CMV retinitis
 - Hepatitis C
 - Hepatitis B
- Dapsone is used in:**
 - Dermatitis herpetiformis
 - Pityriasis rosacea
 - Contact dermatitis
 - Oculocutaneous albinism
- Nevirapine is**
 - NNRTI
 - PI
 - NRTI
 - Entry Inhibitor
- Which of the following antimalarial is a slow acting schizonticide ?**
 - Artemether
 - Mefloquine
 - Pyrimethamine
 - Quinine
- Drug causing ichthyosis and hyperpigmentation, when used in leprosy is:**
 - Rifampicin
 - Dapsone
 - Clofazimine
 - Ethionamide
- Along with INH, which vitamin is given ?**
 - Riboflavin
 - Pyridoxine
 - Niacin
 - Cyanocobalamin
- Chemoprophylaxis in an Englishman visiting chloroquine and mefloquine resistant malaria region is done with:**
 - Primaquine
 - Doxycycline
 - Amodiaquine
 - Hydroxychloroquine
- Which of the following has poorest oral bioavailability?**
 - Oseltamivir
 - Zanamivir
 - Rimantidine
 - Amantadine
- Antitubercular drug which reaches inside the caseous material is?**
 - Isoniazid
 - Rifampicin
 - Pyrazinamide
 - Ethambutol
- Drug of choice for acyclovir resistant herpes is:**
 - Cidofovir
 - Gancyclovir
 - Valacyclovir
 - Foscarnet
- Drug of choice for exo-erythrocytic stage of malaria is:**
 - Chloroquine
 - Primaquine
 - Proguanil
 - Mefloquine
- Side effects of isoniazid are all except:**
 - Hepatitis
 - Optic neuritis
 - Peripheral neuropathy
 - Thrombocytopenia
- Which of the following is a bacteriostatic antitubercular drug?**
 - Streptomycin
 - Ethambutol
 - Isoniazid
 - Rifampicin
- All are true about rifampicin except:**
 - Microsomal enzyme inducer
 - Used in treatment of meningococcal meningitis
 - May cause OCP failure
 - Bactericidal in nature
- Rifampicin acts by inhibiting:**
 - DNA Dependent RNA polymerase
 - RNA dependent DNA polymerase
 - Mycolic acid inhibition
 - Mycolic acid incorporation defects
- Cidofovir can be used for:**
 - Respiratory papillomatosis
 - Herpes simplex
 - CMV
 - All of the above

20. **Peripheral neuropathy not caused by which anti-retroviral drug?**
 - (a) Lamivudine
 - (b) Didanosine
 - (c) Zidovudine
 - (d) Zalcitabine
21. **Antifungal used as cancer chemotherapeutic agent is:**
 - (a) Flucytosine
 - (b) Nystatin
 - (c) Voriconazole
 - (d) Terbinafine
22. **Drug not given for malaria prophylaxis is:**
 - (a) Chloroquine
 - (b) Proguanil
 - (c) Doxycycline
 - (d) Artesunate
23. **Which of the following is a reverse transcriptase inhibitor?**
 - (a) Ritonavir
 - (b) Saquinavir
 - (c) Amprenavir
 - (d) Tenofovir
24. **The most effective antitubercular drug against slow multiplying intracellular mycobacteria is:**
 - (a) Rifampicin
 - (b) Isoniazid
 - (c) Pyrazinamide
 - (d) Ethambutol
25. **Metrifonate is effective against:**
 - (a) Amoebiasis
 - (b) Leishmaniasis
 - (c) Schistosomiasis
 - (d) Giardiasis
26. **The drug used to treat acyclovir resistant Herpes Simplex Virus (HSV) and Varicella Zoster Virus (VZV) infection is:**
 - (a) Foscarnet
 - (b) Valacyclovir
 - (c) Abacavir
 - (d) Ganciclovir
27. **Antimalarial agent safe for use in pregnancy is:**
 - (a) Atovaquone
 - (b) Pyrimethamine
 - (c) Primaquine
 - (d) Proguanil
28. **Pancreatitis is a common complication of which one of the following:**
 - (a) Zidovudine
 - (b) Didanosine
 - (c) Zalcitabine
 - (d) Stavudine
29. **Disulfiram like interaction with alcohol is seen with all of the following drugs except:**
 - (a) Metronidazole
 - (b) Cefoperazone
 - (c) Griseofulvin
 - (d) Satranidazole
30. **Which vitamin is most likely to be deficient in patients on treatment with isoniazid:**
 - (a) Vitamin B₁
 - (b) Vitamin B₂
 - (c) Vitamin B₆
 - (d) Vitamin B₁₂
31. **Which one of the following drug may be used for prevention of relapse of P. vivax infection:**
 - (a) Chloroquine
 - (b) Primaquine
 - (c) Atovaquone
 - (d) Tetracycline
32. **All of the following are anti HIV agents except:**
 - (a) Ritonavir
 - (b) Acyclovir
 - (c) Didanosine
 - (d) Zidovudine
33. **MDR tuberculosis is defined by:**
 - (a) Resistance to all first and second line anti-tubercular agents
 - (b) Resistance to any three first line anti-tubercular agents
 - (c) Resistance to all first line and any three classes of second line anti-tubercular agents
 - (d) Resistance to isoniazid and rifampicin
34. **The infective form of malarial parasite is:**
 - (a) Trophozoites
 - (b) Sporozoites
 - (c) Hypnozoites
 - (d) Merozoites
35. **Isoniazid induced peripheral neuropathy responds to administrations of:**
 - (a) Pyridoxine
 - (b) Riboflavin
 - (c) Thiamine
 - (d) Cobalamin
36. **Which of the following anti-tubercular agent does not cause hepato-toxicity?**
 - (a) Isoniazid
 - (b) Rifampicin
 - (c) Ethambutol
 - (d) Pyrazinamide
37. **All of the following can cause visual adverse effects except:**
 - (a) Ethambutol
 - (b) Rifampicin
 - (c) Chloroquine
 - (d) Digoxin
38. **Scabies can be effectively treated systemically by:**
 - (a) Psoralens
 - (b) Ivermectin

- (c) Permethrin
(d) Contrimoxazole
39. **Drug resistance in *Mycobacterium tuberculosis* is due to:**
(a) Conjugation
(b) Transduction
(c) Mutation
(d) None of the above
40. **The treatment of choice for bacterial vaginosis is:**
(a) Clindamycin
(b) Erythromycin
(c) Ampicillin
(d) Metronidazole
41. **The antifungal which has a bactericidal mode of action against dermatophyte infections in therapeutic doses is:**
(a) Fluconazole
(b) Terbinafine
(c) Itraconazole
(d) Ketoconazole
42. **Which one of the following is not an antiretroviral drug:**
(a) Saquinavir
(b) Ganciclovir
(c) Indinavir
(d) Atazanavir
43. **The drug(s) currently recommended by National AIDS Control Organization for prevention of mother to child transmission of HIV infection are:**
(a) Zidovudine to mother during pregnancy and labour and to baby after delivery
(b) Zidovudine and nevirapine to mother during pregnancy and labour and to baby after delivery
(c) Nevirapine to mother during pregnancy and labour and to baby after delivery
(d) Zidovudine and lamivudine to mother during pregnancy and labour and to baby after delivery
44. **Drug of choice in herpes simplex encephalitis is:**
(a) Acyclovir
(b) Vidarabine
(c) Interferon
(d) Amantadine
45. **The other name for reverse transcriptase is:**
(a) DNA dependent DNA polymerase
(b) RNA dependent RNA polymerase
(c) DNA dependent RNA polymerase
(d) RNA dependent DNA polymerase
46. **First line drug for falciparum malaria in pregnancy is:**
(a) Chloroquine
(b) Quinine
(c) Primaquine
(d) Tetracycline
47. **Which one of the anti-tubercular drug may precipitate gout:**
(a) Pyrazinamide
(b) Rifampicin
(c) Streptomycin
(d) Isoniazid
48. **Which one of the following therapies would be safe in a patient with pulmonary tuberculosis having markedly abnormal liver function:**
(a) Streptomycin + isoniazid
(b) Ethambutol + isoniazid
(c) Rifampicin + isoniazid
(d) Streptomycin + ethambutol
49. **The minimum period required for post-exposure chemoprophylaxis for HIV is:**
(a) 4 weeks
(b) 6 weeks
(c) 8 weeks
(d) 12 weeks
50. **Drug of choice for kala-azar is:**
(a) Sodium stibogluconate
(b) Amphotericin B
(c) Pentamidine
(d) None of the above
51. **Antitubercular drug which should not be given to a patient having both tuberculosis as well as AIDS is:**
(a) INH
(b) Pyrazinamide
(c) Ethambutol
(d) Thiacetazone
52. **Which antitubercular drug is bacteriostatic?**
(a) INH
(b) Pyrazinamide
(c) Rifampicin
(d) Ethambutol
53. **Which antimalarial drug is implicated in causing hypoglycemia?**
(a) Chloroquine
(b) Pyrimethamine
(c) Quinine
(d) Primaquine
54. **Metronidazole is effective in all of the following conditions except:**
(a) Pseudomembranous colitis
(b) Neurocysticercosis
(c) Giardiasis
(d) Amebic liver abscess
55. **Which of the following drugs is not used in the treatment of leprosy?**
(a) Rifampicin
(b) Dapsone
(c) Kanamycin
(d) Clofazimine
56. **Fastest acting drug on the lepra bacilli is:**
(a) Rifampicin
(b) Dapsone

- (c) Kanamycin
- (d) Clofazimine

57. Dapsone is used in the treatment of:

- (a) Malaria
- (b) Dermatitis herpetiformis
- (c) TB
- (d) Kala-azar

58. Which of the following is the major side effect of rifampicin?

- (a) Renal failure
- (b) Hepatotoxicity
- (c) Bone marrow suppression
- (d) Blood dyscrasias

59. Which of the following anti TB drugs can be safely given in a patient with renal failure?

- (a) INH
- (b) Rifampicin
- (c) Streptomycin
- (d) Kanamycin

60. Drug of choice for the treatment of a pregnant woman with P vivax malaria is:

- (a) Quinine
- (b) Chloroquine
- (c) Artemether
- (d) Paracetamol

61. Antifungal drug used for systemic fungal infection is:

- (a) Griseofulvin
- (b) Clotrimazole
- (c) Amphotericin B
- (d) Econazole

62. ATT safe in hepatic failure are:

- (a) Pyrazinamide and ethambutol
- (b) INH and Rifampicin
- (c) Streptomycin and Ethambutol
- (d) Rifampicin and Streptomycin

63. Drug that can cause hyperuricemia is:

- (a) Pyrazinamide
- (b) INH
- (c) Rifampicin
- (d) None of the above

64. Optic neuritis is caused by:

- (a) Ethambutol
- (b) INH
- (c) Rifampicin
- (d) Chloramphenicol

65. The following anti T.B. drug should not be given to AIDS patient:

- (a) Rifampicin
- (b) Ethambutol

- (c) Streptomycin
- (d) Pyrazinamide

66. Which of the following drugs results in the production of orange coloured urine?

- (a) Rifampicin
- (b) Isoniazid
- (c) Pyrazinamide
- (d) Ethambutol

67. Albendazole is effective against all of the following except:

- (a) Roundworm
- (b) Hookworm
- (c) Tapeworm
- (d) Pinworm

68. Acyclovir is used for the following viral infection:

- (a) Rabies virus
- (b) Cytomegalovirus
- (c) Herpes simplex virus
- (d) Human immunodeficiency virus

69. Least hepatotoxic anti TB drug is:

- (a) Ethambutol
- (b) Rifampicin
- (c) Pyrazinamide
- (d) Isoniazid

70. Acyclovir is given in:

- (a) Enteric fever
- (b) Malaria
- (c) Herpes infection
- (d) Bacillary dysentery

71. All of the following drugs can be used for intestinal amoebiasis except:

- (a) Metronidazole
- (b) Chloroquine
- (c) Diloxanide furoate
- (d) Tinidazole

72. Drug of choice for herpes simplex keratitis is:

- (a) Acyclovir
- (b) Ganciclovir
- (c) Amantadine
- (d) Interferon

73. Drug not used in chloroquine resistant malaria is:

- (a) Sulfadoxine-pyrimethamine
- (b) Fluoroquinolones
- (c) Quinine
- (d) Artemisinins

74. Dosage of albendazole in ascariasis is:

- (a) 400 mg once
- (b) 400 mg bd for one day
- (c) 400 mg tds for one day
- (d) 400 mg bd for 5 days

EXPLANATIONS

1. Ans. (c) Rifampicin (Ref: Katzung 11/e p826)

Rifampicin is secreted in bile, so it does not require dose adjustment in renal failure

2. Ans. (a) Amikacin (Ref: KDT 6/e p744)

Amikacin is an aminoglycoside that is most resistant to inactivating enzymes. It is used as a second line antitubercular drug and can be used in MDR tuberculosis management.

3. Ans. (b) Peripheral neuropathy (Ref: KK Sharma 2/e p754)

Acetylase status of a person determines the response of drugs metabolized by acetylation (e.g. isoniazid, sulfonamides, procainamide and hydralazine). Isoniazid is metabolized to acetyl-isoniazid and then to acetyl hydrazine. Accumulation of isoniazid is responsible for peripheral neuropathy whereas acetylhydrazine accumulation may cause hepatotoxicity. Thus, slow acetylators will not be able to metabolize the drug quickly and there can be accumulation of parent drug (isoniazid in this case), leading to peripheral neuropathy. On the other hand, fast acetylators are more prone to develop hepatotoxicity.

4. Ans: (a) Pyridoxine (Ref: Katzung 11/e p825)

Isoniazid can cause peripheral neuropathy due to deficiency of pyridoxine.

5. Ans (b) Rifabutin (Ref: Goodman and Gilman 12/e p1553)

6. Ans. (a) Hemolytic anemia (Ref: Goodman and Gilman 12/e p1564)

Hemolysis develops in almost every individual treated with 200-300 mg dapsone per day. Doses of less than 100 mg in healthy persons and less than 50 mg per day in persons with G-6PD deficiency do not cause hemolysis. Methemoglobinemia is also very common.

7. Ans. (b) Ethionamide (Ref: Goodman Gilman 11/e p1205; Katzung 10/e p772)

- The most common cause of resistance to isoniazid is mutation of the **KatG** gene.
- Kat G gene codes for **catalase-peroxidase** that **activates** the isoniazid (isoniazid is a prodrug).
- So mutations of the Kat G gene results in an inactive catalase peroxidase which cause high level of isoniazid resistance because the prodrug cannot be activated by the catalase peroxidase.
- Another mechanism of resistance to isoniazid is related to mutation in the mycobacterial **Inh A** and **Kas A** genes.
- *The unique feature of mutation in InhA gene is that it also leads to cross resistance to ethionamide.*

8. Ans. (a) Retrobulbar neuritis (Ref: Katzung 10/e p774; KDT 6/e p742)

Ethambutol causes retrobulbar neuritis and can result in red green colour blindness.

9. Ans. (d) Ethambutol (Ref: Katzung 10/e p774; KDT 6/e p742-743)

Isoniazid, rifampicin and pyrazinamide can cause hepatotoxicity whereas ethambutol and streptomycin do not cause hepatotoxicity.

10. Ans. (c) Streptomycin (Ref: KDT 6/e p748)

Streptomycin is absolutely contra-indicated in pregnant female.

11. Ans. (a) Tobramycin (Ref: KDT 6/e p748)

- Aminoglycosides effective in MDR tuberculosis are amikacin, kanamycin and capreomycin. Tobramycin is not effective against mycobacterium.
- Ciprofloxacin and clarithromycin are also useful for tuberculosis.

12. Ans. (b) Isoniazid (Ref: Goodman and Gilman 10/e p1277)

- The most important side effects of isoniazid include rash (2%), fever (1.2%), jaundice (0.6%) and peripheral neuritis (0.2%).
- Mental abnormalities with INH include euphoria, transient impairment of memory, separation of ideas and reality, loss of self control and florid psychosis.
- Ethionamide causes mental depression, drowsiness and asthenia.

13. **Ans. (a) Flu like syndrome is usually seen with rifampicin being taken on daily basis**
- Flu like syndrome is seen more commonly when rifampicin is administered on alternate days.
 - Only first line antitubercular drug that do not require dose adjustment in renal failure is rifampicin.
 - Pyrazinamide and ethambutol can cause hyperuricemia.
 - Ethambutol causes red green colour blindness as early appearing adverse effect.
14. **Ans. (c) Rifampicin (Ref: KDT 6/e p753)**
- Best and the fastest acting drug for leprosy is rifampicin.
 - Clofazimine and dapsone are bacteriostatic agents.
15. **Ans. (d) Rifampicin (Ref: KDT 6/e p741)**
- Rifampicin is a powerful enzyme inducer. It increases the metabolism of protease inhibitors and thus decreases the efficacy of anti-retroviral therapy.
 - Another drug, rifabutin is devoid of these interactions and is the preferred agent for treatment of mycobacterial infections in patients on anti-retroviral therapy.
16. **Ans. (a) Pyrazinamide; (d) Rifampicin; (e) Isoniazid (Ref: KDT 6/e p740-743)**
17. **Ans. (b) Infectious mononucleosis like syndrome; (c) Agranulocytosis; (e) Skin pigmentation (Ref: KDT 6/e p752)**
- Dapsone administration can result in hemolytic anaemia and methemoglobinemia.
 - Other side effects are: agranulocytosis, hepatitis, peripheral neuropathy, gastrointestinal intolerance, headache, pruritus, nephrotic syndrome, fever, rash and psychosis.
 - Cutaneous reaction include: Allergic rashes, fixed drugs eruption, hypermelanosis, phototoxicity and exfoliative dermatitis.
 - **In borderline and lepromatous leprosy, dapsone may result in erythema nodosum leprosum.**
 - A rare syndrome known as **DDS - syndrome or infectious mononucleosis like syndrome or sulfone syndrome** may also be seen.
 - G-6-PD deficiency is not a side effect of dapsone, it is an X-linked recessive disorder.
18. **Ans. (c) Delay or prevent the emergence of resistance (Ref: KDT 6/e p745)**
19. **Ans. (c) Clofazimine should not be given to patients who are intolerant to dapsone or who fail to improve during treatment with dapsone (Ref: KDT 6/e p752, 753)**
- Acedapsone is a repository form of dapsone. Single i.m. injection of acedapsone keep on releasing the drug for 3 months.
 - Rifampicin is used once in a month (supervised dose) for the treatment of leprosy. It prevents the emergence of resistance to dapsone.
 - Clofazimine can result in skin pigmentation, discolouration of secretions and dryness of skin (ichthyosis).
 - Clofazimine has no cross-allergenicity with dapsone.
20. **Ans. (a) One should discontinue treatment if hyperuricemia occurs (Ref: Katzung 10/e p775)**
- Pyrazinamide is a first line antitubercular drug that can cause hyperuricemia and hepatotoxicity.
 - Non gouty arthralgia is very common adverse effect of this drug. Hyperuricemia per se is not the indication for discontinuation of pyrazinamide.
21. **Ans. (a) Respiratory syndrome (Ref: KDT 6/e p741)**
22. **Ans. (c) Intestinal (Ref: KDT 6/e p749)**
Corticosteroids are absolutely contra-indicated in intestinal TB due to risk of perforation.
23. **Ans. (a) Azithromycin (Ref: KDT 6/e p730, 731)**
The regimen used for the treatment of *Mycobacterium avium* complex in AIDS patients is REC (Rifabutin, ethambutol and clarithromycin). These drugs are given once daily. Clarithromycin can be replaced with azithromycin which is long acting and can be administered once a week.
24. **Ans. (b) Rifampicin (Ref: Goodman & Gilman 11/e p1205, 1208, 1211; KDT 6/e p741)**
- Ethambutol is bacteriostatic drug.
 - INH and rifampicin are equally effective against intra as well as extracellular mycobacteria. INH require a concentration of 0.025 µg/ml whereas rifampicin inhibits the growth of bacteria at a concentration of 0.005 µg/ml.
 - Pyrazinamide acts more in acidic pH and it requires a concentration of 12.5 µg/ml.
 - Thus, most active drug for extra-cellular bacteria is rifampicin.

25. **Ans. (b) Ethionamide** (Ref: KDT 6/e p743)
PAS and ethionamide can lead to hypothyroidism
26. **Ans. (a) Rifampicin** (Ref: Goodman & Gilman 11/e p1209; KDT 6/e p742)
27. **Ans. (d) Streptomycin** (Ref: KDT 6/e p743)
Streptomycin and ethambutol are not hepatotoxic. Read carefully, option (c) is ethionamide not ethambutol.
28. **Ans. (d) All of the above** (Ref: KDT 6/e p750)
- Most atypical Mycobacteria are resistant to the usual antitubercular drugs, though pulmonary disease caused by *M. avium* complex or *M. kansasii* may respond to prolonged treatment with Rifampicin, Isoniazid and Ethambutol.
- Drugs that are used are:
 - **Rifabutin**
 - Clofazimine
 - **Quinolones e.g. ciprofloxacin**
 - Newer macrolides like clarithromycin and azithromycin.
29. **Ans. (c) INH** (Ref: KDT 6/e p741)
- Peripheral neuritis and a variety of neurological manifestations (paraesthesias, numbness, mental disturbances, rarely convulsions) are the most important dose dependent toxic effects of INH.
 - These are due to interference with utilization of pyridoxine and its increased excretion in urine.
30. **Ans. (c) Pyrazinamide** (Ref: KDT 6/e p742)
- Arthralgia is caused by pyrazinamide, which may be non-gouty or due to hyperuricemia secondary to inhibition of uric acid secretion in the kidney.
 - Ethambutol also produces hyperuricemia due to interference with urate excretion.
31. **Ans. (d) Rifampicin** (Ref: KDT 6/e p742)
Streptomycin and capreomycin are nephrotoxic whereas ethambutol accumulates in renal failure and thus should be avoided in presence of severe renal failure.
32. **Ans. (b) Ethambutol** (Ref: KDT 6/e p742)
33. **Ans. (b) Clarithromycin** (Ref: KDT 6/e p750)
- Treatment of MAC infection is REC (Rifabutin + Ethambutol + Clarithromycin)
 - Clarithromycin alone can be used for the prophylaxis of MAC infections in HIV positive patients.
 - Azithromycin can also be used in place of clarithromycin.
34. **Ans. (b) Cycloserine** (Ref: KDT 6/e p744)
35. **Ans. (c) B₆** (Ref: KDT 6/e p741)
Pyridoxine (vitamin B₆) is administered for the prevention as well as treatment of isoniazid induced peripheral neuropathy.
36. **Ans. (a) Streptomycin** (Ref: KDT 6/e p743)
Streptomycin and ethambutol do not cross blood brain barrier whereas INH and pyrazinamide have maximum CNS penetration.
37. **Ans. (a) Streptomycin** (Ref: KDT 6/e p742, 743)
Ethambutol and streptomycin are first line anti-tubercular drugs that are NOT hepatotoxic.
38. **Ans. (d) Coronary artery disease** (Ref: KDT 6/e p740-741)
INH causes hepatitis, peripheral neuritis and neurological manifestations (paresthesias, numbness, mental disturbance rarely convulsion). Its toxic metabolite accumulates in the presence of renal failure.
So we are left with last option; coronary artery disease, which is our answer of exclusion.
39. **Ans. (b) Streptomycin + Ethambutol** (Ref: KDT 6/e p742-743)
40. **Ans. (b) INH** (Ref: Katzung 11/e p825)
41. **Ans. (b) Optic neuritis** (Ref: Katzung 11/e p827)
42. **Ans. (a) Dapsone** (Ref: Katzung 11/e p831)
43. **Ans. (d) Mutation** (Ref: Katzung 11/e p824,826,827)

- Resistance to INH occurs due to point mutation in *inhA* or *katG* genes.
- Resistance to rifampicin occurs due to point mutation in *rpoB* genes.
- Resistance to ethambutol is due to mutations resulting in overexpression of *embB* gene.

44. Ans. (a) To prevent peripheral neuritis (Ref: KDT 6/e p741)
45. Ans. (d) Ethambutol (Ref: KDT 6/e p742)
46. Ans. (d) Tuberculosis (Ref: KDT 6/e p752)
47. Ans. (b) Clofazimine (Ref: KDT 6/e p752)
Anti-inflammatory drugs are used in lepra reaction. Steroids, clofazimine and thalidomide can be used.
48. Ans. (c) Pyrazinamide (Ref: KDT 6/e p742)
49. Ans. (c) Rifampicin + Dapsone + Clofazamine (Ref: KDT 6/e p755)
50. Ans. (a) Ocular toxicity (Ref: KDT 6/e p742)
51. Ans. (a) Thalidomide (Ref: KDT 6/e p756)
Steroids are drug of choice for both type 1 as well as type 2 lepra reaction. Thalidomide is used in steroid resistant type 2 lepra reaction.
52. Ans. (b) DNA dependent RNA polymerase inhibition (Ref: KDT 6/e p741)
53. Ans. (d) All (Ref: KDT 6/e p748)
All first line antitubercular drugs can cross placenta. Streptomycin is contraindicated in pregnancy whereas other drugs are found to be safe.
54. Ans. (d) Pyrazinamide (Ref: KDT 6/e p750)
55. Ans. (b) Eflornithine (Ref: KDT 6/e p750)
Eflornithine is used for the treatment of some cases of trypanosomiasis. It is also used topically in women to delay regrowth of facial hair following depilation.
56. Ans. (d) Retrobulbar neuritis (Ref: KDT 6/e p742)
57. Ans. (d) All of the above (Ref: Harrison 17th ed/Table e35.4; American academy of family physicians, <http://www.aafp.org/aafp/980215ap/romero.html>)

MANAGEMENT OF ISONIAZID TOXICITY

- Five gram of IV pyridoxine given over 5 to 10 minutes is sufficient to counteract the neurotoxic effects of isoniazid in most cases.
- Diazepam, 5 to 10 mg administered intravenously, is the initial approach to seizure control, with the dose repeated as necessary.
- The acidosis associated with isoniazid toxicity appears to be lactic acidosis secondary to the seizure activity. Therefore, as the seizures are controlled, the acidosis usually decreases in severity. Since sodium bicarbonate may assist in correcting severe cases of acidosis, its administration should be considered if the pH is less than 7.1.

58. Ans. (d) All of above (Ref: Katzung 11/e p831)
59. Ans. (c) Penicillin (Ref: K.D. Tripathi 6/e p751)
60. Ans. (a) Amphotericin B (Ref: Harrison 18th/1663)
The diagnosis is **rhinocerebral mucormycosis**.
 - Mucormycosis typically occurs in patients with diabetes mellitus, solid organ or hematopoietic stem cell transplantation (HSCT), prolonged neutropenia, or malignancy
 - Amphotericin B deoxycholate remains the only licensed antifungal agent for the treatment of mucormycosis. However, lipid formulations of AMB are significantly less nephrotoxic, can be administered at higher doses, and may be more efficacious than AMB deoxycholate for this purpose.
61. Ans. (c) Potassium (Ref: Katzung 11/e p838)
Renal tubular acidosis and renal wasting of K^+ and Mg^{2+} also may be seen during and for several weeks after therapy. Supplemental K^+ is required in one-third of patients on prolonged therapy

62. Ans. (a) Incorporating it in liposomal complex (Ref: Katzung 11/e p838)

'Liposomal amphotericin B has less nephrotoxicity than conventional preparations':

- AMB bound to lipid vehicles (as in liposomal form) has more affinity for fungal ergosterol and less affinity for human cholesterol. This preferential binding decreases nephrotoxicity without sacrificing efficacy of AMB.
- Saline loading but not dextrose can reduce the reversible pre-renal azotemia
- 5-Flucytosine is added to AMB for synergistic action (not to reduce nephrotoxicity)
- Azoles and AMB have antagonistic interaction.

63. Ans. (b) Mucormycosis (Ref: Harrison 17th/1243, 1262)

- 'Voriconazole is drug of choice for treatment of Aspergillosis. It can also be used for Candida species (including glabrata and krusei), Scedosporium and Fusarium.
- Mucormycosis is treated by amphotericin B. Posaconazole can also be used whereas other azoles are not effective against this fungus.

64. Ans. (a) Ketoconazole (Ref: K.D.T. 6/e p762, 760)

- "Ketoconazole is the first orally effective broad-spectrum antifungal drug useful in both dermatophytosis and deep mycosis".
- "Griseofulvin is active against most dermatophytes but not against candida and other fungi causing-deep mycoses".
- "Nystatin is ineffective in dermatophytosis. Because of higher systemic toxicity it is used only in superficial candidiasis".
- "Tolnaftate is a topical antifungal agent used only for dermatophytosis".

65. Ans. (a) Lesser nephrotoxicity (Ref: Katzung 10th/782; KDT 6/e p759)

Liposomal amphotericin B has lesser adverse effects particularly nephrotoxicity as compared to conventional preparations. This is due to lesser uptake in the tissues like kidney. These are more costlier than conventional preparations of amphotericin B and do not possess other advantages.

66. Ans. (d) Clofazimine (Ref: Goodman & Gilman 11/e p1239-1240; KDT 6/e p752)

Clofazimine is an anti-leprosy drug. Other drugs given in the options are anti-fungal drugs.

67. Ans. (a) Hypokalemia (Ref: KDT 6/e p759)

Amphotericin B can cause three major adverse effects:

- Nephrotoxicity (Renal tubular acidosis with hypokalemia)
- Infusion related reactions
- Anemia

68. Ans. (a) Ketoconazole (Ref: KDT 6/e p761)

- Azoles (e.g. ketoconazole, fluconazole, itraconazole, voriconazole, clotrimazole etc.) act by inhibiting an enzyme, lanosterol-14- α -demethylase. This enzyme is involved in the formation of ergosterol.
- Amphotericin B acts by binding to ergosterol and forming pores in fungal cell membrane.

69. Ans. (d) Amphotericin B (Ref: Harrison 18th/1650, CMDT 2014/1484)

Amphotericin B + 5-flucytosine combination is the treatment of choice for cryptococcal meningitis.

Cryptococcal infection	Drug of Choice
Meningitis	AMB + Flucytosine
Pulmonary	Fluconazole
Extrapulmonary without CNS involvement	Fluconazole

70. Ans. (d) It inhibits demethylation of lanosterol (Ref: KDT 6/e p761)

- Azoles act by inhibiting the enzyme lanosterol-14- α -demethylase resulting in reduced ergosterol synthesis.
- It has very good CNS penetration and oral bioavailability.
- It is not very effective against aspergillosis (voriconazole is the drug of choice).

71. Ans. (d) Any of the above (Ref: KDT 6/e p783)

To prevent the acute reaction due to amphotericin B, patient should be premedicated with

- H_1 antihistaminics like diphenhydramine
- NSAIDs like ibuprofen
- Steroids like prednisone

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72. **Ans. (d) It is only used topically** (Ref: KDT 6/e p765)

- Terbinafine is a CIDAL drug against dermatophytes.
- It can be administered orally or can be applied topically.
- It acts by inhibiting the enzyme squalene epoxidase resulting in accumulation of toxic squalene.

73. **Ans. (d) It is unlikely to produce anti-androgenic side effects** (Ref: KDT 6/e p762)

Ketoconazole is rarely used now a days because of several limitations. Important among them are:

- Poor oral bioavailability
- Limited CNS penetration
- Powerful inhibition of microsomal enzymes
- Anti-androgenic adverse effects like gynaecomastia

Fluconazole is preferred agent because it has

- Very good oral absorption
- Maximum CNS penetration (therefore effective in cryptococcal meningitis).
- No inhibitory action on microsomal enzymes
- No anti-androgenic property.

74. **Ans. (b) Cryptococcal meningitis** (Ref: KDT 6/e p763, 764)

Fluconazole has maximum CNS penetration whereas itraconazole has limited entry in the brain. Therefore fluconazole is preferred over itraconazole for the treatment of cryptococcal meningitis. For all other conditions listed in the question, itraconazole is first choice drug.

75. **Ans. (d) Cytomegalovirus retinitis in AIDS patients** (Ref: KDT 6/e p769, 770)

- Ganciclovir is the drug of choice for CMV infections.
- Acyclovir is highly effective against *Herpes simplex* and *Varicella zoster* (chicken pox and herpes zoster) but it has very little activity against CMV.

76. **Ans. (b) Phosphorylates acyclovir** (Ref: KDT 6/e p768)

Nucleoside/tide analogues (like acyclovir) act by converting to NTPs. First phosphorylation step occurs inside the virus and resistance occurs if there is mutation in this gene.

77. **Ans. (d) Terbinafine** (Ref: KDT 6/e p765)

Fungicidal drugs are amphotericin B and terbinafine. Out of these, amphotericin B cannot be given orally. Thus, the answer is terbinafine.

78. **Ans. (b) Renal tubular acidosis** (Ref: KDT 6/e p759)

Amphotericin B can cause:

- Dose limiting nephrotoxicity (RTA)
- Infusion related reactions (not dose related)
- Hypokalemia
- Hypomagnesemia

79. **Ans. (c) Amphotericin B** (Ref: KDT 6/e p757, 758)

Amphotericin B does not inhibit ergosterol synthesis, instead it binds with ergosterol to form pores in the fungal cell membrane.

80. **Ans. (c) They may decrease the nephrotoxicity of amphotericin B** (Ref: KDT 6/e p758)

Newer liposomal preparations of amphotericin B have the following features:

- Less chances of nephrotoxicity and infusion related reactions
- Lesser uptake in the tissues like kidney
- More expensive
- Similar in efficacy and antifungal spectrum as conventional preparations

81. **Ans. (c) Tinea versicolor** (Ref: CMDT-2010/110)

- Griseofulvin is used for dermatophytoses including Tinea capitis, Tinea cruris, Tinea pedis, Tinea unguum and Tinea corporis etc.
- Tinea versicolor is caused by a yeast *Malassezia furfur*. It is treated by selenium sulfide and ketoconazole shampoo.

82. **Ans. (d) Oseltamivir** (Ref: KDT 6th /777, 778)

Oseltamivir and zanamavir are used for avian influenza (bird flu).

83. **Ans. (a) Streptomyces nodosus** (Ref: KDT 6/e p757)

Organism	Antibiotic obtained
<i>S. pimprina</i>	Hamycin
<i>S. venezuelae</i>	Chloramphenicol
<i>S. erythrae</i>	Erythromycin
<i>S. griseus</i>	Aminoglycosides
<i>S. mediterranei</i>	Rifampicin
<i>S. nodosus</i>	Amphotericin B

84. Ans. (c) **Ciclopirox olamine is effective in systemic mycoses** (Ref: KDT 6/e p766)
- Amphotericin B is the drug of choice for most serious systemic infections but it has to be administered parenterally.
 - Griseofulvin is the drug that is used for the treatment of dermatophytosis by oral route.
 - Fluconazole can be used orally as well as parenterally.
 - Ciclopirox olamine is used only topically for mild fungal infections.
85. Ans. (b) **Clotrimazole** (Ref: KDT 6/e p762)
86. Ans. (c) **Ketoconazole** (Ref: KDT 6/e p761)
87. Ans. (b) **5-Flucytosine (5 FC)** (Ref: Katzung 11/e p838)
88. Ans. (a) **Acyclovir** (Ref: KDT 6/e p768)
89. Ans. (d) **Griseofulvin** (Ref: KDT 6/e p761)
90. Ans. (a) **Lamivudine** (Ref: KDT 6/e p712, Katzung 11/e p870)
Now, the drug of choice for hepatitis B is entecavir.
91. Ans. (d) **Griseofulvin** (Ref: KDT 6/e p760-761)
92. Ans. (d) **Griseofulvin** (Ref: KDT 6/e p760)
93. Ans. (d) **Clotrimazole** (Ref: KDT 6/e p762)
94. Ans. (c) **Entecavir** (Ref: KDT 6/e p778)
95. Ans. (d) **Inhibition of ergosterol synthesis** (Ref: KDT 6/e p765)
96. Ans. (d) **Amphotericin B** (Ref: KDT 6/e p758)
97. Ans. (b) **Fluconazole** (Ref: CMDT 2014/1482)
98. Ans. (b) **Herpes simplex** (Ref: KDT 6/e p768)
99. Ans. (a) **Adrenal insufficiency** (Ref: Katzung 11/e p839, KK Sharma 2/e p768)
100. Ans. (a) **IV amphotericin B** (Ref: KDT 6/757-765)
101. Ans. (c) **Used in anti retroviral therapy** (Ref: KDT 6/e p778)
Adefovir is approved, at lower and less toxic doses, only for treatment of HBV infection.
102. Ans. (b) **Acyclovir** (Ref: KDT 6/e p768)
103. Ans. (c) **Optic neuritis** (Ref: Goodman and Gilman 12/e p1659)
HAART therapy is highly active anti-retroviral therapy for treatment of HIV infection and AIDS.
- All NRTIs commonly cause lactic acidosis, hepatomegaly and steatosis.
 - All protease inhibitors are associated with lipodystrophy syndrome characterized by hypercholesterolemia, weight gain, insulin resistance and hyperglycemia.
- Thus, steatosis, lipodystrophy and hypercholesterolemia can be observed commonly in patients taking HAART whereas optic neuritis is not a common adverse effect of antiretroviral drugs.
104. Ans. (a) **Ritonavir** (Ref: KK Sharma 2/e p793)
Ritonavir is a protease inhibitor and can cause hypertriglyceridemia and hypercholesterolemia.
- All protease inhibitors are metabolized by liver and all can cause metabolic abnormalities including hypercholesterolemia, diabetes mellitus, hyperlipidemia, insulin resistance and altered fat distribution (lipodystrophy).
 - Atazanavir is devoid of this adverse effect.
 - Tesamorelin is a synthetic analogue of growth hormone releasing factor indicated to reduce excess abdominal fat in HIV-infected patients with lipodystrophy.

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105. **Ans. (b) As reverse transcriptase inhibitor** (Ref: *Katzung 11/e p861-862*)
106. **Ans. (c) Nevirapine** (Ref: *Katzung 11/e p862*)
Nevirapine and zidovudine are used to prevent vertical transmission of HIV from pregnant females to the baby.
107. **Ans. (a) Raltegravir** (Ref: *Katzung, 11/e p866*)
RalTEGRAvir is an inTEGRAse inhibitor used in HIV.
108. **Ans. (a) Saquinavir** (Ref: *Katzung 11/e p58, 863*)
All the drugs given in the options are microsomal enzyme inhibitors. Among protease inhibitors, ritonavir is the strongest inhibitor of CYP3A4 enzymes whereas saquinavir is the weakest.
109. **Ans. (d) Abacavir** (Ref: *KDT 6/e p772-773*)
All drugs ending with navir are protease inhibitors. Abacavir is an NRTI.
110. **Ans. (a) Didanosine** (Ref: *Katzung 11/e p858*)
- All NRTIs can cause pancreatitis and peripheral neuropathy.
 - Maximum risk of pancreatitis is associated with didanosine and maximum incidence of peripheral neuropathy is seen with stavudine.
 - Lamivudine is safest NRTI as it has minimum risk of pancreatitis and peripheral neuropathy.
111. **Ans. (b) CYP3A4 inhibition by ritonavir** (Ref: *Katzung 10/e p810; KDT 6/e p773*)
Ritonavir is a microsomal enzyme inhibitor particularly of CYP3A4. It decreases the metabolism of other drugs and thus lower dose of lopinavir can be used in treatment of HIV when combined with ritonavir.
112. **Ans. (a) Non-nucleoside reverse transcriptase inhibitor (NNRTI)** (Ref: *KDT 6/e p772*)
113. **Ans. (c) Stavudine** (Ref: *WHO recommendations to treat adult and adolescent HIV/76*)
Stavudine has maximum incidence of peripheral neuropathy whereas didanosine is associated with maximum risk of acute pancreatitis.
114. **Ans. (c) Abacavir** (Ref: *KDT 6/e p767*)
- All protease inhibitors end with 'NAVIR' like nelfinavir, saquinavir and ritonavir.
 - Abacavir is an NRTI.
115. **Ans. (a) Lamivudine** (Ref: *KDT 6/e p771, 772*)
Emtricitabine and lamivudine are safest NRTIs. These are not associated with peripheral neuropathy or pancreatitis.
116. **Ans (d) Saquinavir causes maximum induction of CYP3A4** (Ref: *Katzung 10/e p808*)
- All protease inhibitors are substrates of hepatic CYP 3A4 and thus undergo extensive oxidative metabolism in liver.
 - Several of these agents are also the inhibitor of CYP 3A4 and thus lead to drug interactions.
 - Saquinavir inhibits CYP3A4 and do not induce it. It is weakest inhibitor of CYP3A4 among protease inhibitors
 - These act as the substrate for P-glycoprotein.
117. **Ans. (a) Mutation at reverse transcriptase** (Ref: *KDT 6/e p770, 771*)
Zidovudine is a nucleoside reverse transcriptase inhibitor, which is a viral enzyme. HIV undergoes mutations in this enzyme to become resistant to NRTIs.
118. **Ans. (a) Nausea and vomiting; (b) Anaemia; (c) Steatosis** (Ref: *KDT 6/e p771*)
- **Anaemia** and neutropenia are the most important and dose related adverse effects of zidovudine.
 - **Nausea**, anorexia, abdominal pain, headache, insomnia and myalgia are common at start of therapy but diminishes later.
 - Myopathy, lactic acidosis, hepatomegaly with steatosis, convulsion, and encephalopathy are infrequent.
- [Harrison 17th/1954-1955]*
119. **Ans. (a) Zalcitabine; (d) Stavudine** (Ref: *KDT 6/e p767*)
120. **Ans. (a) Interacts with terfenadine; (b) G.I. symptoms are seen** (Ref: *CMDT 2010/1229; KDT 6th /773*)

- Ritonavir is a protease inhibitor anti-retroviral drug.
- Ritonavir is a microsomal enzyme inhibitor and it interacts with **terfenadine**, macrolide antibiotics, rifampicin, warfarin, etc.
- *It is predominantly eliminated from the body in feces (86% unchanged drug and metabolites) with minor urinary elimination (11% mostly metabolites).*
- Adverse Effects:
 - G.I. symptoms are most frequent
 - Lipodystrophy syndrome
 - Paraesthesia
 - Hepatic toxicity

121. Ans. (c) Zidovudine; (d) Cotrimoxazole; (e) Ganciclovir (Ref: CMDT 2010/454)

Drug causing bone marrow suppression in patients with HIV infection:

- Zidovudine
- Dapsone
- Trimethoprim/Sulfamethoxazol (Cotrimoxazole)
- Pyrimethamine
- 5-Flucytosine
- Ganciclovir
- Interferon α
- Foscarnet

122. Ans. (b) Ganciclovir; (e) Cidofovir (Ref: KDT 6/e p770, Katzung 11/e p851)

CMV causes retinitis in AIDS patient. Treatment of CMV: IV ganciclovir, Intravitreal ganciclovir, foscarnet, fomivirsen and cidofovir.

123. Ans. (a) Saquinavir; (c) Nelfinavir (Ref: KDT 6/e p767)

All protease inhibitors end with NAVIR.

124. Ans. (b) It causes marked neurotoxicity (Ref: KDT 6/e p771)

Stavudine is an NRTI that is responsible for maximum peripheral neuropathy.

125. Ans. (a) Lamivudine (Ref: KDT 6/e p772)

126. Ans. (d) Serving as an allosteric inhibitor of HIV reverse transcriptase (Ref: KDT 6/e p772)

Allosteric inhibitor means Non-nucleoside reverse transcriptase inhibitor.

127. Ans. (a) Indinavir (Ref: KDT 6/e p772, 773)

Protease results in the formation of final structural and functional proteins by post translational modification of HIV viral proteins. Drugs in this group are indinavir, saquinavir, lopinavir, ritonavir, amprenavir etc.

128. Ans. (c) Enfuvirtide (Ref: KDT 6/e p774)

It is a fusion inhibitor useful in the treatment of HIV infections.

129. Ans. (c) Treat the patient with clarithromycin, ethambutol and rifabutin (Ref: KDT 6/e p750)

Mycobacterium avium complex infection is treated with combination of rifabutin, ethambutol and clarithromycin.

130. Ans. (d) Administer zidovudine with lamivudine for 4 weeks (Ref: KDT 6/e p776)

131. Ans. (c) Ganciclovir (Ref: KDT 6/e p770)

- Ganciclovir is the drug of choice for CMV infections.
- It should not be combined with zidovudine because both have bone marrow suppressant property.

132. Ans. (b) Nucleoside reverse transcriptase inhibition (Ref: KDT 6/e p770-771)

133. Ans. (c) Neutropenia (Ref: Katzung 11/e p856)

134. Ans. (b) Emtricitabine (Ref: KDT 6/e p778)

135. Ans. (b) Dose lower for blocking HIV replication than HBV replication (Ref: CMDT 2014/654-655)

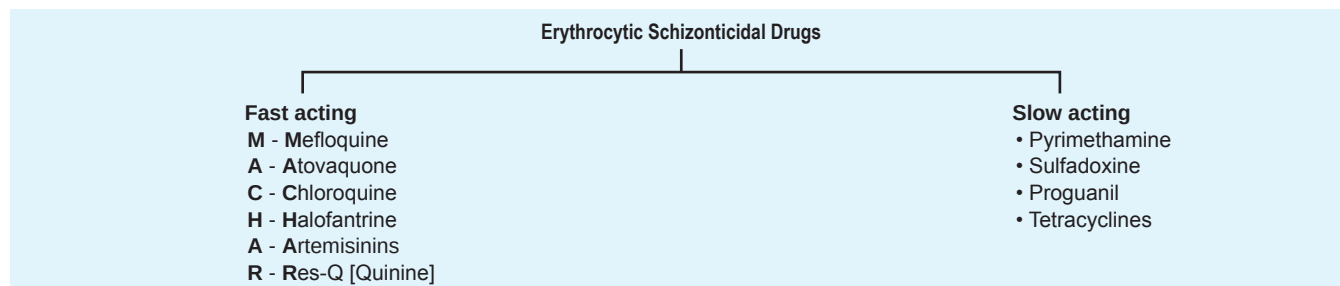
- Lamivudine can be used for both HIV as well as HBV. The dose for HIV is 150 mg twice a day whereas a lower dose of 100 mg daily is used in HBV.
- It should not be used alone as resistance develops quickly.
- Seroconversion from HBeAg positive to anti HBe occurs in only 20% of patients.

Review of Pharmacology

136. Ans. (a) **Anemia** (Ref: KDT 6/e p771)
137. Ans. (a) **Protects against acquiring the HIV infection** (Ref: KDT 6/e p776)
138. Ans. (c) **< 200/microL** (Ref: KDT 6/e p775)
139. Ans. (b) **Abacavir** (Ref: Katzung 11/e p857, CMDT 2014/1294)
140. Ans. (c) **Tenofovir** (Ref: Katzung 11/e p859)
141. Ans. (d) **Ritonavir** (Ref: Katzung 11/e p863)
142. Ans. (b) **Saquinavir** (Ref: KDT 6/e p767)
143. Ans. (c) **Efavirenz** (Ref: KDT 6/e p772, 774)
144. Ans. (a) **Fusion inhibitor** (Ref: KDT 6/e p774)
145. Ans. (c) **Thioacetazone** (Ref: KDT 6/e p743, Harrison's 17th/1181, 346)
146. Ans. (d) **Stavudine** (Ref: KDT 6/e p776)
147. Ans. (b) **Gp 41** (Ref: KDT 6/e p774)
148. Ans. (c) **Raltegravir** (Ref: Harrison 17th/1191; Katzung 11//866)
149. Ans. (a) **Atazanavir** (Ref: Katzung 11/e p863)
Unlike other protease inhibitors, atazanavir does not appear to be associated with dyslipidemia, fat redistribution or metabolic syndrome'
150. Ans. (c) **> 480g total dose** (Ref: Goodman and Gilman 12/e p1405, American academy of ophthalmology)
- Criteria of High Risk for Developing Chloroquine Retinopathy**
- Dosage > 6.5 mg/kg hydroxychloroquine or > 3 mg/kg chloroquine
 - Duration of Use > 5 years
 - High fat level (unless dosage is appropriately low)
 - Presence of renal/liver disease
 - Presence of concomitant retinal disease
 - Age > 60 years
- Previously cumulative dose of > 1g/Kg was considered as a high risk factor which is now not considered.
151. Ans (b) **Artesunate plus quinine** (Ref: CMDT 2010/1356)
- The WHO recommended ACTs include:**

 - Artemether-lumefantrine
 - Artesunate-amodiaquine
 - Artesunate-mefloquine
 - Artesunate-sulfadoxine-pyrimethamine
 - Dihydroartemisinin-piperaquine
152. Ans. (c) **Artesunate** (Ref: Harrison 17th/Table 203-6; KDT 6/e p794)
153. Ans. (a) **DLE** (Ref: Katzung 10/e p849; KDT 6/e p786)
154. Ans. (d) **Clindamycin** (Ref: Katzung 10/e p855; KDT 6/e p714)
- Tetracycline and clindamycin are active against erythrocytic schizonts of all human malarial parasite. Doxycycline is commonly used in the treatment of falciparum malaria in conjunction with quinine, allowing a shorter and well tolerated course of quinine.
 - Clindamycin is slowly active against erythrocytic schizonts and can be used in conjunction with quinine in those for whom doxycycline is not recommended, such as children and pregnant women.
 - Thus, the answer is clindamycin because:
 - In chloroquine resistant malaria, chloroquine will be ineffective.
 - Tetracycline and doxycycline are contra-indicated in children (due to risk of bone and teeth abnormalities).
155. Ans. (c) **Antimalarial** (Ref: KDT 6/e p795, 796)
Like halofantrine, lumefantrine is also used for the treatment of malaria.

156. Ans. (c) Pyrimethamine (Ref: KDT 6/e p790)



157. Ans. (a) Chloroquine; (b) Hydroxychloroquine (Ref: Khurana 3rd/499; G & G 11/e p1035)
 Bull's eye maculopathy is the appearance of macula in which circular bands of different shades of pink and orange are visible. It may be caused by chloroquine and hydroxychloroquine.

158. Ans. (b) Causal prophylactic (Ref: KDT 6/e p782)

Stage	Clinical Use
Preerythrocytic	Causal prophylaxis
Erythrocytic	– Clinical cure – Suppressive prophylaxis
Exo-Erythrocytic	– Radical cure
Gametocytic	– Prevention of transmission

159. Ans. (a) Artemether (Ref: KDT 6/e p792)

Artemisinin derivatives like dihydroartemisinin, arteether and artemether etc. are fastest acting antimalarial drugs.

160. Ans. (a) Chloroquine (Ref: KDT 6/e p786, 788)

- DOC for malaria in pregnant – chloroquine
- DOC for chloroquine resistant malaria in pregnant – Quinine

161. Ans. (b) Mefloquine (Ref: KDT 6th /787, 788)

Mefloquine is effective as a single dose treatment of malaria. It can be used for both chloroquine sensitive as well resistant bacteria.

162. Ans. (d) All of the above (Ref: KDT 6/e p786)

163. Ans. (a) Quinine (Ref: KDT 6/e p789)

Among the given options, quinine is the best answer. DOC for uncomplicated chloroquine resistant *P. falciparum* malaria is ACT [artemisinin-based combination therapy.]

164. Ans. (b) Primaquine (Ref: KDT 6/e p791)

165. Ans. (a) High volume of distribution (Ref: KDT 6/e p786)

166. Ans. (a) Quinine (Ref: KDT 6/e p789)

167. Ans. (d) *P. vivax* and *P. ovale* (Ref: KDT 6/e p784)

168. Ans. (d) Mefloquine (Ref: KDT 6/e p787)

169. Ans. (b) Rapid recrudescence of malaria (Ref: KDT 6/e p793)

170. Ans. (b) Lumefantrine (Ref: KDT 6/e p796)

171. Ans. (a) Hypoglycemia (Ref: KDT 6/e p789)

172. Ans. (c) Proguanil (Ref: KDT 6/e p909)

173. Ans. (c) It has increased tissue binding (Ref: KDT 6/e p567-568)

174. Ans. (a) Quinine (Ref: CMDT 2010, 1358)

175. Ans. (c) Primaquine (Ref: KDT 6/e p784)

176. Ans. (d) Above 1300 L (Ref: Katzung 11/e p39)

177. Ans. (c) **Cryptosporidium** (Ref: Goodman Gilman 12/e p1433)

Pyruvate ferredoxin oxidoreductase (PFOR) enzyme dependent electron transfer is essential for anaerobic metabolism in many protozoa and bacterial species. The drug that acts by interfering with this reaction is **nitazoxanide**. It is the only drug available for cryptosporidiosis. It is also **approved for treatment of Giardiasis**.

178. Ans. (a) **Dapsone** (Ref: KDT 6/e p746,754)

- Rifampicin (600 mg) is used as once monthly supervised dose in multibacillary as well as pauci-bacillary leprosy.
- Clofazimine (300 mg) is used as a once monthly supervised dose in multibacillary leprosy which is followed by 50 mg unsupervised daily dose.
- Dapsone (100 mg) is administered as a once daily unsupervised dose in both pauci-bacillary as well as multibacillary leprosy.
- Under DOTS guidelines; Rifampicin + Isoniazid + Pyrazinamide + Ethambutol are given as supervised dose of anti-tubercular drugs.

179. Ans. (d) **Hydroxychloroquine** (Ref: CMDT – 2010/1352-1353)

Drugs used for visceral leishmaniasis (kala azar) are:

- Liposomal amphotericin B (Drug of choice)
- Sodium stibogluconate (Most commonly used)
- Pentamidine
- Paromomycin
- Miltefosine (oral)
- Sitamaquine (oral)

180. Ans. (a) **Sporotrichosis** (Ref: Harrison 17th/1265)

Previously oral saturated solution of KI was used for sporotrichosis but now oral itraconazole is the drug of choice for cutaneous and lymphocutaneous sporotrichosis.

181. Ans. (a) **Antimalarial** (Ref: KDT 6/e p796)

Pyronaridine is an anti-malarial agent related to amodiaquine. It is highly effective against chloroquine resistant falciparum malaria. Currently it is being evaluated in combination with artesunate.

182. Ans. (a) **Didanosine** (Ref: KDT 6/e p771)

- Didanosine is most commonly implicated anti-retroviral drug in causing acute pancreatitis.
- Maximum chances of peripheral neuropathy are seen with stavudine.

183. Ans. (d) **Paromomycin is effective in extra-intestinal amoebiasis.** (Ref: KDT 6/e p806, 807; Katzung 10/e p859)

Paromomycin and diloxanide furoate are luminal amoebicides.

184. Ans. (d) **Diloxanide furoate** (Ref: KDT 6/e p801)

185. Ans. (b) **Quiniodochlor** (Ref: KDT 6/e p802)

8-hydroxyquinolones like quiniodochlor can result in SMON.

186. Ans. (b) **Amphotericin B** (Ref: CMDT 2012/1452)

187. Ans. (d) **All of the above** (Ref: KDT 6/e p813, 814)

- Ivermectin is the drug of choice for onchocerciasis (river blindness) and strongyloidosis.
- It is also effective against other filarial worms
- It can also be used orally for the treatment of scabies and pediculosis
- DEC is contraindicated in onchocerciasis

188. Ans. (d) **Pneumocystosis** (Ref: KDT 6/e p686)

Metronidazole is not effective against pneumocystis infections. DOC for this condition is cotrimoxazole.

189. Ans. (a) **Metronidazole** (Ref: KDT 6/e p798, 799)

Metronidazole is least effective luminal amoebicide because it is almost completely absorbed in small intestine and little drug is available to act in the colon.

190. Ans. (b) Melarsoprol (Ref: Katzung 10/e p863)

Treatment of trypanosomiasis is:

African sleeping sickness

- Early Haemolympathic stage : Suramin
- Late CNS Stages : Melarsoprol
- **South American disease (Chagas disease)** : Nifurtimox

191. Ans. (b) Praziquantal (Ref: KDT 6/e p814, 815)

Drug of choice for treatment of flukes (except liver fluke) and cestodes	: Praziquantal
Drug of choice for treatment of liver fluke	: Triclabendazole
Drug of choice for treatment of filariasis	: DEC
Drug of choice for treatment of onchocerca and strongyloides	: Ivermectin
For rest all helminthes	: Albendazole

192. Ans. (b) Ivermectin (Ref: KDT 6/e p813, 814)

Ivermectin is used for onchocerca and strongyloides, for all other nematodes, DOC is albendazole and for cestodes and flukes, DOC is praziquantal.

193. Ans. (d) Primaquine (Ref: KDT 6/e p791)**194. Ans. (c) Metronidazole** (Ref: KDT 6/e p799)

Drugs used for the treatment of pseudomembranous colitis are

- Metronidazole (Drug of choice)
- Vancomycin

195. Ans. (c) Acyclovir (Ref: Katzung 10/e p793; KDT 6/e p769)

Both indinavir and acyclovir can cause nephrotoxicity and renal stone formation. But indinavir is metabolized mainly in the liver and acyclovir is excreted unchanged in the urine.

196. Ans. (c) Liver (Ref: Katzung 10/e p869)

Albendazole if used for long times at high doses can lead to hepatotoxicity.

197. Ans. (d) Terbinafine (Ref: Katzung 11/e p842)

The diagnosis is Tinea capitis and terbinafine is used for the treatment. Male pattern baldness starts from anterior portion and scalp and are non-pruritic will family history. The treatment of latter is finasteride.

198. Ans. (a) Chloroquine (Ref: Kanski Clinical Ophthalmology 6/e p842-843)

Chloroquine can cause Bull's eye maculopathy. The risk of retinotoxicity increases significantly with cumulative dose of more than 300g (i.e. 250 mg daily for 3 years). It is rare if duration is less than one year.

199. Ans. (c) Praziquantal (Ref: KDT 6/e p435-436)

Praziquantal is the drug of choice for all trematode and cestode infestations except Fasciola hepatica (triclabendazole) and hydatid disease (albendazole)

200. Ans. (c) Cycloserine (Ref: KDT 6/e p744)

- Rifampicin, INH and pyrazinamide are first line drugs for TB that are hepatotoxic.
- Ethionamide is also hepatotoxic. Remember, ethambutol is not hepatotoxic.
- Cycloserine does not cause hepatotoxicity. Its major adverse effect is neuropsychiatric reactions.

201. Ans. (b) Albendazole (Ref: KDT 6/e p810)**202. Ans. (c) Piperazine** (Ref: KDT 6/e p811-812)

Drug	Mechanism of action
Albendazole	Blocks glucose uptake
Pyrantel Pamoate	Spastic Paralysis
Piperazine	Flaccid Paralysis
Ivermectin	Tonic Paralysis

203. Ans. (c) Chloroquine is effective only in hepatic amoebiasis (Ref: KDT 6/e p801)

- **Drugs used for the treatment of amoebiasis are:**
 - luminal ameobicide only *e.g.*, Diloxanide furoate, paromomycin and quiniodochlor.
 - Tissue ameobicide only *e.g.*, Chloroquine.
 - Both tissue as well as luminal ameobicides *e.g.*, Metronidazole, emetine etc.
- Metronidazole is the drug of choice for all forms of amoebiasis except very mild intestinal disease and carrier state.
- Diloxanide furoate is the agent of choice for mild intestinal amoebiasis and carriers.
- Emetine and dehydroemetine are rarely used now due to their emetic and cardiotoxic potential.)

204. Ans. (a) Filariasis (Ref: KDT 6/e p812)

- DEC kills microfilaria (Mf) of *W. bancrofti* and *B. malayi* from peripheral blood in 7 days, but microfilaria present in nodules and transudate are not killed.
- DEC is active against Mf of both *Loa-loa* and *Onchocerca* (but not against adult worms of *onchocerca*).

205. Ans. (b) Chloroquine (Ref: KDT 6/e p786)

206. Ans. (c) Albendazole (Ref: KDT 6/e p810)

207. Ans. (a) Metronidazole (Ref: KDT 6/e p799)

208. Ans. (c) Onchocercosis (Ref: KDT 6/e p810)

209. Ans. (d) Albendazole (Ref: KDT 6/e p809)

210. Ans. (d) 40 mg/kg single dose (Ref: KDT 6/e p814)

The dose in children (2-6 years) is 1g single dose. So, the best answer is option "A"

211. Ans. (a) Albendazole (Ref: KDT 6/e p809)

212. Ans. (a) Filariasis (Ref: KDT 6/e p814)

213. Ans. (b) Kala azar (Ref: KDT 6/e p806)

214. Ans. (d) Streptomycin (Ref: KDT 6/e p743)

215. Ans. (d) Lamivudine (Ref: KDT 6/e p771)

Lamivudine is a nucleoside reverse transcriptase inhibitor used in the treatment of HIV infections. Low dose of this drug can be used *alone or in combination with IFN- α for chronic HBV infections* (because it has longer intracellular $t_{1/2}$ in HBV than in HIV).

216. Ans. (d) Albendazole (Ref: Katzung 11/e p924)

217. Ans. (d) Albendazole (Ref: Katzung 11/e p924)

218. Ans. (c) Albendazole and praziquantel (Ref: K.D. Tripathi 6/e p815)

ANSWERS OF RECENT QUESTIONS ASKED BY NATIONAL BOARD

1. Ans (c) Increased metabolism of OCPs (Ref: KDT 7/e p768)
2. Ans (c) Praziquantel (Ref: KDT 7/e p850, 853-855)
3. Ans (a) 75 mg BD x 5 days orally (Ref: KDT 7/e p802)
4. Ans (a) Herpes keratitis (Ref: KDT 7/e p800)
5. Ans (a) Dermatitis herpetiformis (Ref: Goodman Gilman 12/e p1219)
6. Ans (a) NNRTI (Ref: KDT 7/e p808)
7. Ans (c) Pyrimethamine (Ref: KDT 7/e p818)
8. Ans (c) Clofazimine (Ref: KDT 7/e p782)

9. Ans. (b) Pyridoxine (Ref: KDT 7/e p767)
10. Ans. (b) Doxycycline (Ref: KDT 7/e p819)
11. Ans. (b) Zanamivir (Ref: KDT 7/e p801, 802)
12. Ans. (b) Rifampicin (Ref: KDT 7/e p772)
13. Ans. (d) Foscarnet (Ref: CMDT 2014 p1308)
14. Ans. (b) Primaquine (Ref: KDT 7/e p820)
15. Ans. (d) Thrombocytopenia (Ref: KDT 7/e p767)
16. Ans. (b) Ethambutol (Ref: KDT 7/e p769)
17. Ans. (b) Used in treatment of meningococcal meningitis (Ref: KDT 7/e p768)
 - Rifampicin is drug of choice for prophylaxis of meningococcal meningitis.
 - Penicillins are used for treatment of meningococcal meningitis.
18. Ans. (a) DNA Dependent RNA polymerase (Ref: KDT 7/e p768)
19. Ans. (d) All of the above (Ref: Goodman Gilman 12/e p1601)
 - Cidofovir can be used for
 - Acyclovir resistant Herpes simplex
 - CMV retinitis
 - Molluscum contagiosum
 - Anogenital warts
 - Respiratory papillomatosis
20. Ans. (a) Lamivudine (Ref: KDT 7/e p808)
21. Ans. (a) Flucytosine (Ref: KDT 7/e p791)
22. Ans. (d) Artesunate (Ref: KDT 7/e p818, 830)
23. Ans. (d) Tenofovir (Ref: KDT 7/e p808)
24. Ans. (c) Pyrazinamide (Ref: KDT 7/e p772)
25. Ans. (c) Schistosomiasis (Ref: KDT 7/e p1458)
26. Ans. (a) Foscarnet (Ref: KDT 7/e p800)
27. Ans. (d) Proguanil (Ref: KDT 7/e p1402)
28. Ans. (b) Didanosine (Ref: KDT 7/e p807)
29. Ans. (d) Satranidazole (Ref: KDT 7/e p840)
30. Ans. (c) Vitamine B₆ (Ref: KDT 7/e p767)
31. Ans. (b) Primaquine (Ref: KDT 7/e p828)
32. Ans. (b) Acyclovir (Ref: KDT 7/e p806-811)
33. Ans. (d) Resistance to isoniazid and rifampicin (Ref: KDT 7/e p776)
34. Ans. (b) Sporozoites (Ref: Goodman Gilman 12/e p1384)
35. Ans. (a) Pyridoxine (Ref: KDT 7/e p767)
36. Ans. (c) Ethambutol (Ref: KDT 7/e p769)
37. Ans. (b) Rifampicin (Ref: KDT 7/e p768)
38. Ans. (b) Ivermectin (Ref: KDT 7/e p854)
39. Ans. (c) Mutation (Ref: KDT 7/e p773)
40. Ans. (d) Metronidazole (Ref: KDT 7/e p838)
41. Ans. (b) Terbinafine (Ref: KDT 7/e p796)
42. Ans. (b) Ganciclovir (Ref: KDT 7/e p801)

43. Ans. (a) Zidovudine to mother during pregnancy and labour and to baby after delivery (Ref: KDT 7/e p815)
44. Ans. (a) Acyclovir (Ref: KDT 7/e p800)
45. Ans. (d) RNA dependent DNA polymerase (Ref: KDT 7/e p806)
46. Ans. (b) Quinine (Ref: KDT 7/e p819)
47. Ans. (a) Pyrazinamide (Ref: KDT 7/e p769)
48. Ans. (d) Streptomycin + ethambutol (Ref: KDT 7/e p777)
49. Ans. (a) 4 weeks (Ref: KDT 7/e p815)
50. Ans. (b) Amphotericin B (Ref: KDT 7/e p845)
51. Ans. (d) Thiacetazone (Ref: KDT 7/e p771)
52. Ans. (d) Ethambutol (Ref: KDT 7/e p769)
53. Ans. (c) Quinine (Ref: KDT 7/e p825-826)
54. Ans. (b) Neurocysticercosis (Ref: KDT 7/e p838-839)
55. Ans. (c) Kanamycin (Ref: KDT 7/e p780)
56. Ans. (a) Rifampicin (Ref: KDT 7/e p782)
57. Ans. (b) Dermatitis herpetiformis (Ref: Goodman Gilman 12/e p1823)
58. Ans. (b) Hepatotoxicity (Ref: KDT 7/e p768)
59. Ans. (b) Rifampicin (Ref: KDT 7/e p768)
60. Ans. (b) Chloroquine (Ref: KDT 7/e p823)
61. Ans. (c) Amphotericin B (Ref: KDT 7/e p787)
62. Ans. (c) Streptomycin and Ethambutol (Ref: KDT 7/e p777)
63. Ans. (a) Pyrazinamide (Ref: KDT 7/e p769)
64. Ans. (a) Ethambutol (Ref: KDT 7/e p769)
65. Ans. (a) Rifampicin (Ref: KDT 7/e p768)
66. Ans. (a) Rifampicin (Ref: KDT 7/e p768)
67. Ans. (c) Tapeworm (Ref: KDT 7/e p851)
68. Ans. (c) Herpes simplex virus (Ref: KDT 7/e p799)
69. Ans. (a) Ethambutol (Ref: KDT 7/e p769)
70. Ans. (c) Herpes infection (Ref: KDT 7/e p799)
71. Ans. (b) Chloroquine (Ref: KDT 7/e p837)
72. Ans. (a) Acyclovir (Ref: KDT 7/e p800)
73. Ans. (b) Fluoroquinolones (Ref: KDT 7/e p820)
74. Ans. (a) 400 mg once (Ref: KDT 7/e p851)

Neoplastic cells are quite similar to normal cells, therefore the drugs targeted to kill these cells can also kill normal cells. As most of these drugs are acting on rapidly dividing cells, the normal cells having quick turnover are most susceptible to toxicity. *Bone marrow suppression, alopecia and mucositis* are thus commonly caused by anti-cancer drugs. New drugs targeting specific steps in the cells are devoid of these adverse effects.

Anticancer drugs may be divided (on the basis of stage of cell cycle at which these act) into two groups – cell cycle specific (CCS) and cell cycle non-specific (CCNS). CCS drugs are effective when the cells are proliferating whereas CCNS drugs are effective whether the cells are dividing or are in the resting phase.

Table 15.1: Cell cycle effects of anticancer drugs

(Ref. Katzung 11/e p938)

CCS Drugs	CCS Drugs	CCNS Drugs
G ₁ - S	Etoposide	Platinum compounds
S	Antimetabolites	Alkylating agents
G ₂ - M	Bleomycin Etoposide [Ref Harrison 17th/525]	Anthracyclines Dactinomycin
M	Vinca alkaloids Taxanes Ixabepilone Estramustine	Mitomycin Camptothecins

Initially, the anticancer drugs were developed based on murine L1210 leukemia model. This model has a growth fraction of 100% (i.e. all cells are actively dividing). Based on this murine model **cytotoxic drugs act with first order kinetics** i.e. a constant proportion of cells are killed with a given dose rather than constant number of cells. For example same dose of a drug will be required to reduce tumor population from 1000 to 100 as is needed to reduce it from 100 to 10. This is called '**log kill hypothesis**'.

However, human solid tumors donot follow this model, because, growth fraction of the tumor is not constant but decreases exponentially with time. *Growth fraction peaks when tumor is approximately 37% of its maximum size*, this model is known as **Gompertzian model**.

CLASSIFICATION

Alkylating Agents

i.	Nitrogen mustards: Mechlorethamine, cyclophosphamide, ifosfamide, melphalan, chlorambucil
ii.	Ethylenimines: Thio-TEPA, hexamethylmelamine (altretamine)
iii.	Alkyl sulfonates: Busulfan
iv.	Nitrosoureas: Carmustine, lomustine, streptozocin
v.	Triazines : Procarbazine, dacarbazine, temozolomide

Platinum compounds

Cisplatin, carboplatin, oxaliplatin.

Antimetabolites

i.	<i>Pyrimidine analogs</i> : 5-FU, cytarabine, gemcitabine
ii.	<i>Purine analogs</i> : 6-MP, 6-thioguanine, pentostatin, cladribine
iii.	<i>Folic acid analogs</i> : Methotrexate, pemetrexed

Natural products

i.	<i>Vinca alkaloids</i> : Vincristine, vinblastine, vinorelbine
ii.	<i>Taxanes</i> : Paclitaxel, docetaxel
iii.	<i>Epipodophyllotoxins</i> : Etoposide, teniposide
iv.	<i>Camptothecins</i> : Topotecan, irinotecan
v.	<i>Antitumor antibiotics</i> : Anthracyclines (daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone), bleomycin, dactinomycin, mitomycin-C
vi.	<i>Enzymes</i> : L-asparaginase

Hormones and related agents

i.	<i>Corticosteroids</i> : Prednisolone, prednisone
ii.	<i>Antiestrogens</i> : SERMs (tamoxifen, toremifene) aromatase inhibitors (aminoglutethimide, formestane, exemestane, anastrozole, letrozole, toremifene)
iii.	<i>Progestins</i> : Medroxyprogesterone acetate
iv.	<i>Estrogens</i> : Diethylstilbestrol, ethinyl estradiol
v.	<i>Androgens</i> : Testosterone
vi.	<i>Antiandrogens</i> : Flutamide
vii.	<i>GnRH analogs</i> : Leuprolide, goserelin, nafarelin, busurelin, histerelin
viii.	<i>GnRH antagonists</i> : Cetrorelix, ganirelix, abarelix

Miscellaneous Agents

i.	<i>Biological response modifiers</i> : Recombinant IL-2 (aldesleukin), GM-CSF (sargramostim), G-CSF (filgrastim), monoclonal antibodies (rituximab, trastuzumab etc.)
ii.	<i>Substituted urea</i> : Hydroxyurea
iii.	<i>Adrenal cortex suppressant</i> : Mitotane
iv.	<i>Tyrosine kinase inhibitors</i> : Imatinib, gefitinib, erlotinib
v.	<i>Retinoids</i> : Isotretinoin
vi.	<i>Arsenic compounds</i> : As_2O_3
vii.	<i>Adenosine deaminase inhibitor</i> : Pentostatin

Alkylating Agents

All alkylating agents and related drugs (procarbazine, dacarbazine and platinum compounds) are **CCNS drugs** and thus act on both resting as well as dividing cells. These drugs alkylate nucleophilic groups on DNA bases (**N7 of guanine is most susceptible**) and may lead to cross-linking of bases, abnormal base-pairing and DNA strand breakage. **Gastrointestinal distress, bone marrow suppression, alopecia, secondary leukemias and sterility are common adverse effects of all the alkylating agents.**

Nitrogen Mustards

- **Cyclophosphamide** is a **prodrug** and is activated by hepatic biotransformation to aldophosphamide. One of its degradation products is **acrolein** that is responsible for **hemorrhagic cystitis** (its characteristic adverse effect). This adverse effect can be decreased by vigorous hydration and by the use of mercapto ethane sulfonic acid



N7 of guanine is most susceptible position for alkylation

(mesna). Cyclophosphamide may also result in **cardiac dysfunction, pulmonary toxicity and syndrome of inappropriate ADH secretion**. Ifosfamide produces *chloroacetaldehyde* (nephrotoxic) and *acrolein* as metabolites. Ifosfamide has same toxicity profile as cyclophosphamide, however it has **HIGHER risk of neurotoxicity and hemorrhagic cystitis**. Cyclophosphamide is the **drug of choice for Wegener's granulomatosis**. It is a powerful vesicant

- **Mechlorethamine** is best known for its use in **Hodgkin's disease**. It is a **powerful vesicant**.
- **Melphalan** is the drug of choice for **multiple myeloma**.

Cyclophosphamide is the drug of choice for Wegener's granulomatosis.

Nitrosoureas can cause delayed neutropenia.

Nitrosoureas

Drugs like **carmustine** (BCNU), **lomustine** (CCNU) and **semustine** (methyl CCNU) etc. are highly lipid soluble and can cross blood brain barrier. Thus, these are used for the treatment of **brain tumors like gliomas**. These can cause **delayed neutropenia**.

- Dacarbazine primarily affects RNA and protein synthesis unlike alkylating agent.
- **Streptozocin** can destroy beta cells of pancreas, and is thus used for *islet cell tumors*. It has minimum bone marrow toxicity.

Other Alkylating Agents

- **Busulfan** causes adrenal insufficiency, *pulmonary fibrosis*, skin hyperpigmentation and hyperuricemia.
- **Procarbazine** is **most leukemigenic** and causes **disulfiram like reaction** with alcohol. It also causes CNS effects like hypnosis and vivid dreams.
- **Chlorambucil** spares myelocytes, used for CLL.

HEMORRHAGIC CYSTITIS

Drugs causing:

- Ifosfamide
- Cyclophosphamide

Metabolite responsible

- Acrolein

Treatment

- Mesna

DISTINCTIVE TOXICITIES OF ALKYLATING AGENTS

Drug	Toxicity
Cyclophosphamide	Alopecia, Hemorrhagic cystitis, SIADH
Ifosfamide	Hemorrhagic cystitis, SIADH
Busulfan	Pulmonary fibrosis, Hyperpigmentation, Adrenal insufficiency
Procarbazine	Secondary leukemias, Disulfiram like reaction, Behavioral changes, CNS depression
Cisplatin	Emesis, Nephrotoxicity, Peripheral sensory neuropathy, Ototoxicity

Platinum Compounds

These include **cisplatin, carboplatin and oxalplatin**. These are *not alkylating agents* in true sense but are discussed here because of similar mechanism of action. Only difference is that these *use platinum* instead of alkyl group to form dimers of DNA. Most common adverse effect of these agents is **nausea and vomiting (maximum among all anti-cancer drugs)**. These drugs are mild bone marrow suppressants and are **nephrotoxic, ototoxic as well as neurotoxic**. *Cisplatin* is most *nephrotoxic* whereas *carboplatin* is more *hematotoxic* (bone marrow suppressant). Carboplatin has less nephrotoxic, ototoxic and neurotoxic potential than cisplatin. **Oxaliplatin is effective against the cells showing resistance to cisplatin or carboplatin. Its dose limiting toxicity is neurotoxicity** (peripheral neuropathy).

- It is important to establish chloride diuresis prior to cisplatin therapy in order to *prevent renal toxicity*. Chloride diuresis has *no effect on ototoxicity*.
- Cisplatin is always given as **slow i.v. infusion** (never bolus) to prevent intense nausea and acute rise in serum creatinine.
- *Aluminium inactivates cisplatin*, therefore aluminium containing equipments or needles should not be used with cisplatin.
- **Amifostine** is labelled for *reduction* of cisplatin induced *nephrotoxicity*.
- **Amifostine** is also used to *reduce xerostomia* in patients undergoing irradiation of head and neck involving parotid.
- Cisplatin has less chances of causing bone marrow suppression.

Amifostine is indicated for

- Reduction of cisplatin induced nephrotoxicity.
- To reduce xerostomia in patients undergoing irradiation

- **Cisplatin** reduces all ions in serum i.e. causes hypomagnesemia, hypokalemia, hypocalcemia and hypophosphatemia. (Remember, *cyclosporine*, an immunosuppressive drug cause hyperkalemia).
- Cisplatin has been associated with development of AML, usually 4 years or more after treatment.

Note:

- Nitrosoureas and ifosfamide may lead to renal failure.
- All alkylating agents are myelosuppressive.
- Nitrosoureas and mechlorethamine have strong vesicant properties (cause local irritation and damage).
- Alkylating agents also can cause sterility and secondary leukemias (less common with cyclophosphamide).
- All alkylating agents have caused pulmonary fibrosis.
- In high dose, all alkylating agents can cause veno-occlusive disease of liver which can be reversed by defibrotide.

ANTIMETABOLITES

These drugs act in the **S-phase** of cell cycle (CCS drugs), thus only dividing cells are responsive. These drugs possess immunosuppressive properties apart from their antineoplastic effects.

Folic Acid Analogs

Methotrexate and **pemetrexed** are the **inhibitors of dihydrofolate reductase (DHFRase)**. These drugs also inhibit thymidylate synthase (TS) and the enzymes involved in early purine synthesis. Methotrexate forms polyglutamates inside the cell that helps to trap it within the cells and thus is important for cytotoxicity to neoplastic cells. **Methotrexate resistance** can occur due to *impaired transport of methotrexate into cells, production of altered forms of DHFRase that have decreased affinity for the inhibitor, increased concentrations of intracellular DHFRase through gene amplification or altered gene regulation, decreased ability to synthesize methotrexate polyglutamates* and increased expression of a drug efflux transporter, of the MRP (multidrug resistance protein) class. Methotrexate can be **sequestered in third-space collections** and leech back into general circulation, causing prolonged immunosuppression. Clearance of methotrexate depends on renal function and **vigorous hydration is required to prevent its crystallization in renal tubules**. It is the **drug of choice** for the treatment of **choriocarcinoma**. It is also useful for acute leukemias, non-Hodgkin lymphoma, cutaneous T-cell lymphoma and breast cancer. It can be used by intrathecal route for *meningeal leukemias*. Pemetrexed is approved for treatment of *mesothelioma*. *Folic acid and vitamin B₁₂ supplementation decreases the toxicity of pemetrexed without interfering with its clinical efficacy*. Methotrexate is **also indicated in the management of rheumatoid arthritis, psoriasis and ectopic pregnancy**. Adverse effects of methotrexate are **bone marrow suppression and mucositis**. The toxicity of methotrexate to normal cells can be **reduced** by administration of **N₁₀ formyl-tetrahydrofolic acid (folinic acid, citrovorum factor or leucovorin)**. This strategy is known as *leucovorin rescue*. *Leucovorin do not prevent neurotoxicity*. Alkalinization of urine can also reduce methotrexate toxicity. In extreme cases, toxicity can be treated by dialysis or administration of **GLUCARPIDASE**, a methotrexate cleaving enzyme. Long term use of methotrexate may also lead to **hepatotoxicity**, pulmonary infiltrates and fibrosis. NSAIDs like aspirin, penicillins and cephalosporins may decrease the renal excretion of methotrexate and result in toxicity. **Pralatrexate** is a similar drug indicated for peripheral T-cell lymphoma.

Purine analogs

6-mercaptopurine (6-MP) and **6-thioguanine (6-TG)** are the purine antimetabolites that are activated by hypoxanthine-guanine phosphoribosyl transferase (HGPRTase). The resulting nucleotides inhibit several enzymes in purine biosynthesis and metabolism. 6-MP is metabolized by xanthine oxidase. When administered along with **allopurinol** (*xanthine*

**Uses of Methotrexate**

- Inhibit – Immunosuppressant
- C – Crohn's disease
- A – Abortion
- N – Non Hodgkin Lymphoma
- C – Choriocarcinoma
- E – Ectopic pregnancy
- R – Rheumatoid arthritis



Methotrexate is the drug of choice for the treatment of choriocarcinoma.



The toxicity of methotrexate to normal cells can be reduced by administration of N₁₀ formyl-tetrahydrofolic acid (folinic acid, citrovorum factor or leucovorin).



In extreme cases, methotrexate toxicity can be treated by dialysis or administration of GLUCARPIDASE, a methotrexate cleaving enzyme.

oxidase inhibitor), the **dose of 6-MP (and also azathioprine) should be reduced to 1/4th** of the original dose. Purine antimetabolites are used mainly for the treatment of leukemias (both acute leukemias and CML). Dose limiting toxicity is bone marrow suppression but hepatotoxicity can also result. Other important purine analogs are fludarabine phosphate and cladribine (adenine analogs). Because **cladribine** is resistant to degradation by adenosine deaminase, it is **drug of choice** for the treatment of **hairy cell leukemia**. **Fludarabine** is *drug of choice* for chronic lymphocytic leukemia (**CLL**). *Use of pentostatin with fludarabine may result in severe pulmonary toxicity.* All purine analogs may cause immunosuppression on long-term use and patients should be given cotrimoxazole for prophylaxis of *Pneumocystis*.

When administered along with allopurinol the dose of 6-MP (and also azathioprine) should be reduced to 1/4th of the original dose.

Pyrimidine Analogs

- Drugs in this group include **cytarabine** (cytosine arabinoside), **5-fluorouracil (5-FU)**, **capecitabine**, **gemcitabine**, **5-azacytidine** and **decitabine**.
- Cytarabine** is the single *most effective agent for induction of remission in AML*.
- Cytarabine is activated by kinases to form arabinoside CTP that is an inhibitor of DNA polymerase.
- High dose of **cytarabine** can lead to neurotoxicity (**ataxia and peripheral neuropathy**).
- 5-FU is converted to 5'-dUMP that inhibits TS. Its major route of metabolism is by conversion to CO₂ and elimination by respiratory pathway.
- Capecitabine** is an **oral pro-drug of 5-FU**. It can cause hyperbilirubinemia.
- Thiopurines (6MP and 6-TG) are metabolized by the thiopurine methyl transferase (TPMT) whereas 5-FU is catabolized by dihydropyrimidine dehydrogenase (DPD). Both TPMT and DPD have pharmacogenetic deficiencies in some persons.
- Capecitabine and 5-FU** can cause **hand and foot syndrome** (a form of erythromelalgia manifested as tingling, numbness, pain, erythema, swelling and increased pigmentation).
- Leucovorin augments the action of 5-FU.*
- 5 FU cause single strand breaks and thus affects both DNA & RNA.
- Gemcitabine** is a *very potent radiosensitizer*.
- Gemcitabine** is the **drug of choice for pancreatic cancer**.
- 5'-Azacytidine** acts by **DNA hypomethylation** and is approved for treatment of **myelodysplasia**.
- Decitabine is another drug acting by same mechanism.

Fludarabine is drug of choice for chronic lymphocytic leukemia (CLL).

Hand and Foot Syndrome is caused by:

- 5 - FU
- Capecitabine
- Doxorubicin

Capecitabine and 5-FU can cause hand and foot syndrome

DISTINCTIVE TOXICITIES OF ANTIMETABOLITES

6-MP and 6 TG	Hepatotoxicity
Methotrexate	Mucositis, hepatotoxicity
5-FU	Hand and foot syndrome, neurotoxicity
Capecitabine	Hand and foot syndrome, Hyperbilirubinemia
Cytarabine	Cerebellar ataxia
Fludarabine	Arthralgia
Gemcitabine	Diarrhea

Note:

- All antineoplastic antimetabolites can cause bone marrow suppression.
- Alkylating agents are used for chronic leukemias whereas antimetabolites are commonly used for acute leukemias.

Gemcitabine is the drug of choice for pancreatic cancer.

Radiosensitizers

- Gemcitabine
- Dactinomycin
- Metronidazole
- 5-FU
- Mitomycin-C
- Hydroxyurea
- Fludarabine
- Paclitaxel
- Irinotecan

Mitotic Spindle Inhibitors

Vinca Alkaloids

Vincristine, vinblastine and vinorelbine are the vinca alkaloids that act by **inhibiting polymerization of microtubules** (thus inhibiting formation of mitotic spindle). Therefore, these are effective in M-phase of cell cycle. Vinblastine causes bone marrow suppression

 Marrow sparing cytotoxic drugs

- Vincristine
- Bleomycin
- L-asparaginase

whereas **vincristine** is 'marrow sparing' but is neurotoxic (peripheral neuropathy). Vinca alkaloids can also result in **SIADH**.

- **Vinblastine's** most important clinical use is the curative therapy of *metastatic testicular tumors*.
- **Vincristine with glucocorticoids** is the *treatment of choice* for inducing remission in *childhood leukemias*. It can also be used for *pediatric solid tumors* (Wilm's tumor, neuroblastoma and rhabdomyosarcoma) and *lymphomas*.

Taxanes

Paclitaxel and docetaxel interfere with mitotic spindle formation by **preventing disassembly of microtubules**. Paclitaxel causes hypersensitivity reactions (due to Cremophor-containing vehicle) whereas docetaxel is devoid of this adverse effect. **Protein bound paclitaxel (nab-paclitaxel)** has *decreased risk of hypersensitivity reactions*. Both of these drugs can cause *bone marrow suppression* and *neurotoxicity*. Cisplatin decreases paclitaxel clearance and paclitaxel can decrease doxorubicin clearance. **Cabazitaxel** is a microtubule inhibitor indicated in combination with prednisone for hormone refractory metastatic prostate cancer.

Ixabepilone

It is a new drug approved for treatment of *advanced breast carcinoma* resistant to anthracyclines and taxanes. It is given in combination with capecitabine. It acts by *binding to tubulin and promoting microtubule stabilization*, thereby arresting cells in the G₂-M phase of cell cycle.

Erbulin Mesylate

It is a microtubule inhibitor recently approved for treatment of patients with metastatic breast cancer.

Estramustine

It is a **combination of estrogen and mechlorethamine** (nitrogen mustard) and is used for the treatment of **prostatic carcinoma**. It acts as *anti-mitotic drug* by binding to tubulin. It can produce estrogenic side effects (gynaecomastia and impotence).

Topoisomerase Inhibitors**Camptothecins**

Irinotecan and **topotecan** are obtained from *Camptotheca acuminata* tree and act by **inhibiting topoisomerase I** (this enzyme nicks, introduces negative supercoils and reseals the DNA strand). Topotecan is used in advanced ovarian carcinoma and is excreted by renal route. **Irinotecan is a prodrug** that is converted in the liver to an active metabolite, SN-38. It is eliminated in bile and feces and thus its **dose should be reduced in hepatic failure**. **Irinotecan is now the treatment of choice for advanced colorectal carcinoma in combination with 5-FU**.

- Dose limiting toxicity of *topotecan* is *neutropenia* whereas it is *diarrhea* for *irinotecan*.
- Irinotecan can also lead to myelosuppression.
- *Irinotecan can also result in a cholinergic syndrome* (manifested as diarrhea, sweating, hypersalivation, lacrimation, rhinorrhea, abdominal cramps and bradycardia) due to inhibition of acetylcholine esterase. It occurs within 24 hours.

Epipodophyllotoxins

Podophyllotoxin was used for its emetic, cathartic and antihelminthic effects. It acts by binding to tubulin but its derivatives; **etoposide** and **teniposide** act by **inhibiting topoisomerase II** resulting in DNA damage through strand breakage. These drugs act at the junction of late S and early G₂ phase of cell cycle. These drugs can cause *gastrointestinal distress and myelosuppression*.

- Etoposide is indicated for testicular, prostatic and oat cell carcinoma [of lung].
- **Etoposide therapy can result in acute non-lymphocytic** (acute monocytic or monomyelocytic) **leukemia**. This leukemia develops at a *short time interval* (1 to 3 years) after the end of therapy as compared to alkylating agents induced leukemia (require

 Irinotecan is now the treatment of choice for advanced colorectal carcinoma in combination with 5-FU.

 Etoposide induced secondary leukemia

- Develops at short time interval
- Lacks preceding myelodysplastic stage.

4-5 years). Another distinguishing feature of this leukemia is *absence of myelodysplastic period preceding leukemia*.

- At high doses, *etoposide is hepatotoxic*.

Antitumor Antibiotics

This group includes **anthracycline antibiotics** (*doxorubicin* also known as *adriamycin*, *daunorubicin*, *epirubicin* and *idarubicin*), mitoxantrone, bleomycin, dactinomycin and mitomycin. **Except bleomycin (acts in G₂ phase), all other drugs are CCNS drugs.** All antitumor antibiotics are obtained from *Streptomyces*.

- Anthracycline antibiotics act by inhibiting topoisomerase II. Doxorubicin and daunorubicin are primarily used in acute leukemias whereas idarubicin and epirubicin display broader activity against solid tumors (breast carcinoma, Osteosarcoma, Ewing's sarcoma and soft tissue sarcoma). These agents also generate semiquinone free radicals that are responsible for cardiotoxicity (manifested in the form of dilated cardiomyopathy and congestive heart failure). This adverse effect can be reduced by using α -tocopherol and dexrazoxane (a free radical scavenger). Liposomal forms of these drugs have decreased cardiac toxicity. Dilated cardiomyopathy is cumulative, dose-dependent and may present even after discontinuation of the anthracyclines. Earliest morphological feature is swelling of endoplasmic reticulum. It is followed by loss of cardiomyocytes (myofibrillar dropout). Symptoms are similar to CHF including exertional dyspnea, orthopnea and peripheral edema. These drugs also can cause red coloured urine (not hematuria). Another important feature of these drugs is that these can cause "radiation recall reaction" (erythema and desquamation of skin seen at the sites of prior radiation exposure). Mitoxantrone seems to be less cardiotoxic than the other drugs of this group. Mitoxantrone has been approved for AML, advanced hormone resistant prostate cancer and treatment of late stage, secondary progressive multiple sclerosis. It is less cardiotoxic but can result in acute promyelocytic leukemia. Valrubicin is approved for intravesical therapy of BCG-refractory urinary bladder carcinoma in situ.
- Dactinomycin (Actinomycin-D) acts by inhibiting DNA dependent RNA synthesis. It is indicated for solid tumors in children (rhabdomyosarcoma and wilm's tumor) and choriocarcinoma. It is a radiosensitizer (like metronidazole and 5-FU).
- **Bleomycin** is a CCS *glycopeptide* drug that acts in the G₂ phase by causing DNA strand breakage and free radical formation. It can result in *cutaneous toxicity* (hyperpigmentation, hyperkeratosis, erythema and ulcers), pneumonitis, **pulmonary fibrosis**, hypersensitivity and mucocutaneous reactions. **Earliest indicator of an adverse effect is decreased in DLco.** It causes **necrosis of type I pneumocytes** that results in compensatory **hyperplasia of type II pneumocytes**. Bleomycin is *metabolized by bleomycin hydrolase*, whose concentration is less in skin and lungs (thus major organs involved in toxicity). Bleomycin toxicity may *become apparent after exposure to transient very high PIO₂* because bleomycin dependent electron transport is dependent on O₂.
- **Mitomycin** acts as an **alkylating agent**. It may be used as **intravesical therapy** to treat **superficial bladder cancers** and **anal carcinoma** (with radiation therapy). Rarely, it *can cause hemolytic uremic syndrome*. It is **best available** drug for use as an adjuvant to X-ray radiation **to attack hypoxic tumor cells**. (because, it is converted to active alkylating agent by reduction). It can cause **delayed bronchospasm**. It is also used in patients with **tracheal or laryngeal stenosis**.

Anthracycline induced cardiotoxicity can be reduced by using α -tocopherol and dexrazoxane (a free radical scavenger).

Anthracyclines can cause "radiation recall reaction"

Earliest indicator of bleomycin induced pulmonary fibrosis is decrease in DLco.

Mitomycin C is used in patients with tracheal or laryngeal stenosis

DISTINCTIVE TOXICITIES OF NATURAL ANTICANCER DRUGS

Bleomycin	Pulmonary fibrosis (Marrow sparing)
Anthracyclines	Cardiotoxicity
Paclitaxel	Peripheral neuropathy, Hypersensitivity
Docetaxel	Peripheral neuropathy, Fluid retention
Irinotecan	Diarrhea
Vincristine	Peripheral neuropathy (Marrow sparing), SIADH



Imatinib is the drug of choice for CML and gastro-intestinal stromal tumor (GIST).

Note: All natural anticancer products can cause bone marrow suppression except bleomycin and vincristine.

Tyrosine Kinase Inhibitors

- **Imatinib** is an oral drug used for chronic phase of CML. It acts by inhibiting tyrosine kinase activated due to *abl-bcr fusion* (t 9, 22; Philadelphia chromosome). It is a **competitive inhibitor of ATP-binding of the abl kinase** in the inactive conformation. **Dasatinib** and **Nilotinib** are similar drugs used in case of imatinib resistance. **Imatinib is the drug of choice for CML and gastro-intestinal stromal tumor (GIST).**
- **Geftinib and Erlotinib** are inhibitors of tyrosine kinase associated with **epidermal growth factor receptor (EGFR)**. These are indicated for *non-small cell lung cancer*. **Erlotinib** is especially effective in cases affecting *women, nonsmokers*, and persons of *Asian ethnicity* as well as cases involving *adenocarcinoma and bronchioalveolar carcinoma* histology. Erlotinib is also indicated for **pancreatic carcinoma** with gemcitabine. **Food increases the absorption** of Erlotinib to 100%. It is metabolized by **CYP3A4** enzyme system. Acneiform **skin rash, diarrhea, anorexia and fatigue** are the most common adverse effects of this drug. Molecular studies have shown that patients with EGFR mutations respond to **Erlotinib** at significantly high rates, but patients with Kras mutations do not respond and should not be offered this drug.
- **Sorafenib and Sunitinib** are small molecules that **inhibit multiple tyrosine kinases**. Both can be used for *renal cell cancer*. In addition *sorafenib* is indicated for *hepatocellular cancer* and *sunitinib* for *GIST*. These can cause hypertension as an adverse effect.
- **Lapatinib** is indicated for breast carcinoma. It inhibits tyrosine kinase associated with EGFR and her-2/neu receptors.
- **Pazopanib** is a multi targeted tyrosine kinase inhibitor against VEGF receptors, PDGF receptor and c-kit. It is approved for treatment of **advanced renal cell carcinoma**.
- All tyrosine kinase inhibitors are metabolized by CYP 3A4 enzymes. Thus, these have the potential of drug interactions.
- All tyrosine kinase inhibitors can be administered orally.

7

TK inhibitors for NSCLC

A	–	Afatinib
E	–	Erlotinib
C	–	Crizotinib
	–	Ceritinib
G	–	Geftinib

7

TK inhibitors for RCC

P	–	Pazopanib
A	–	Axitinib
S	–	Sorafenib
S	–	Sunitinib

7

TK inhibitors for malignant melanoma

D	–	Dabrafenib
V	–	Vemurafenib
T	–	Trametinib

7

TK inhibitors for GIST

S	–	Sunitinib
I	–	Imatinib
R	–	Regorafenib

Drug	Inhibit TK activated by	Indication
Afatinib	EGFR, HER-2, HER-4	Non-small cell lung carcinoma (NSCLC)
Axitinib	VEGFR-1,2,3	Advanced renal cell carcinoma
Bosutinib	abl-bcr, src	CML
Ceritinib	ALK	NSCLC
Crizotinib	c-MET, ALK	Non-small cell lung carcinoma
Cabozantinib	c-MET, VEGFR-2	Medullary carcinoma thyroid
Dabrafenib	BRAF	Metastatic melanoma
Dasatinib	abl-bcr	CML
Erlotinib	EGFR	Non-small cell lung carcinoma Pancreatic carcinoma
Geftinib	EGFR	Non-small cell lung carcinoma
Ibrutinib	Btk	CLL
Imatinib	abl-bcr, c-KIT, PDGF	CML GIST
Lapatinib	her-2/neu, erb-B2	Breast carcinoma
Lenvatinib	VEGF	I ¹³¹ refractory differentiated thyroid cancer
Nilotinib	abl-bcr	CML
Pazopanib	VEGFR-1,2,3 PDGFR α, β c-KIT	Advanced renal cell carcinoma

Contd...

Contd...

Drug	Inhibit TK activated by	Indication
Ponatinib	abl-bcr	CML Philadelphia positive ALL
Regorafenib	VDGFR2, TIE2	Colorectal carcinoma GIST
Ruxolitinib	JAK 1,2	Myelofibrosis
Sorafenib	VEGFR, PDGFR RAF	Renal cell carcinoma Hepatocellular carcinoma
Sunitinib	VEGFR, PDGFR c-KIT, FLT-3 RET	Renal cell carcinoma Pancreatic neuroendocrine tumors GIST
Tofacitinib	JAK	Rheumatoid arthritis
Trametinib	MEK	Metastatic melanoma
Vandetanib	VEGFR, EGFR	Medullary carcinoma thyroid
Vemurafenib	BRAF	Malignant melanoma

N

Ado-trastuzumab mertansine is a **conjugate** of trastuzumab (monoclonal antibody against her-2) and mertansine (microtubule inhibitor). It is approved for treatment of her-2 positive metastatic breast cancer

N

Pertuzumab is a monoclonal antibody against her-2/neu. It is used in combination with trastuzumab (bind to different region of her-2 receptor) for metastatic breast carcinoma.

Monoclonal Antibodies

Trastuzumab is a monoclonal antibody against her-2/neu gene product. It is useful for the treatment of **breast carcinoma** but **cardiotoxicity** limits its use. Recently, It has also been approved for cancer of stomach or gastroesophageal junction. **Rituximab** is a monoclonal antibody useful for **non-Hodgkin lymphoma**. **Alemtuzumab** is used for **B-cell CLL** and **cetuximab**, **panitumumab** and **bevacizumab** can be used for **colorectal carcinoma**.

	Monoclonal antibody	Targeted against	Indication	Comments
1.	Rituximab	CD-20	Non-Hodgkin lymphoma	
2.	Alemtuzumab	CD-52	Low grade lymphomas and CLL	
3.	Trastuzumab	HER 2/neu	Breast carcinoma	Can cause cardiotoxicity
4.	Cetuximab and panitumumab	EGFR	EGFR-positive metastatic colorectal carcinoma	Cause rash, hypomagnesemia and interstitial lung disease
5.	Bevacizumab	VEGF	Metastatic colorectal carcinoma	Combined with 5-FU
6.	Gemtuzumab Ozogamicin	CD-33	CD-33 positive AML	Linked to calicheamicin
7.	¹³¹ I-Tositumomab ⁹⁰ Y-Ibritumomab tiuxetan	CD-20	Relapsed lymphomas	Conjugated with radioisotopes
8.	Denileukin diftitox	–	Recurrent cutaneous T-cell lymphoma	Recombinant IL-2 plus diphtheria toxin
9.	Denosumab	RANK/L	Giant cell tumor of bone	Also used in osteoporosis
10.	Obinutuzumab	CD-20	CLL	Used in combination with chlorambucil
11.	Pertuzumab	HER-2	Breast cancer	It inhibits dimerization of HER-2 with other HER-receptors
12.	Ipilimumab	CTLA4	Malignant melanoma	
13.	Ramucirumab	VEGFR2	Gastroesophageal adenocarcinoma Non small cell lung carcinoma	Act as angiogenesis inhibitor

Contd...

Contd...

	Monoclonal antibody	Targeted against	Indication	Comments
14.	Nivolumab	PD-1	Non small cell Lung cancer Metastatic melanoma	Inhibits interaction of PD-1 with ligands on T-cells
15.	Dinutuximab	Glycolipid GD2	Children with high risk neuroblastoma	- Used in combination with GM-CSF, IL-2 and retinoic acid - GD2 is expressed on neuroblastoma cells
16.	Blintatumomab	CD-19 and CD-3	Philadelphia negative B-cell ALL	
17.	Pembrolizumab	PD-1	Metastatic melanoma	

M

Rituximab is a monoclonal antibody against CD20. It is used for treatment of:

- R – Rh. arthritis
- e
- L – Lupus (SLE)
- I – ITP
- A – Autoimmune hemolytic anemia
- N – Non-Hodgkin Lymphoma
- C – CLL
- e

- **Cetuximab** is a monoclonal antibody *against EGFR*. It is approved for *colon cancer* [with irinotecan] and *head and neck cancer* [with radiation therapy]. Its main adverse effects are skin rash, hypomagnesemia and hypersensitivity reactions.
- **Panitumumab** is a fully human monoclonal antibody **against EGFR**. It is similar to cetuximab but do not cause hypersensitivity reactions [because it is fully human]. It is approved for **colo-rectal cancer**.
- **Bevacizumab** is a monoclonal antibody against vascular endothelial growth factor (VEGF). Latter is an essential requirement for angiogenesis. It is approved for *colorectal, breast, glioblastoma, metastatic renal cell carcinoma and non-small cell lung cancer*. Its main safety concerns are hypertension, thromboembolism, wound healing complications and gastrointestinal perforations.

HORMONES AND RELATED AGENTS

Glucocorticoids

Prednisolone is the most commonly used glucocorticoid in cancer chemotherapy. It is used for the combination chemotherapy in leukemia and lymphomas. It is **also combined with ondansetron** for the management of chemotherapy induced **vomiting**.

Estrogens

Previously **high dose estrogen** therapy was used for the treatment of **breast carcinoma** but now it has been replaced with antiestrogen therapy. Estrogen is also effective in **prostate cancer** because it suppresses androgen production.

Progestins

These include **medroxyprogesterone acetate, hydroxyprogesterone caproate and megestrol**. These are useful as second line hormonal therapy for metastatic hormone dependent **breast cancer and endometrial cancer**. In addition, progestins stimulate appetite and restore a sense of well being.

Androgen Inhibitors (Antiandrogens)

Flutamide, enzalutamide and bicalutamide bind to androgen receptor and inhibit the actions of androgens. These are thus effective for the treatment of **prostatic carcinoma**. These are used **along with gonadotropin releasing hormone agonists**. This strategy is known as **complete androgen blockade**. *Flutamide can cause hot flushes, hepatic dysfunction and gynaecomastia.*

Gonadotropin Releasing Hormone (GnRH) Agonists

Goserelin, nafarelin, and leuprolide act as agonists of LHRH. Continuous administration of these agents lead to transient release of LH and FSH (and thus **flaring up** of symptoms in prostatic carcinoma) followed by inhibition of release of gonadotropins. These are indicated in the management of advanced **prostatic carcinoma**. Main adverse effects include transient flaring up of disease, hot flushes, impotence, gynaecomastia and osteoporosis.

N

Abiraterone acts by inhibiting 17- α hydroxylase and is indicated in refractory prostate cancer

GnRH Antagonists

Cetrorelix, ganirelix, degarelix and abarelix are the antagonists of LHRH. These drugs decrease the release of gonadotropins without causing initial stimulation. *Degarelix has been approved for the treatment of prostatic carcinoma without the risk of flare up reaction.*

Antiestrogens

Tamoxifen and **toremifen** are selective estrogen receptor modulators (SERMs) that are useful for chemoprevention as well as treatment of both early stage and metastatic **breast carcinoma**. These can lead to transient flare up reaction, menopausal symptoms and other estrogenic adverse effects. **Fulvestrant** is *pure ER antagonist* (selective estrogen receptor down regulator; SERD) having improved safety profile, faster onset and long duration. It is indicated for metastatic breast cancer.

Aromatase is an enzyme responsible for the conversion of androstenedione (an androgen precursor) to estrone (estrogenic hormone). Drugs inhibiting aromatase include aminoglutethimide, anastrozole, exemestane and letrozole. These are classified into first generation (aminoglutethimide), second generation (formestane, fadrozole, rogletimide) and third generation (exemestane, anastrozole, letrozole and vorozole) drugs. Aromatase inhibitors are useful in advanced breast carcinoma. Adverse effects include hot flushes, arthralgia and fatigue. Aminoglutethimide also causes adrenal insufficiency and myelosuppression.

M

Fulvestrant

- Is a SERD
- Indicated in tamoxifen-resistant breast cancer
- Safer than SERMs
- Faster onset
- Long duration

SELECTED TOXICITIES OF HORMONAL AGENTS

• Flutamide	Hot flushes, liver dysfunction
• SERMs	Menopausal symptoms, fluid retention, thromboembolism, increased incidence of endometrial cancer
• Progestins	Fluid retention
• Corticosteroids	Fluid retention, hypertension, diabetes, increased susceptibility to infections
• GnRH agonists	Transient flare up reaction, hot flushes, impotence, gynaecomastia, osteoporosis
• Aminoglutethimide	Adrenal insufficiency, myelosuppression, rash
• Aromatase inhibitors	Fatigue, hot flushes, arthralgia

N

Ziv-aflibercept is a fusion protein against VEGF and placental growth factor. It is approved for **metastatic colorectal carcinoma** in combination with FOLFIRI

OTHER ANTICANCER DRUGS

L-Asparaginase

It is an enzyme used for the treatment of **leukemias and lymphomas**. These tumors require exogenous asparagine for growth. L-asparaginase acts by depleting this amino acid in the serum. It is administered by i.v. route and may cause **severe hypersensitivity reactions, acute pancreatitis and cortical vein thrombosis**.

Pentostatin

This drug is used for the treatment of **hairy cell leukemia** (DOC is *cladribine*). It acts by **inhibiting the enzyme adenosine deaminase** (although the name is statin but it has no HMG CoA reductase inhibiting action).

Octreotide

It is a **long acting somatostatin analog** and is useful in the treatment of **islet cell carcinoma** (decreases both insulin and glucagon secretion). Other uses of octreotide include secretory diarrheas, **esophageal varices and acromegaly**.

Plicamycin

It is used for **hypercalcemia of malignancy** and **metastatic testicular carcinoma** because it decreases serum calcium levels.

Hydroxyurea

It is the drug used for **sickle cell anemia, essential thrombocytosis and polycythemia vera**. It can also be used in **CML**. It acts by inhibiting ribonucleoside reductase (rate limiting step in



Tretinon and As_2O_3 are used for treatment of acute Promyelocytic leukemia [M₃-AML]

synthesis of DNA). In sickle cell anemia, it increases the solubility of hemoglobin by *inducing the synthesis of fetal hemoglobin* (reduces vaso-occlusive events). In essential thrombocytosis, it is the drug of choice (**if not responding, anagrelide may be added**). It can be used orally for all these purposes.

Tretinoin (ATRA)

All-trans retinoic acid (ATRA) induces 70% or more rate of complete remission in *acute promyelocytic leukemia*.

It can cause various toxicities:

Vitamin A toxicity	Headache, fever, dryness, skin rash, pruritis, conjunctivitis
Retinoic acid syndrome	Fever, leucocytosis, dyspnea, weight gain, pulmonary infiltrates, pleural or pericardial effusion.
CNS toxicity	Dizziness, anxiety, depression, confusion, agitation
Hypercholesterolemia	
Hypertriglyceridemia	
Abdominal pain and diarrhea	

7

Lenalidomide is approved for treatment of **mantle cell lymphoma** and multiple myeloma

As₂O₃

It is used for the treatment of **acute promyelocytic leukemia (APML)**. It may cause *hyperglycemia* and *prolonged QT interval*. Like tretinoin, it also acts as a differentiating agent.

Sipuleucel-T

It is a cell-based cancer immunotherapy for **prostate cancer**. Patient's antigen presenting cells are extracted by leukapheresis and are incubated with a fusion protein (consisting of prostatic acid phosphatase and GM-CSF). This is then re-infused into the patient to cause an immune response against the tumor cells carrying prostatic acid phosphatase antigen. It is approved for hormone refractory prostate cancer.

Thalidomide

- Its major actions are:
 - Inhibition of angiogenesis
 - Inhibition of TNF- α
 - Increased production of IL-10
 - Reduces phagocytosis
 - Alteration of adhesion molecule expression
 - Enhances cell- mediated immunity via interactions with T- cells.
- Currently, it is indicated for
 - Multiple myeloma at initial diagnosis
 - Relapsed- refractory cases of multiple myeloma
 - Erythema nodosum leprosum (Provides dramatic relief; drug of choice for steroid resistant cases)
 - Skin manifestations of SLE
- Its major adverse effects are:
 - Teratogenicity
 - Peripheral neuropathy
 - Constipation
 - Rash
 - Hypothyroidism
 - Increased risk of DVT
- Immunomodulatory derivatives of thalidomide are called IMiDs. One of these is Lenalidomide, which is approved as a first line therapy for multiple myeloma with dexamethasone and bortezomib.
- Another group of thalidomide analogs are called SelCIDs (Selective cytokine Inhibitory Drugs).

This drug was used in 1960s as a sedative and anti-emetic drug (for morning sickness) but was banned because of teratogenic effects (phocomelia). Now it has come again in the market for use as an anticancer drug in **multiple myeloma and melanoma**. **Lenalidomide** is its more potent and non-teratogenic derivative. It has recently been **approved for mantle cell lymphoma** also *Thalidomide* most commonly *causes sedation and constipation* in cancer patients. It can also cause *peripheral sensory neuropathy*. Two enantiomers of thalidomide (R and S) are present but these are interconvertible in body, therefore racemic mixture is used. **Pomalidomide** is a newer thalidomide analogue.

Ingenol mebutate

It is an inducer of apoptosis specifically indicated for topical treatment of **actinic keratosis** of face, scalp, trunk and extremities.

Idelalisip

It is a small molecular inhibitor of PI3 kinase delta. It is approved for oral treatment of **relapsed CLL, follicular B-cell NHL and SLL**.

Temsirolimus

It is a prodrug that is converted to sirolimus (rapamycin). Latter is a specific inhibitor of mTOR. It is approved for **advanced renal cell carcinoma**. It is associated with interstitial lung disease.

Palbociclib

It is an orally effective cyclin dependent kinase (cdk) 4 and 6 inhibitor. It is approved in combination with letrozole for post-menopausal women with ER + ve and HER-2 negative **breast cancer**.

Omacetaxine

It is a protein synthesis inhibitor approved for **chronic phase of CML**. It binds to A-site and prevents elongation step in protein synthesis.

Proteasome inhibitors

Bortezomib and carfilzomib act by *inhibiting proteasome* resulting in down regulation of NF- κ B (involved in cell survival). These have been approved for treatment of *resistant multiple myeloma*.

Zolendronic Acid

It is a *bisphosphonate* indicated for the treatment of bony metastases and multiple myeloma.

Histone deacetylase inhibitors

Vorinostat and Romidepsin are *histone deacetylase inhibitors* approved for *cutaneous T-cell lymphoma*. **Panobinostat** is a new drug in this category that is approved for multiple myeloma. **Belinostat** is another drug in this group approved for relapsed or refractory peripheral T-cell lymphoma.

Mitotane

It is indicated for the palliation of *inoperable adrenocortical carcinoma*. Concomitant spiro-lactone interferes with adrenal suppression produced by mitotane.

Olaparib

It is a poly ADP-ribose polymerase (PARP) inhibitor used for oral treatment of **ovarian cancer**.

Aldesleukin

It is **recombinant IL-2** and can be used for the management of **renal cell carcinoma** and **malignant melanoma**.



Vorinostat and Romidepsin are histone deacetylase inhibitors approved for cutaneous T-cell lymphoma.

Adjuvant chemotherapy is administered after surgery or radiotherapy while neoadjuvant chemotherapy means administration of anti-cancer drugs before surgery or radiotherapy.

Denileukin Deftitox

It is a **combination of IL-2 with diphtheria toxin** and is used for **cutaneous T cell lymphoma**. *Adjuvant chemotherapy* is administered after surgery or radiotherapy while *neoadjuvant* chemotherapy means administration of anti-cancer drugs before surgery or radiotherapy.

Neoadjuvant chemotherapy is used for cancers of

- Bladder
- Breast
- Colorectal
- Esophagus
- Stomach
- Lung (non-small cell)

Drugs Used to Prevent Toxicity of Anti-Cancer Drugs

Neoadjuvant chemotherapy is used for cancers of

- Bladder
- Breast
- Colorectal
- Esophagus
- Stomach
- Lung (non-small cell)

Drug	Mechanism	Indications
Allopurinol	Inhibit xanthine oxidase	Prevent hyperuricemia from tumor lysis syndrome
Rasburicase	Recombinant urate oxidase	Prevent hyperuricemia from tumor lysis
Mesna	Neutralizing agent	Prevent hemorrhagic cystitis due to ifosfamide and high dose cyclophosphamide
Leucovorin	Replete Tetrahydrofolic acid	Rescue after high dose methotrexate
Amifostine	Prevent radiation-induced xerostomia and	Prevent radiation-induced xerostomia and cisplatin-induced nephrotoxicity
Dexrazoxane	Iron-chelator	Prevent cardiotoxicity due to anthracyclines
Palifermin	Keratinocyte growth factor	Prevent mucositis following chemotherapy
Pilocarpine	Cholinergic agonist	Radiation-induced xerostomia
Pamidronate and Zoledronate	Bisphosphonates	Hypercalcemia of malignancy
Epoetin-alpha and Darbopoetin-alpha	Erythropoietin	Anemia
Filgrastim, Peg-Filgrastim,	G-CSF and	Febrile neutropenia prophylaxis
Sargramostim	GM-CSF	
Oprelvekin	IL-11	Thrombocytopenia
Ondansetron	5-HT ₃ antagonist	Nausea and vomiting
Granisetron		
Palonosetron		
Aprepitant	NK-1 antagonist	Cisplatin-induced delayed vomiting

Therapy of choice for various cancers

(Ref: CMDT 2015/1597-1599)

	Diagnosis	Treatment of choice
1.	ALL	Induction: Vincristine + Prednisolone + Daunorubicin + Asparaginase + Intrathecal Methotrexate
		Consolidation: Hyper-CVAD alternated with Cytarabine + Methotrexate
2.	AML	Cytarabine + Daunorubicin/Idarubicin
3.	CML	Imatinib (or Nilotinib or Dasatinib)

Contd...

Contd...

	Diagnosis	Treatment of choice
4.	CLL	FCR or Fludarabine
5.	Hairy-cell leukemia	Cladribine
6.	Hodgkin disease	ABVD
7.	Non-Hodgkin Lymphoma	CHOP-R (FCR for low grade)
8.	Multiple Myeloma	Bortezomib + Dexamethasone + Lenalidomide
9.	Waldenstrom macroglobulinemia	Plasmapheresis ± Bortezomib (With or without rituximab)
10.	Polycythemia vera	Hydroxyurea
11.	Non-small cell lung cancer	Cisplatin + Vinorelbine ± Bevacizumab
12.	Small cell lung cancer	Cisplatin + Etoposide
13.	Mesothelioma	Cisplatin + Pemetrexed
14.	Head and Neck cancer	Cisplatin + 5-FU
15.	Esophageal cancer	Cisplatin + 5-FU
16.	Uterine cancer	Progestins / Tamoxifen/Aromatase inhibitors OR Cisplatin + Doxorubicin
17.	Ovarian cancer	Paclitaxel + Carboplatin
18.	Cervical cancer	Cisplatin + Paclitaxel (or cisplatin with radiation)
19.	Breast cancer	Endocrine : Tamoxifen (Pre-menopausal) Aromatase inhibitor (Post-menopausal) Adjuvant chemotherapy : Doxorubicin + Cyclophosphamide + Docetaxel ± Trastuzumab
20.	Choriocarcinoma	Methotrexate / Dactinomycin
21.	Testicular cancer	BEP
22.	Kidney cancer	Sunitinib or sorafenib
23.	Bladder cancer	Gemcitabine + Cisplatin
24.	Prostate cancer	GnRH agonist ± Antiandrogen
25.	Astrocytoma/Glioblastoma multiforme	Temozolomide + Radiation
26.	Neuroblastoma	Cyclophosphamide + Doxorubicin + Cisplatin + Etoposide
27.	Thyroid cancer	I ¹³¹ / Sorafenib (Vandetanib for medullary carcinoma)
28.	Stomach cancer	Epirubicin + Cisplatin + 5-FU
29.	Pancreatic cancer	Gemcitabine ± Cisplatin/Erlotinib
30.	Colon cancer	FOLFOX-6 ± Bevacizumab FOLFIRI ± Bevacizumab (for more advanced disease)
31.	Rectal cancer	Radiotherapy + 5- FU
32.	Anal cancer	Radiation + 5-FU + Mitomycin C
33.	Insulinoma	Interferon / Streptozocin
34.	Osteosarcoma	Doxorubicin / Cisplatin / Ifosfamide / High dose methotrexate [Any 2 drugs]
35.	Soft tissue sarcoma	MAID
36.	Gastrointestinal stromal tumors (GIST)	Imatinib or sunitinib
37.	Melanoma	Ipilimumab / Vemurafenib / IL-2
38.	Hepatocellular carcinoma	Sorafenib
39.	Kaposi sarcoma	Liposomal doxorubicin/daunorubicin

Contd...

Contd...

	Diagnosis	Treatment of choice
40.	Adrenal cancer	Mitotane
41.	Carcinoid	Streptozocin + 5-FU or Bevacizumab alone

Abbreviations:

Hyper - CVAD	C yclophosphamide + V incristine + A driamycin (Doxorubicin) + D examethasone
ABVD	A driamycin + B leomycin + V inblastine + D acarbazine
CHOP - R	C yclophosphamide + H ydroxydaunorubicin (Doxorubicin) + O ncovin (Vincristine) + P rednisone + R ituximab
FCR	F ludarabine + C yclophosphamide + R ituximab
BEP	B leomycin + E toposide + C isplatin
FOLFOX - 6	FOL inic acid (Leucovorin) + 5- FU + Ox aliplatin
FOLFIRI	FOL inic acid + 5- FU + IRI notecan
MAID	M esna + A driamycin + I fosfamide + D acarbazine

MULTIPLE CHOICE QUESTIONS

CYTOTOXIC DRUGS

- Topical mitomycin-C is used in:** (AI 2012)
 - Sturge-Weber syndrome
 - Laryngotracheal stenosis
 - Endoscopic angiofibroma
 - Skull base osteomyelitis
- Which group of anticancer drugs temozolomide belong to:** (AI 2012)
 - Oral alkylating agent
 - Antitumor Antibiotic
 - Antimetabolite
 - Mitotic Spindle Inhibitor
- Methotrexate is used for the management of all of these conditions except:** (AIIMS May 2011)
 - Rheumatoid arthritis
 - Psoriasis
 - Sickle cell anemia
 - Organ transplantation
- All of the following are true regarding ifosfamide EXCEPT:** (AIIMS May 2011)
 - Metabolised by cytochrome p450 enzymes
 - Less neurotoxic than cyclophosphamide
 - Chloroacetaldehyde is the metabolite of ifosfamide
 - It is a nitrogen mustard
- Alkalinisation of urine ameliorates the toxicity of which of the following drugs?** (AI 2011)
 - Arabinoside-cytosine
 - Ifosfamide
 - Cisplatin
 - Methotrexate
- Pulmonary fibrosis is seen with:** (AI 2011, AIIMS Nov 2002)
 - Bleomycin
 - Cisplatin
 - Methotrexate
 - Actinomycin D
- Methotrexate resistance is due to:** (AIIMS Nov 2010)
 - Depletion of folate
 - Overproduction of DHFRase
 - Overproduction of thymidylate kinase
 - Decreased DHFRase
- Hemorrhagic cystitis is caused by:** (AIIMS Nov 2010)
 - Cyclophosphamide
 - 6 Mercaptopurine
 - 5 Fluorouracil
 - Busulfan
- Most important dose-limiting toxicity of cancer chemotherapy is:** (AIIMS May 2010)
 - Gastrointestinal toxicity
 - Neurotoxicity
 - Bone marrow suppression
 - Nephrotoxicity
- Which of the following parameters is not monitored in a patient on methotrexate therapy?** (Delhi PG - 2011)
 - Liver function tests
 - Lung function test
 - Eye examination
 - Hemogram
- Most emetogenic anticancer drug is:** (AIIMS May 2009)
 - Cisplatin
 - Carboplatin
 - High dose cyclophosphamide
 - High dose methotrexate
- Cerebellar toxicity is seen with:** (AIIMS May 2009)
 - Cisplatin
 - Cytarabine
 - Bleomycin
 - Actinomycin D
- All are alkylating agents, except:** (AIIMS May 2010) (AIIMS May 2009) (AIIMS Nov 2008) (AI 2007, DNB 2008)
 - 5-Fluorouracil
 - Melphalan
 - Cyclophosphamide
 - Chlorambucil
- Which of the following can be given orally?** (AIIMS May 2009)
 - Cytosine arabinoside
 - Cisplatin
 - Doxorubicin
 - Mesna
- 'Hand and Foot' syndrome can be caused by:** (AI 2009)
 - Cisplatin
 - Vincristine
 - Capecitabine
 - Mitomycin-C
- Which of the following anti-cancer drugs is cell cycle specific?** (AI 2009)
 - Ifosfamide
 - Melphalan
 - Vinblastine
 - Cyclophosphamide
- Topical mitomycin-C is used in:** (AI 2009)
 - Sturge-Weber syndrome
 - Laryngotracheal stenosis
 - Endoscopic angiofibroma
 - Skull base osteomyelitis

18. **Bleomycin toxicity affects which type of cells:** (AI 2009)
 - (a) Type-I pneumocytes
 - (b) Type-II pneumocytes
 - (c) Endothelial cells
 - (d) Pulmonary alveolar macrophages
19. **SIADH is caused by all EXCEPT:** (AIIMS May 2008)
 - (a) Vincristine
 - (b) Vinblastine
 - (c) Actinomycin D
 - (d) Cyclophosphamide
20. **Sustained neutropenia is seen with?** (AIIMS May 2008)
 - (a) Vinblastine
 - (b) Cisplatin
 - (c) Carmustine
 - (d) Cyclophosphamide
21. **Ifosfamide belongs to which group of anticancer drugs?** (AIIMS Nov 2008)
 - (a) Alkylating agents (AI 2009)
 - (b) Antimetabolites (DNB 2008)
 - (c) Mitotic inhibitors
 - (d) Topoisomerase inhibitors
22. **Which of the following anticancer drug is excreted by lungs?** (AIIMS Nov 2008)
 - (a) 5-Fluorouracil
 - (b) Cyclophosphamide
 - (c) Doxorubicin
 - (d) Cisplatin
23. **Mechanism of action of paclitaxel is:** (AI 2008)
 - (a) Topoisomerase inhibition (Kolkata 2009)
 - (b) Increases the polymerization of tubulin (UP 2005)
 - (c) Inhibits protein synthesis
 - (d) Alkylation of DNA
24. **Which antineoplastic drug is a peptide?** (AI 2008)
 - (a) Bleomycin
 - (b) Aspartame
 - (c) Valinomycin
 - (d) Dactinomycin
25. **Leucovorin is used to decrease the toxicity of:**
 - (a) Methotrexate (AI 2008, DNB 2001, TN 2002)
 - (b) 6-Mercaptopurine
 - (c) Thio-TEPA
 - (d) Cytosine arabinoside
26. **All-trans-retinoic acid is used in treatment of:** (AI 2008)
 - (a) Acute promyelocytic leukemia
 - (b) A.L.L.
 - (c) CML
 - (d) Transient myeloproliferative disorder
27. **Which of the following anticancer drugs can cause hypercoagulable state?** (AI 2007)
 - (a) 5-FU
 - (b) L-asparaginase
 - (c) Melphalan
 - (d) Carmustine
28. **Anticancer drug causing SIADH as an adverse effect is:** (AI 2007)
 - (a) Vincristine
 - (b) Paclitaxel
 - (c) Dacarbazine
 - (d) Cyclophosphamide
29. **High dose methotrexate is used for the treatment of:** (AI 2007)
 - (a) Osteosarcoma
 - (b) Rhabdomyosarcoma
 - (c) Retinoblastoma
 - (d) Ewing's sarcoma
30. **Which of the following drugs is topoisomerase 1 inhibitor?** (AI-2005)
 - (a) Doxorubicin
 - (b) Irinotecan
 - (c) Etoposide
 - (d) Vincristine
31. **All of the following anticancer agents cause bone marrow suppression EXCEPT:** (AI 2004)
 - (a) Chlorambucil
 - (b) Daunorubicin
 - (c) Doxorubicin
 - (d) Flutamide
32. **All of the following statements about methotrexate are correct EXCEPT:** (AI 2001)
 - (a) Folinic acid enhances the action of methotrexate
 - (b) Methotrexate inhibits dihydrofolate reductase
 - (c) Non-proliferative cells are resistant to methotrexate
 - (d) Methotrexate is used in the treatment of psoriasis
33. **Mesna is given with cyclophosphamide to:** (AI 2000)
 - (a) Increase absorption
 - (b) Decreased excretion
 - (c) Ameliorate hemorrhagic cystitis
 - (d) Decrease metabolism
34. **Which of the following is an anti-metabolite?**
 - (a) Methotrexate (AIIMS May, 2007)
 - (b) Cyclosporine
 - (c) Etoposide
 - (d) Vinblastine
35. **Which of the following drugs is associated with untoward side effect of renal tubular damage?**
 - (a) Cisplatin (AIIMS May, 2006)
 - (b) Streptozocin
 - (c) Methysergide
 - (d) Cyclophosphamide
36. **Which of the following chemotherapeutic agents is associated with secondary leukemia?** (AIIMS May, 2006)
 - (a) Vinblastine
 - (b) Paclitaxel
 - (c) Cisplatin
 - (d) Bleomycin

37. Which of the following statements is FALSE regarding vincristine? (AIIMS Nov, 2004)
- It is an alkaloid
 - Its use is associated with neurotoxicity
 - It does not cause alopecia
 - It is a useful drug for induction of remission in acute lymphoblastic leukemia
38. A patient with cancer developed extreme degree of radiation toxicity. Further history revealed that the dose adjustment of a particular drug was missed during the course of radiotherapy. Which of the following drugs required a dose adjustment during radiotherapy in order to prevent radiation toxicity? (AIIMS May, 2004, DPG 2009)
- Vincristine
 - Dactinomycin
 - Cyclophosphamide
 - 6-Mercaptopurine
39. Sterile hemorrhagic cystitis is caused by: (AIIMS Nov, 2003, MPPG 2001) (RJ 2002)
- Busulfan
 - Ketoprofen
 - Methicillin
 - Cyclophosphamide
40. A 50 year old woman, Hema has been diagnosed with locally advanced breast cancer and recommended for chemotherapy. She has five years history of myocardial infarction and congestive heart failure. Which antineoplastic drug should be best avoided? (AIIMS Nov, 2003)
- Anthracycline
 - Alkylating agent
 - Platinum compound
 - Bisphosphonates
41. Sodium 2-mercapto ethane sulfonate is used as a protective agent in: (AIIMS May, 2003)
- Radiotherapy
 - Cancer chemotherapy
 - Lithotripsy
 - Hepatic encephalopathy
42. A patient receiving allopurinol requires dose reduction of: (AIIMS May, 2001)
- 6-Mercaptopurine
 - Cyclophosphamide
 - 6-Thioguanine
 - Cimetidine
43. Which of the following are alkylating agents? (PGI Dec, 2007)
- Cyclophosphamide
 - Ifosfamide
 - Paclitaxel
 - Methotrexate
 - Vincristine
44. Anticancer drugs of plant origin is/are: (PGI June, 2004)
- Vincristine
 - Isotretinoin
 - Bleomycin
 - Methotrexate
45. Alkylating agents are: (PGI Dec, 2004)
- Vincristine
 - Actinomycin-D
 - Chlorambucil
 - 5-Fluorouracil
 - Cyclophosphamide
46. Which of the following drugs are anticancer antibiotics? (PGI June, 2003)
- Vancomycin
 - Actinomycin D
 - Bleomycin
 - Mithramycin
 - Vincristine
47. Metaphase arrest is caused by: (PGI Dec, 2002)
- Griseofulvin
 - Vincristine
 - Paclitaxel
 - Colchicine
 - Etoposide
48. The mechanism of anticancer action of fluorouracil is:
- Cross linking of double stranded DNA and the resulting inhibition of DNA replication and transcription
 - Cytotoxicity resulting from a metabolite that interferes with the production of dTMP
 - Irreversible inhibition of dihydrofolic acid reductase
 - Selective action on DNA polymerase
49. A cell cycle specific anticancer drug that acts mainly in the M phase of the cycle is:
- Cisplatin
 - Etoposide
 - Methotrexate
 - Paclitaxel
50. Maintenance of high urinary pH is important during methotrexate treatment because:
- Bladder irritation is reduced
 - It decreases renal tubular secretion of methotrexate
 - Leucovorin toxicity is increased in a dehydrated patient
 - Methotrexate is a weak acid
51. All of the following statements about methotrexate are true EXCEPT:
- It is cell cycle specific and kills cells in the S phase
 - Its toxicity primarily affects bone marrow and epithelial structures
 - Folic acid reverses its toxic effects
 - It is the drug of choice for choriocarcinoma
52. Mechanism of action of vincristine in the treatment of ALL is:
- Inhibition of topoisomerase II to cause breaks in DNA strands
 - Alkylation and cross linking DNA strands

- (c) Inhibition of DNA mediated RNA synthesis
(d) Inhibition of polymerization of tubulin to form microtubules
53. All of the following statements about vincristine are true EXCEPT:
(a) It acts by inhibiting mitosis
(b) Its prominent adverse effect is peripheral neuropathy
(c) It does not suppress bone marrow
(d) It is a drug of choice for solid tumors.
54. All of following statements about are true about 6-mercaptopurine EXCEPT:
(a) It is metabolized by xanthine oxidase
(b) It does not cause hyperuricemia
(c) Its dose should be reduced when allopurinol is given concurrently
(d) It is an active metabolite of azathioprine
55. Pentostatin acts by inhibiting:
(a) RNA dependent DNA polymerase
(b) Aldolase
(c) Adenosine deaminase
(d) Adenyl cyclase
56. Hand and foot syndrome is an adverse effect of:
(a) 5-Fluorouracil
(b) Bleomycin
(c) Etoposide
(d) Actinomycin D
57. Side effects of cisplatin include all of the following EXCEPT:
(a) Nausea and vomiting
(b) Nephrotoxicity
(c) Blindness
(d) Ototoxicity
58. Most common side effect of 5-fluorouracil is:
(a) G.I. toxicity
(b) Bone marrow depression
(c) Cardiotoxicity
(d) Neurotoxicity
59. Which of the following is a common side effect of cisplatin?
(a) Diarrhea
(b) Vomiting
(c) Pulmonary fibrosis
(d) Alopecia
60. The antimetabolite 'X' inhibits DNA polymerase and is one of the most active drugs in the treatment of leukemia. Although myelo-suppression is dose limiting, the drug may also cause cerebellar dysfunction, including ataxia and dysarthria. Which of the following can be 'X'?
(a) Bleomycin
(b) Cytarabine
(c) Mercaptopurine
(d) Methotrexate
61. Which of the following antineoplastic drugs should not be administered to a chronic alcoholic patient due to risk of development of disulfiram like reaction?
(a) Dacarbazine
(b) Procarbazine
(c) Melphalan
(d) Hydroxyurea
62. Roopa Devi, a 65-year-old female with ovarian cancer is being treated with cisplatin-based chemotherapy. All of the following are used to limit the toxicity of cisplatin except:
(a) N-acetylcysteine
(b) Slow rate of infusion
(c) Chloride diuresis
(d) Amifostine
63. Roopmati, A 56-year-old female with lymph-node-positive breast cancer was treated with systemic chemotherapy. Four weeks later, she developed frequent urination, suprapubic pain, dysuria, and hematuria. Which of the following could have prevented this patient's condition?
(a) Folinic acid
(b) Mesna
(c) Dexrazoxane
(d) Amifostine
64. Sunder, a young male was diagnosed as suffering from acute myeloid leukemia. He was started on induction chemotherapy with doxorubicin based regimens. Induction regimen was successful. Two months later, he presents to OPD with swelling of both the feet and breathlessness on climbing the stairs. He also complains the he had to wake up many times because of breathlessness. Which of the following is most likely responsible for this patient's symptoms?
(a) Restrictive cardiomyopathy
(b) Hypertrophic cardiomyopathy
(c) Dilated cardiomyopathy
(d) Pericardial fibrosis
65. Which of the following anticancer drugs can cross blood brain barrier? (DELHI-PG-2008)
(a) Cisplatin
(b) Nitrosourea
(c) Vincristine
(d) Vinblastine
66. Which of the following drugs produce significant nephrotoxicity? (DELHI-PG-2007)
(a) Cisplatin
(b) Carboplatin
(c) Vinblastine
(d) Vincristine
67. Folinic acid counteracts the toxicity of: (DPG 2002)
(a) Doxorubicin
(b) Methotrexate
(c) Cyclophosphamide
(d) Fluorouracil

68. Toxicity of nitrogen mustards can be decreased by: (DPG 2000)
 (a) Amifostine
 (b) Folinic acid
 (c) GM-CSF
 (d) MESNA
69. Which one of the following alkaloids is used as anti-cancer agent? (MPPG 2007) (MPPG 2004)
 (a) Vincristine
 (b) Papaverine
 (c) Ephedrine
 (d) Atropine
70. The antimalignancy drug which is potentially cardio-toxic is: (MPPG 2005) (RJ 2002) (TN 2000)
 (a) Doxorubicin
 (b) Bleomycin
 (c) Fluorouracil
 (d) Dacarbazine
71. "Stocking and glove" neuropathy is seen in: (UP 2005)
 (a) Vinblastine
 (b) Paclitaxel
 (c) Etoposide
 (d) Mitoxantrone
72. Which of the following anti-cancer drug is NOT 'S'-phase specific? (MH 2008)
 (a) Methotrexate
 (b) Mercaptopurine
 (c) Ifosfamide
 (d) Thioguanine
73. All are alkylating agents except: (Bihar 2005)
 (a) Cyclophosphamide
 (b) Lomustine
 (c) Busulfan
 (d) Zalcitabine
74. Cisplatin does not cause: (AP 2003)
 (a) Cardiomyopathy
 (b) Nephrotoxicity
 (c) Neuropathy
 (d) Tinnitus
75. Cyclophosphamide can cause: (AP 2003)
 (a) Hemorrhagic cystitis
 (b) Cardiomyopathy
 (c) Neuropathy
 (d) Convulsions
76. Which of the following is not an early adverse effect of methotrexate? (Kolkata 2009)
 (a) Hepatic fibrosis
 (b) Myelosuppression
 (c) Nausea
 (d) Stomatitis
77. Which of the following is not an antineoplastic antibiotic? (Kolkata 2009)
 (a) Actinomycin D
 (b) Doxorubicin
 (c) Bleomycin
 (d) Spiramycin
78. Leucovorin rescue is related to: (Kolkata 2006)
 (a) Methotrexate toxicity
 (b) Cyclophosphamide toxicity
 (c) Oncovin toxicity
 (d) Cisplatin toxicity
79. Which of the following causes peripheral neuritis? (Kolkata 2007)
 (a) Methotrexate
 (b) Vincristine
 (c) Busulfan
 (d) Cyclophosphamide
80. Alkylating agents include: (PGI June, 2002)
 (a) Doxorubicin
 (b) Chlorambucil
 (c) Vinblastine
 (d) Busulfan
 (e) Methotrexate

NEW DRUGS AND MISCELLANEOUS

81. Which of the following is used to treat hormone-responsive breast cancer? (AIIMS May, 2012)
 (a) Adriamycin
 (b) Clomiphene citrate
 (c) Diethylstilbestrol
 (d) Tamoxifen
82. Which of the following is a radioprotector? (AI 2012)
 (a) Colony stimulating factor
 (b) Amifostine
 (c) Cisplatin
 (d) Methotrexate
83. Use of tamoxifen in carcinoma of breast patients does not lead to the following side effects: (AIIMS May 2011)
 (a) Thromboembolic events
 (b) Endometrial carcinoma
 (c) Cataract
 (d) Cancer in opposite breast
84. Thalidomide was once used for treating emesis of pregnancy. Later it was withdrawn from market due to side effects. But it was reintroduced for certain indications like multiple myeloma. All of the following are side effects of thalidomide except: (AI 2011)
 (a) Hypothyroidism
 (b) Diarrhea
 (c) Teratogenicity
 (d) Deep Vein Thrombosis

85. All are true about Erlotinib except: (AI 2011)
 (a) Used in non small cell carcinoma of lung
 (b) It is a small molecule tyrosine kinase inhibitor acting as EGFR antagonist
 (c) Food decreases absorption
 (d) It causes skin rashes and diarrhea
86. Thalidomide is used in all of the following except: (AIIMS May 2010) (AIIMS May 2009)
 (a) HIV associated peripheral neuropathy
 (b) HIV associated aphthous (mouth) ulcers
 (c) Behcet syndrome
 (d) Erythema nodosum leprosum
87. All of the following are true about thalidomide except:
 (a) Used in pregnancy as anti-emetic but withdrawn due to teratogenicity (AI 2010)
 (b) Can be used in multiple myeloma as primary treatment as well as in refractory disease
 (c) Causes euphoria and diarrhea
 (d) Can be used in erythema nodosum leprosum
88. Which of the following drug acts by inhibiting tyrosine kinase activated by EGF receptor as well as HER2?
 (a) Imatinib (AI 2010)
 (b) Gefitinib
 (c) Erlotinib
 (d) Lapatinib
89. Tyrosine kinase inhibitors are first line treatment in:
 (a) Gastrointestinal stromal tumors (AI 2010)
 (b) Receptor mediated neuroendocrine tumors
 (c) Breast cancer
 (d) Renal cell carcinoma
90. Cetuximab (an EGFR antagonist) can be used in:
 (a) Palliation in head and neck cancer (AIIMS May 2009)
 (b) Anal canal carcinoma
 (c) Gastric carcinoma
 (d) Lung carcinoma
91. Amifostine is protective to all EXCEPT: (AI 2009)
 (a) Salivary glands
 (b) Skin
 (c) CNS
 (d) GIT
92. Imatinib is used in the treatment of? (AIIMS May 2008)
 (a) Chronic myelomonocytic leukemia
 (b) Myelodysplastic syndrome
 (c) Acute lymphoid leukemia
 (d) Gastro intestinal stromal tumors
93. Rituximab is used in all EXCEPT: (AIIMS May 2008)
 (a) Non Hodgkin lymphoma
 (b) Paroxysmal nocturnal hemoglobinuria
 (c) Rheumatoid arthritis
 (d) Systemic lupus erythematosus
94. A 56 year old female presented with breast carcinoma and she was prescribed herceptin (trastuzumab). Which of the following statements regarding this drug is true? (AIIMS Nov 2008)
 (a) It is an antibody produced entirely from mouse containing no human component.
 (b) It is a monoclonal antibody produced by injecting her-2 antigen.
 (c) It is a polyclonal antibody
 (d) It is a monoclonal antibody containing only human component
95. Thalidomide, used for multiple myeloma, is:
 (a) Associated with diarrhea (DPG 2009)
 (b) Characterized by enantiomeric interconversions
 (c) Metabolized extensively by hepatic CYP system
 (d) Safe for use in pregnant females
96. Which of the following anticancer drugs acts by hypomethylation? (AI 2007)
 (a) Gemcitabine
 (b) 5-FU
 (c) Decitabine
 (d) Homoharringtonine
97. All the following are hormonal agents used against breast cancer EXCEPT: (AI 2004)
 (a) Letrozole
 (b) Exemestane
 (c) Taxol
 (d) Tamoxifen
98. Gemcitabine is effective in: (AI 2002)
 (a) Head and neck cancers
 (b) Pancreatic cancer
 (c) Small-cell lung cancer
 (d) Soft tissue sarcoma
99. Arsenic is useful in the treatment of: (AIIMS May, 2007)
 (a) Acute promyelocytic leukemia
 (b) Myelodysplastic syndrome
 (c) Transient myeloproliferative disorder
 (d) All of the above
100. Mechanism of action of imatinib mesylate is: (AIIMS May, 2007)
 (a) Increase in metabolism of P glycoprotein
 (b) Blocking the action of P glycoprotein
 (c) Blocks the action of chimeric fusion protein of bcr-abl
 (d) Non-competitive inhibition of ATP binding site
101. The drug imatinib acts by the inhibition of:
 (a) Tyrosine kinase (AIIMS May, 2006)
 (b) Glutathione reductase
 (c) Thymidylate synthetase
 (d) Protein kinase
102. The new drug pemetrexed useful in breast cancer belongs to which of the following category of the drugs? (AIIMS Nov, 2005)
 (a) Antitumor agent
 (b) Alkylating agent
 (c) Hormonal agent
 (d) Antimetabolite

103. Phocomelia is due to teratogenic effect of: (DPG 2002)
 (a) Thalidomide
 (b) Chlorpromazine
 (c) Methotrexate
 (d) Carbamazepine
104. Drug that is radioprotective is: (RJ 2003)
 (a) Paclitaxel
 (b) Vincristine
 (c) Etoposide
 (d) Amifostine
105. Rituximab is used in: (DELHI-PG-2007)
 (a) Hodgkin's disease
 (b) Acute myeloid leukemia
 (c) Non-Hodgkin lymphoma
 (d) Multiple myeloma
112. Treatment of choice for chronic myeloid leukemia is: (AI 2008)
 (a) Imatinib
 (b) Hydroxyl-urea
 (c) Interferon-alpha
 (d) Cytarabine
113. Which is the most active single chemotherapeutic agent in the treatment of leiomyosarcoma? (AI 2004)
 (a) Adriamycin
 (b) Daunorubicin
 (c) Methotrexate
 (d) Cisplatin
114. A 35 yr old patient is having carcinoma lung with a past history of lung disease. Which of the following drugs should not be given? (AI 2000)
 (a) Vinblastine
 (b) Bleomycin
 (c) Mithramycin
 (d) Adriamycin
115. Which of the following immunosuppressants is not used for the treatment of cancers?
 (a) Cyclophosphamide
 (b) Cyclosporine
 (c) Methotrexate
 (d) 6- Mercaptopurine
116. Which of the following drugs is not used in prostate carcinoma?
 (a) Finasteride
 (b) Diethylstilbesterol
 (c) Testosterone
 (d) Flutamide
117. Sterility is caused by:
 (a) Vinca alkaloids
 (b) Alkylating agents
 (c) Antimetabolites
 (d) Actinomycin D
118. Neoadjuvant chemotherapy is used in all except: (DPG 2010)
 (a) Esophageal carcinoma
 (b) Breast carcinoma
 (c) Thyroid carcinoma
 (d) Non-small cell carcinoma of lung
119. Chemotherapy is not useful in: (AP 2002)
 (a) Chondrosarcoma
 (b) Wilm's tumor
 (c) Choriocarcinoma
 (d) All
120. All cause myelosuppression except: (Kolkata 2005)
 (a) Docetaxel
 (b) Vincristine
 (c) Methotrexate
 (d) Irinotecan
106. Which of the following drug is used for the treatment of sickle cell anemia? (AIIMS May 2011)
 (a) Hydroxyurea
 (b) Cisplatin
 (c) Paclitaxel
 (d) Carboplatin
107. Which of the following drug is used in the treatment of estrogen dependent breast carcinoma? (AIIMS Nov 2010)
 (a) Tamoxifen
 (b) Methotrexate
 (c) Paclitaxel
 (d) Adriamycin
108. Drug locally used for tracheal stenosis is: (AI 2010)
 (a) Mitomycin C
 (b) Doxorubicin
 (c) Bleomycin
 (d) Clindamycin
109. In treatment of osteosarcoma, all of the following are used EXCEPT: (AI 2009)
 (a) High dose methotrexate
 (b) Cyclophosphamide
 (c) Vincristine
 (d) Doxorubicin
110. Which of the following drugs is used for the treatment of refractory histiocytosis? (AIIMS Nov 2008)
 (a) High dose methotrexate
 (b) High dose cytarabine
 (c) Cladribine
 (d) Fludarabine
111. A patient on treatment for leukemia, develops chest pain, pulmonary infiltrates and pleural effusion. The likely cause is: (DPG 2009)
 (a) Daunorubicin
 (b) Hydroxyurea
 (c) Cytarabine
 (d) Tretinoin

121. Proliferation independent agents include all the following except: (Karnataka 2002)
- Vincristine
 - Carmustine
 - Melphalan
 - Cyclophosphamide
122. People with high risk for development of breast cancer should be treated by prophylactic administration of: (Karnataka 2002)
- Tamoxifen
 - Aminoglutethimide
 - Diethylstilbestrol
 - Flutamide
123. Which of the following is widely used in the management of carcinoma breast? (DPG 2007)
- Actinomycin-D
 - Bleomycin
 - Doxorubicin
 - Dacarbazine
124. Allopurinol potentiates action of: (DPG 2002)
- Azathioprine
 - Busulfan
 - Actinomycin
 - Procarbazine

RECENT QUESTIONS ASKED BY NATIONAL BOARD

- Which of the following anticancer drugs is not derived from plants?
 - Irinotecan
 - Doxorubicin
 - Paclitaxel
 - Etoposide
- Resistance to methotrexate develops due to ?
 - Rapid cancer cell multiplication
 - Deficiency of thymidylate kinase
 - Deficiency of thymidylate synthetase
 - Increased production of dihydrofolate reductase
- All are true regarding sunitinib except -
 - It inhibits tyrosine kinase
 - It is used for renal cell carcinoma
 - It is used for the treatment of GIST
 - It is excreted primarily in urine
- About vinca alkaloids, true is -
 - Inhibits mitotic spindle
 - Enhances polymerization of tubulin
 - Inhibits topoisomerase I
 - Inhibits topoisomerase II
- Mesna is used in -
 - Hemorrhagic cystitis
 - Acute promyelocytic leukemia
 - Serous otitis media
 - Polycythemia vera
- Finasteride is a:
 - 5- α reductase inhibitor
 - Phosphodiesterase inhibitor
 - Alpha blocker
 - Androgen receptor blocker
- Which of the following anti-neoplastic drugs SHOULD NOT be given by rapid IV infusion ?
 - Cyclophosphamide
 - Cisplatin
 - Bleomycin
 - Cytosine arabinoside
- Mechanism of action of vincristine is -
 - Tubulin inhibitor
 - Antimetabolite
 - Adenylate cyclase inhibitor
 - Anti folate
- Which of the following antineoplastic and immunosuppressant drugs is a dihydrofolate reductase inhibitor?
 - Methotrexate
 - Adriamycin
 - Vincristine
 - Cyclophosphamide
- The drug of choice in choriocarcinoma is:
 - Methotrexate
 - Actinomycin-D
 - Vincristine
 - 6-Thioguanine
- Microtubule formation is inhibited by:
 - Paclitaxel
 - Vincristine
 - Etoposide
 - Irinotecan
- Imatinib primarily acts by inhibiting:
 - BCR-ABL
 - Tyrosine kinase
 - PGDFR
 - None
- True about Bicalutamide is:
 - Binds to androgen receptor
 - Causes gynaecomastia
 - It can be given as monotherapy in prostatic carcinoma
 - All are true
- Drug of choice for neutropenia due to cancer chemotherapy is:
 - Vitamin B-12
 - IL-11
 - Filgrastim
 - Erythropoietin

15. **Drug not acting on tubulin is:**
 - (a) Bleomycin
 - (b) Colchicine
 - (c) Paclitaxel
 - (d) Vincristine
16. **All drugs are used in treatment of breast carcinoma except:**
 - (a) Tamoxifen
 - (b) Flutamide
 - (c) Cyclophosphamide
 - (d) Letrozole
17. **Which antineoplastic drug has a very high cardiac toxicity?**
 - (a) Bleomycin
 - (b) Actinomycin-D
 - (c) Doxorubicin
 - (d) Mitomycin-C
18. **Regarding trastuzumab, all of the following are true except:**
 - (a) Shows better response in combination with paclitaxel
 - (b) Used in non-metastatic breast cancer
 - (c) Causes upregulation of HER2/neu
 - (d) Do not cause bone marrow toxicity
19. **Methotrexate resistance is due to:**
 - (a) Increased concentrations of intracellular DHFR through gene amplification
 - (b) Failure of efflux pumps
 - (c) Bacterial modification
 - (d) Increased synthesis of poly glutamates
20. **Which of the following is not an antimetabolite?**
 - (a) Methotrexate
 - (b) 5 Fluorouracil
 - (c) Gemcitabine
 - (d) Vincristine
21. **Cyclophosphamide is:**
 - (a) Alkylating agent
 - (b) Antitumor antibiotic
 - (c) Monoclonal antibody
 - (d) Antimetabolites
22. **Most characteristic side effect of adriamycin is:**
 - (a) Nephrotoxicity
 - (b) Neurotoxicity
 - (c) Cardiotoxicity
 - (d) Hemorrhagic cystitis
23. **Mechanism of action of 5-FU is:**
 - (a) Antimetabolite
 - (b) Direct DNA chelating agent
 - (c) Anti-Mitotic
 - (d) Topoisomerase inhibitor
24. **Anticancer drug that causes lung fibrosis is:**
 - (a) Bleomycin
 - (b) Cisplatin
 - (c) Fulvestrant
 - (d) Tamoxifen
25. **Treatment of chronic phase of CML is:**
 - (a) Imatinib
 - (b) Hydroxyurea
 - (c) Interferon
 - (d) Cytarabine
26. **Which of the following is not an alkylating agent?**
 - (a) Chlorambucil
 - (b) Ifosfamide
 - (c) Nitrosourea
 - (d) Cladribine
27. **Ifosfamide belong to which class?**
 - (a) Alkylating agent
 - (b) Antimetabolite
 - (c) Taxanes
 - (d) Antibiotics
28. **Which of the following is not an alkylating agent?**
 - (a) 5-FU
 - (b) Busulfan
 - (c) Cyclophosphamide
 - (d) Melphalan
29. **Pulmonary fibrosis is caused by:**
 - (a) Methotrexate
 - (b) Cyclophosphamide
 - (c) Mercaptopurine
 - (d) Busulfan
30. **Thalidomide acts through:**
 - (a) Inhibiting angiogenesis
 - (b) Inhibiting thymidylate synthase
 - (c) Inhibition of Topo-isomerase I
 - (d) Inhibition of Topo-isomerase II
31. **The chemotherapeutic agent of choice for concurrent chemoradiation in carcinoma cervix is:**
 - (a) Paclitaxel
 - (b) Hydroxyurea
 - (c) 5 FU (fluorouracil)
 - (d) Cisplatin
32. **Medical adrenalectomy is seen with:**
 - (a) Vincristine
 - (b) Vinblastine
 - (c) Mitotane
 - (d) Methotrexate
33. **Which of the following is a highly emetogenic chemotherapy drug:**
 - (a) 5-Fluorouracil
 - (b) Paclitaxel
 - (c) Vincristine
 - (d) Cisplatin

34. Pulmonary fibrosis is side effect associated with the use of:
 (a) Actinomycin
 (b) Bleomycin
 (c) Doxorubicin
 (d) Mithramycin
35. Bleomycin toxicity primarily involves:
 (a) Liver
 (b) Bone marrow
 (c) Skin
 (d) Lungs
36. Which of the following is used to treat methotrexate toxicity:
 (a) Folic acid
 (b) Folinic acid
 (c) Riboflavin
 (d) Cyanocobalamine
37. Peripheral neuropathy as a side effect is caused by which of the following anti cancer drugs:
 (a) Vincristine
 (b) Cyclophosphamide
 (c) Etoposide
 (d) Irinotecan
38. Regimen used in non-Hodgkin's Lymphoma is:
 (a) CHOP
 (b) COPP
 (c) MOPP
 (d) ABVD
39. The combination chemotherapy used in Hodgkin's Lymphoma:
 (a) Adriamycin, Bleomycin, Vincristine, Dacarbazine
 (b) Adriamycin, Bleomycin, Vinblastine, Dacarbazine
 (c) Actinomycin, BCNU, Vincristine, DTIC
 (d) Actinomycin, Bleomycin, Vinblastine, Dacarbazine
40. Which of the following is an inhibitor of dihydrofolate reductase:
 (a) Phenytoin
 (b) Alcohol
 (c) Methotrexate
 (d) Yeast
41. The following are alkylating agents except:
 (a) Cyclophosphamide
 (b) Methotrexate
 (c) Mechlorethamine
 (d) Busulfan
42. Drug useful in breast cancer is:
 (a) Tamoxifen
 (b) Cyproterone
 (c) Testosterone
 (d) Chlorambucil
43. Which of the following drug causes hemorrhagic cystitis?
 (a) Cyclophosphamide
 (b) Cycloserine
 (c) Ciprofloxacin
 (d) Cyclosporine
44. Anti cancer drug causing nephrotoxicity
 (a) Cyclophosphamide
 (b) Busulfan
 (c) Cisplatin
 (d) Procarbazine
45. Medical adrenalectomy is done with:
 (a) Aminoglutethimide
 (b) Methotrexate
 (c) Melphalan
 (d) Flutamide

EXPLANATIONS

- Ans. (b) Laryngotracheal stenosis** (Ref: American College of Chest Physicians, 2008)
 - Application of topical mitomycin C after endoscopic dilation of laryngotracheal stenosis reduces the rate of restenosis.
 - It is also useful for anal carcinoma and superficial bladder cancer.
- Ans. (a) Oral alkylating agent** (Ref: Goodman Gilman 12/e p1687)
Temozolomide is an alkylating agent that can be given orally.
- Ans. (c) Sickle cell anemia** (Ref: Katzung 12/e p645, 989)
Methotrexate is used for the management of:

• Rheumatoid arthritis	• Psoriasis
• Juvenile chronic arthritis	• Psoriatic arthritis
• Ankylosing spondylitis	• Polymyositis
• Dermatomyositis	• Wegener's granulomatosis
• Giant cell arteritis	• Systemic lupus Erythematosus
• Vasculitis	• Graft versus host disease
• Cancers (choriocarcinoma, breast cancer etc.)	

- Ans. (b) Less neurotoxic than cyclophosphamide** (Ref: Goodman and Gilman 12/e p1684)
Ifosfamide is more neurotoxic than cyclophosphamide
 - Mechlorethamine, ifosfamide and cyclophosphamide are examples of nitrogen mustard group of alkylating agents.
 - These are metabolized by cytochrome p450 enzymes.
 - Ifosfamide produces chloroacetaldehyde and acrolein as metabolites. Acrolein results in hemorrhagic cystitis whereas chloroacetaldehyde is responsible for nephrotoxicity.
 - Ifosfamide has same toxicity profile as cyclophosphamide although it causes GREATER platelet suppression, neurotoxicity, nephrotoxicity and hemorrhagic cystitis.
- Ans. (d) Methotrexate** (Ref: Goodman and Gilman, 12/e p85)
Alkalinization of urine speeds the clearance of weakly acidic drugs like aspirin, phenobarbitone, chlorpropamide and methotrexate etc.
- Ans. (a) Bleomycin** (Ref: Katzung, 11/e p953)
Bleomycin is a marrow sparing drug but it causes pulmonary fibrosis and skin toxicity as adverse effects. Another anticancer drug causing pulmonary fibrosis is busulfan.
- Ans (b) Overproduction of DHFRase** (Ref: Goodman and Gilman, 11/e p1336)
Mechanisms of methotrexate resistance
 - Impaired transport of methotrexate into cells
 - Production of altered forms of DHFR that have decreased affinity for the inhibitor
 - Increased concentrations of intracellular DHFR through gene amplification or altered gene regulation
 - Decreased ability to synthesize methotrexate polyglutamates
 - Increased expression of a drug efflux transporter, of the MRP (multidrug resistance protein) class.
- Ans (a) Cyclophosphamide** (Ref: Katzung, 11/e p500)
Cyclophosphamide is a **prodrug** and is activated by hepatic biotransformation to aldophosphamide. One of its degradation products is **acrolein** that is responsible for **hemorrhagic cystitis** (its characteristic adverse effect). This adverse effect can be decreased by vigorous hydration and by the use of mercapto ethane sulfonic acid (**mesna**).
- Ans. (c) Bone Marrow suppression** (Ref: CMDT 2010/1499)
Depression of bone marrow is usually the most significant dose limiting toxicity with cancer chemotherapy.

10. Ans. (c) Eye examination (Ref: CMDT 2010, 1501)

Methotrexate toxicities include:

- Myelosuppression
- Nephrotoxicity
- Hepatotoxicity
- Neurotoxicity (with intrathecal administration and high-dose therapy)
- Photosensitivity
- Pulmonary toxicity
- Multiple drug interactions which may enhance toxicities (avoid aspirin, penicillins, NSAIDs, omeprazole, TMP-SMZ)

11. Ans. (a) Cisplatin (Ref: CMDT 2010/1508)

Cisplatin is the most emetogenic anticancer drug.

12. Ans. (b) Cytarabine (Ref: Katzung 11/e p945)

Cytarabine causes cerebellar ataxia.

13. Ans. (a) 5-Fluorouracil (Ref: Katzung 11/e p945)

5-Fluorouracil is an antimetabolite whereas melphalan, cyclophosphamide and chlorambucil are alkylating agents.

14. Ans. (d) Mesna (Ref: Drug facts and comparisons 2010, 3107)

Anticancer drugs and supportive care agents that can be given orally are:

Cyclophosphamide	Melphalan	Procarbazine
Temozolomide	Busulfan	Chlorambucil
Nitrosoureas (Lomustine, carmustine)	6-Mercaptopurine	Capecitabine
All tyrosine kinase inhibitors (Dasatinib, Erlotinib, Gefitinib, Imatinib, etc.)	Altretamine	Hydroxyurea
Thalidomide and lenalidomide	Testosterone receptor blockers e.g. flutamide	SERMs, e.g. tamoxifen
Aromatase inhibitors e.g. anastrozole	Allopurinol	Leucovorin
Pilocarpine	Mesna	

15. Ans. (c) Capecitabine (Ref: Katzung 10th/889)

5-FU, capecitabine and liposomal doxorubicin can cause hand and foot syndrome. Generally, this disease affects infants and children. Adults with immunodeficiency can also be affected.

16. Ans. (c) Vinblastine (Ref: Katzung 11/e p774)

Vinblastine is a M phase specific vinca alkaloid whereas bleomycin acts selectively on G₁ phase of cell cycle.

17. Ans. (b) Laryngotracheal stenosis (Ref: American College of Chest Physicians, 2008)

- Mitomycin is an anti-tumor antibiotic with alkylating agent like property. It is used in **superficial cancer of urinary bladder and for squamous cell carcinoma of anus**.
- The drug has radiomimetic effects, and also sensitizes hypoxic tumor cells to the effects of hypoxia.
- Application of topical mitomycin C after endoscopic dilation of laryngotracheal stenosis reduces the rate of restenosis.

18. Ans. (a) Type I pneumocyte (Oncologic Emergencies by Sai Ching p92)

Bleomycin causes necrosis of Type I pneumocytes that results in compensatory hyperplasia of type-II pneumocytes. Same kind of injury can also occur in response to radiations. In experimental models, this type of injury has been ameliorated by keratinocyte growth factor.

19. Ans. (c) Actinomycin D (Ref: Harrison 17th/2222)

Drugs causing syndrome of inappropriate ADH (SIADH) secretion

• Vasopressin or desmopressin	• Chlorpropamide
• Oxytocin, high dose	• Vincristine or vinblastine
• Carbamazepine	• Nicotine
• Phenothiazines	• Cyclophosphamide
• Tricyclic antidepressants	• Monoamine oxidase inhibitors
• Serotonin reuptake inhibitors	

20. Ans. (c) Carmustine (Ref: Goodman Gilman 11/e p1330; KDT 6/e p822)

- **Myelosuppression** leading to neutropenia, thrombocytopenia and anemia is seen with most of the **anticancer** drugs.
- The characteristic feature of myelosuppression produced by **carmustine** is that it causes *delayed and prolonged myelosuppression*.

21. Ans. (a) Alkylating Agents (Ref: Principles of Pharmacology, 1st/869; KDT 6/e p819)

Ifosfamide is an alkylating agent.

22. Ans. (a) 5-Fluorouracil (Ref: Lippincott 2nd/382, Dolly's Therapeutic Drugs, 2nd/F-104)

- 5-Fluorouracil is rapidly metabolized in liver to produce biologically inactive metabolites which are eventually converted to carbon dioxide and eliminated by lungs.
- Excretion of 80% of 5-FU can be accounted for by conversion to carbon dioxide within 12 hour of administration though its excretion in urine is only 15%.
- Also note other drugs excreted by lungs are procainamide, procaine and antipyrine.

23. Ans. (b) Increases the polymerization of tubulin (Ref: Katzung 10th/893; KDT 6/e p825)

Taxanes (paclitaxel and docetaxel) act by increasing the polymerization of tubulin whereas vinca alkaloids (vincristine, vinblastine and vinorelbine) cause inhibition of tubulin polymerization. Both of these drugs act by causing the disruption of mitosis and are active in M-phase of cell cycle.

24. Ans. (a) Bleomycin (Ref: Katzung 10th/895, KDT 6/e p826)

- *Bleomycin is a small peptide.....(Katzung)*
- *Bleomycin is a mixture of closely related glycopeptide antibiotics having potent anti-tumor activity.....(KDT)*

25. Ans. (a) Methotrexate (Ref: Katzung 10th/887; KDT 6/e p823)

- Toxicity of methotrexate can be reversed by the administration of 5-formyltetrahydrofolate (leucovorin or citrovorum factor). Folic acid in the diet is in dihydrofolate form. It is ineffective in reversing methotrexate toxicity.

26. Ans. (a) Acute promyelocytic leukemia (Ref: Harrison 17th/389, 447)

All-trans-retinoic acid is used in the treatment of acute promyelocytic leukemia

Treatment of Acute promyelocytic leukemia

- Usually all the cases of AML *other than acute promyelocytic* leukemia are treated with cytarabine + anthracycline.
- But in case of acute promyelocytic leukemia, tretinoin is used for induction.
- When acute promyelocytic leukemia is treated with anthracycline and cytarabine, DIC is induced by the release of granule components of dying tumour cells
- On the other hand, tretinoin produces a complication known as retinoic acid syndrome, which occurs in the first 3 weeks of treatment and is characterized by fever, dyspnea, chest pain, pulmonary infiltrates, pleural and pericardial effusions.
- If the patient is refractory to tretinoin therapy, **arsenic trioxide** is used.

27. Ans. (b) L-asparaginase (Ref: Katzung 11/e p955)

- L-asparaginase causes the breakdown of asparagine and thus interferes with protein synthesis. It can inhibit the production of clotting factors (responsible for cerebral hemorrhage) as well as anti-clotting proteins (can lead to cortical vein thrombosis and other hypercoagulable states).

28. Ans. (a) Vincristine (Ref: Harrison's 17th/2222)

Review of Pharmacology

29. Ans. (a) Osteosarcoma (Ref: Harrison's 17th/612)

- Drugs used for osteosarcoma are:
 - Doxorubicin
 - Ifosfamide
 - Cisplatin
 - High dose methotrexate with leucovorin

30. Ans. (b) Irinotecan (Ref: KDT 6/e p825, 826)

Camptothecin derivatives like topotecan and irinotecan act by inhibiting topoisomerase-I whereas Epipodophyllotoxins (etoposide and teniposide) and anthracyclines (doxorubicin, daunorubicin etc.) act by inhibiting topoisomerase-II.

31. Ans. (d) Flutamide (Ref: KDT 6/e p828)

- Flutamide is an anti-androgen. Most hormonal agents are devoid of bone marrow suppressant effect.
- Alkylating agents, antimetabolites, natural products and other directly cytotoxic agents are myelosuppressants.
- Vincristine and bleomycin are marrow sparing.

32. Ans. (a) Folinic acid enhances the action of methotrexate (Ref: KDT 6/e p823)

- Methotrexate is an antimetabolite that acts by inhibiting DHFRase.
- Its toxicity can be decreased by the administration of folinic acid but not by folic acid.
- It is the *drug of choice* for choriocarcinoma
- It is also used as a *first line DMARD*.
- Other uses include psoriasis and for ectopic pregnancy.
- It is a cell cycle specific drug (S-phase), therefore dividing cells are more sensitive whereas resting cells are resistant to methotrexate.

33. Ans. (c) Ameliorate hemorrhagic cystitis (Ref: KDT 6/e p833)

34. Ans. (a) Methotrexate (Ref: KDT 6/e p823)

Methotrexate is an antimetabolite that acts by inhibiting DHFRase.

35. Ans. (a) Cisplatin (Ref: KDT 6/e p827, 828)

- Cisplatin is a highly emetic and nephrotoxic agent.
- Streptozocin causes destruction of β -cells of pancreas and may result in hyperglycemia.
- Methysergide can cause retroperitoneal fibrosis on long term use.
- Cyclophosphamide can result in hemorrhagic cystitis.

36. Ans. (c) Cisplatin (Ref: KDT 6/e p827, 828; Katzung 10th/886)

- Alkylating agents bind to DNA and has the potential to introduce mutations. Therefore, these agents can cause secondary leukemias. Procarbazine is most important drug implicated in causation of secondary leukemias.
- Cisplatin acts by similar mechanism and can cause leukemia.

37. Ans. (c) It does not cause alopecia (Ref: KDT 6/e p824, 825)

- Vincristine is a vinca alkaloid.
- It is used for the induction of remission in ALL.
- It is a marrow sparing drug but causes peripheral neuropathy, alopecia and SIADH as adverse effects.

38. Ans. (b) Dactinomycin (Ref: Katzung 10th/894)

Anthracyclines and actinomycin-D (dactinomycin) can cause severe radiation toxicity. This is known as *radiation recall syndrome*.

39. Ans. (d) Cyclophosphamide (Ref: KDT 6/e p833)

40. Ans. (a) Anthracycline (Ref: Katzung 10th/893, 894)

Anthracyclines like doxorubicin, daunorubicin, idarubicin and epirubicin are implicated in causing cardiotoxicity. This adverse effect is due to the generation of iron mediated free radicals. Dexrazoxane is a free radical scavenger that can be used to prevent cardiotoxicity due to anthracyclines.

41. Ans. (b) Cancer chemotherapy (Ref: KDT 6/e p833)

Sodium-2-mercapto ethane sulfonic acid (mesna) is used to ameliorate the hemorrhagic cystitis caused by cyclophosphamide and ifosfamide.

42. **Ans. (a) 6-Mercaptopurine** (Ref: KDT 6/e p208)
- Allopurinol is an inhibitor of uric acid synthesis. It acts by inhibiting the enzyme 'xanthine oxidase'. This drug is commonly prescribed to a patient on anticancer therapy because destruction of cells results in increased formation of uric acid.
 - 6-Mercaptopurine is also metabolized by xanthine oxidase. If allopurinol is administered to a patient receiving 6-MP, toxicity may occur due to increased plasma concentration of 6-MP. Therefore if both are given concurrently, dose of 6-MP should be decreased to 25% of the normal.
43. **Ans. (a) Cyclophosphamide; (b) Ifosfamide** (Ref: KDT 6/e p819-820)
44. **Ans. (a) Vincristine; (b) Isotretinoin** (Ref: Goodman & Gilman 9/e p1257 KDT 6/e p824)
- Vincristine is the extract of **Periwinkle plant** (*Vinca rosea*). The extracts of this plant yields: Vincristine, Vinblastine, Vinleurosine, Vinrosidine.
 - Bleomycin is the fermentation product of *Strep. verticillins*.
 - Isotretinoin is 13-cis retinoic acid used in skin cancer, also having a plant source.

45. **Ans. (c) Chlorambucil; (e) Cyclophosphamide** (Ref: KDT 6/e p819-820)

46. **Ans. (b) Actinomycin D; (c) Bleomycin; (d) Mithramycin** (Ref: KDT 6/e p820)

The anticancer antibiotics are:

- **Actinomycin - D** (Dactinomycin)
- **Doxorubicin**
- Daunorubicin (Rubidomycin)
- Mitoxantrone
- Bleomycin
- Mitomycin C
- Mithramycin (plicamycin)

These drugs are obtained from micro-organisms and have prominent antitumour activity.

47. **Ans. (b) Vincristine; (c) Paclitaxel; (d) Colchicine** (Ref: KDT 6/e p824-825)
- Drugs causing metaphase arrest are:
 - Vincristine
 - Vinblastine
 - Paclitaxel
 - Colchicine
 - Griseofulvin interferes with mitosis and result in multinucleated and stunted fungal hyphae. It also cause abnormal metaphase configurations; however it does not cause metaphase arrest. It does not inhibit polymerization of tubulin but somehow disorients microtubules.
48. **Ans. (b) Cytotoxicity resulting from a metabolite that interferes with the production of dTMP** (Ref: KDT 6/e p824)
- 5-Fluorouracil (5-FU) is an antimetabolite. It is a thymidine analogue and acts by conversion to 5'-dUMP. Latter inhibits the formation of dTMP and results in thymineless death of cells.
49. **Ans. (d) Paclitaxel** (Ref: KDT 6/e p830)
- Vinca alkaloids (vincristine, vinblastine and vinorelbine) and taxanes (paclitaxel and docetaxel) act in M-phase of cell cycle.
 - Vinca alkaloids inhibits the formation whereas taxanes inhibit the breakdown of mitotic spindle.
50. **Ans. (d) Methotrexate is a weak acid** (Ref: KDT 6/e p823)
- Methotrexate is a weak acid and is reabsorbed in acidic urinary pH. Higher plasma concentration may result in toxicity. Therefore, to decrease the reabsorption through renal tubules, high urinary pH must be maintained.
51. **Ans. (c) Folic acid reverse its toxic effects** (Ref: KDT 6/e p823)
- Folinic acid (leucovorin) is used to reverse the adverse effect of methotrexate. Folic acid is ineffective. All other statements are true as discussed earlier.
52. **Ans. (d) Inhibition of polymerization of tubulin to form microtubules** (Ref: KDT 6/e p24, 825)
53. **Ans. (d) It is a drug of choice for solid tumors** (Ref: KDT 6/e p824, 825)
- Vincristine is a vinca alkaloid. It acts in M-phase of cell cycle by inhibiting the formation of spindle. It is a marrow sparing drug and causes peripheral neuropathy as a prominent adverse effect. It is used for the treatment of hematological malignancies like Hodgkin's lymphoma and leukemias. It is ineffective against solid tumors.

54. **Ans. (b) It does not cause hyperuricemia** (Ref: KDT 6/e p823, 824)
- All anticancer drugs can result in hyperuricemia by causing the destruction of excess cells.
 - Azathioprine is an immunosuppressant drug that acts by generating 6-MP.
 - 6-MP is metabolized by xanthine oxidase. Its dose should be reduced when allopurinol is given concurrently.
55. **Ans. (c) Adenosine deaminase** (Ref: Katzung 10th/920)
- Pentostatin and cilastatin are not statins i.e. these do not act by inhibiting HMG-CoA reductase.
 - Pentostatin acts by inhibiting adenosine deaminase.
 - It is used for the treatment of hairy cell leukemia.
 - Drug of choice for hairy cell leukemia is cladribine.
56. **Ans. (a) 5-Fluorouracil** (Ref: Katzung 11/e p947)
Capecitabine and 5-FU can cause hand and foot syndrome.
57. **Ans. (c) Blindness** (Ref: KDT 6/e p827, 828)
Cisplatin is the most emetic and nephrotoxic anticancer drug.
58. **Ans. (a) G.I. toxicity** (Ref: KDT 6/e p824; Harrison 16/e p596)
- Diarrhea is the most common adverse effect of 5-FU.
 - It can also cause hand and foot syndrome and bone marrow suppression.
59. **Ans. (b) Vomiting** (Ref: KDT 6/e p827, 828)
Drug of choice for cisplatin induced vomiting is 5HT₃ antagonist like ondansetron.
60. **Ans. (b) Cytarabine** (Ref: Katzung 10th/888)
Cerebellar dysfunction is a prominent and distinctive adverse effect of cytarabine.
61. **Ans. (b) Procarbazine** (Ref: KDT 6/e p827)
62. **Ans. (a) N-acetylcysteine** (Ref: Harrison 18th/697)
N-acetylcysteine is used for paracetamol poisoning whereas slow intravenous infusion and chloride diuresis along with amifostine can limit cisplatin induced nephrotoxicity.
63. **Ans. (b) Mesna** (Ref: Katzung 11/e p941)
The patient described in the question has hemorrhagic cystitis caused by drugs like cyclophosphamide and ifosfamide. Hemorrhagic cystitis during therapy with cyclophosphamide or ifosfamide is caused by the urinary excretion of the toxic metabolite acrolein. This can be prevented by aggressive hydration, bladder irrigation, and administration of mesna, a sulfhydryl compound that binds acrolein in the urine.
64. **Ans. (c) Dilated cardiomyopathy** (Ref: Katzung 11/e p952)
- Anthracyclines (daunorubicin, doxorubicin, epirubicin and idarubicin) can cause severe cardiotoxicity manifesting as dilated cardiomyopathy and arrhythmias.
 - The anthracycline chemotherapeutic agents (doxorubicin, daunorubicin, epirubicin and idarubicin) form free radicals in the myocardium. Their most severe side effect is a cumulative dose-related dilated cardiomyopathy. It presents with symptoms of left and right ventricular CHF.
65. **Ans. (b) Nitrosourea** (Ref: KDT 6/e p822)
Nitrosoureas like carmustine, lomustine and semustine can cross blood brain barrier and thus are used for treatment of gliomas.
66. **Ans. (a) Cisplatin** (Ref: KDT 6/e p827, 828)
Cisplatin is most emetogenic and highly nephrotoxic anticancer drug.
67. **Ans. (b) Methotrexate** (Ref: KDT 6/e p823)
68. **Ans. (c) GM-CSF** (Ref: Katzung 10th/538)
Nitrogen mustards like mechlorethamine cause bone marrow suppression as major adverse effect. Leucopenia can be reversed by sargramostim (recombinant GM-CSF). All nitrogen mustards do not cause hemorrhagic cystitis, therefore mesna is not the answer.

69. Ans. (a) Vincristine (Ref: KDT 6/e p824)
70. Ans. (a) Doxorubicin (Ref: KDT 6/e p826)
71. Ans. (b) Paclitaxel (Ref: Katzung 11/e p950)
72. Ans. (c) Ifosfamide (Ref: Katzung 11/e p938, KDT 6/e p827)
73. Ans. (d) Zalcitabine (Ref: KDT 6/e p819-820)
74. Ans. (a) Cardiomyopathy (Ref: KDT 6/e p828)
75. Ans. (a) Hemorrhagic cystitis (Ref: KDT 6/e p822)
76. Ans. (a) Hepatic fibrosis (Ref: Katzung 11/945) KDT 6/823)
77. Ans. (d) Spiramycin (Ref: KDT 6/e p826)
78. Ans. (a) Methotrexate toxicity (Ref: KDT/6/e p823)
79. Ans. (b) Vincristine (Ref: KDT 6/e p825)
80. Ans. (b) Chlorambucil; (d) Busulfan (Ref: KDT 6/e p819-820)
81. (d) Tamoxifen (Ref: KDT 6/e p304)
- Estrogen receptor positive breast cancers are amenable to treatment with anti-estrogen drugs like
- SERMs: Tamoxifen, Toremifene and Toremifene
 - SERDs: Fulvestrant
 - Aromatase inhibitors: Letrozole, Anastrozole, Exemestane

82. Ans (b) Amifostine (Ref: KK Sharma 2/e p858)

Amifostine is used for reducing the toxicities of anticancer drugs. It is indicated for:

1. Cisplatin induced nephrotoxicity.
2. Radiation induced xerostomia

Amifostine is used to prevent radiation induced toxicity whereas colony stimulating factors are used for management of chemotherapy induced leucopenia.

- Amifostine scavenges free radicals produced by radiation and inactivates active species through formation of thioether conjugates. Amifostine has been approved by the USA FDA as a radioprotector. It is also known as "Ethyol".
- Since amifostine acts by scavenging the free radicals, it must be given before the radiation. It is of no use in radiation protection after the event.

83. Ans (d) Cancer in opposite breast (Ref: Goodman and Gilman 12/e p1179, CMDT 2010, 1505)

- Tamoxifen is a SERM that acts as antagonist at estrogen receptors in the breast. It decreases the risk of contralateral breast cancer and is approved for primary prevention of breast cancer in women at high risk.

Adverse effects of Tamoxifen include:

• Hot flushes	• Vaginal discharge or bleeding
• Menstrual irregularities	• Thromboembolic events (rare)
• Endometrial hyperplasia	• Cataracts
• Hepatotoxicity	• Tumor flare

84. Ans. (b) Diarrhea (Ref: KDT, 6/e p85, Katzung, 11/e p973, Goodman and Gilman, 11/e p897)

- Thalidomide causes constipation and not diarrhea
- The most common adverse effects reported in cancer patients are sedation and constipation, while the most serious one is treatment-emergent peripheral sensory neuropathy

85. Ans. (c) Food decreases absorption (Ref: Katzung, 11/e p954-955, Goodman and Gilman, 12/e p1736)

- Erlotinib is an EGFR tyrosine kinase inhibitor.
- It is indicated for treatment of non-small cell lung carcinoma and **pancreatic carcinoma** (with gemcitabine).
- **Food increases the absorption** of Erlotinib by 100%.
- It is metabolized by CYP3A4 enzyme system.
- Acneiform **skin rash, diarrhea, anorexia and fatigue** are the most common adverse effects of this drug.

86. **Ans. (a) HIV associated peripheral neuropathy** (Ref: CMDT-2010/1510)
- 'Thalidomide cause neuropathy as an adverse effect, therefore should not be used in HIV neuropathy'
 - Thalidomide was banned due to its teratogenic potential (phocomelia) but has been re-introduced due to its immunomodulatory and anti-cancer properties. It has been approved for multiple myeloma and erythema nodosum leprosum and is being tried for myelodysplastic syndrome, melanoma, Behcet disease, HIV associated ulcers and graft versus host disease.
87. **Ans. (c) Causes euphoria and diarrhea** (Ref: Katzung 11/e p973-974)
'Thalidomide cause constipation and not diarrhea'
88. **Ans. (d) Lapatinib** (Ref: CMDT- 2010/668)
- Lapatinib is a new oral drug that acts as a dual HER-2 and EGF-receptor tyrosine kinase inhibitor. It is recently approved for trastuzumab-resistant HER-2/neu positive metastatic breast cancer in combination with capecitabine
 - Imatinib inhibits tyrosine kinase activated due to abl-bcr gene fusion and is the drug of choice for CML and GIST.
 - Gefitinib and Erlotinib are inhibitors of EGF receptor induced tyrosine kinase. These are indicated for non-small cell lung carcinoma.
89. **Ans. (a) Gastrointestinal stromal tumors** (Ref: CMDT-2010/1474)
- Tyrosine kinase inhibitor, imatinib is the drug of choice for GIST. Resistant tumors may respond to another tyrosine kinase inhibitor, sunitinib.
 - GIST originates from interstitial cells of Cajal.
 - Most common site of GIST is stomach followed by small intestine.
 - About 90% of GIST have mutation in KIT, a receptor tyrosine kinase.
 - About 90% of stromal tumors stain positively for CD117.
90. **Ans. (a) Palliation in head and neck cancer** (Ref: Harrison 17th/502,550)
Cetuximab is a monoclonal antibody against EGF receptor. It is used for the treatment of **refractory colorectal cancer** and **squamous cell carcinoma of head and neck**.
91. **Ans (c) CNS** (Ref: Katzung 9/e p1309; Harrison 17th/671)
Amifostine (**WR-2721**) is an organic thiophosphate analog designed to produce preferential cytoprotection of normal tissues from cytotoxic therapies. The preferential cytoprotection is due to the activation of amifostine by membrane-bound alkaline phosphatase to the free thiol, **WR-1065**, the active form. This activation occurs to a greater extent in normal tissue sites than in tumor cells. The free thiol acts as a potent scavenger of free radicals and superoxide anions to inactivate the reactive species of cisplatin and radiation therapy. At present, this agent is approved to reduce the incidence of nephrotoxicity in ovarian cancer and non-small cell lung cancer in conjunction with cisplatin-based chemotherapy and to reduce the incidence of xerostomia in patients undergoing radiation therapy for head and neck cancer.
- From this discussion, we can conclude that amifostine is protective to salivary glands (reduces xerostomia) and GIT (prevents esophagitis). Its xerostomia preventing action can also be considered to be protective to skin.
92. **Ans. (d) Gastrointestinal stromal tumors** (Ref: KDT 6/e p828)
- **Imatinib is a competitive inhibitor of tyrosine kinase.**
 - **Imatinib shows remarkable therapeutic benefit in patients with:**
 - CML (BCR-ABL)
 - GIST (KIT mutation positive)
 - HES (Hypereosinophilic syndrome)
 - Dermatofibrosarcoma protuberans

Note: CMML is a type of myelodysplastic syndrome where azacytidine is used.

93. **Ans. (b) Paroxysmal nocturnal hemoglobinuria** (Ref: Goodman Gilman 11/e p1376)
- Rituximab is a chimeric antibody that target **CD 20** B cell antigen.
 - **Use of Rituximab**
 - Lymphoma B cell lymphomas
 - Low grade lymphomas
 - Mantle cell lymphomas
 - Relapsed aggressive B cell lymphomas
 - Chronic lymphocytic leukemia
 - SLE (Harrison 17th/2082 Fig. 313.3)

- **Rheumatoid arthritis** (Rituximab has been approved for the treatment of active rheumatoid arthritis when combined with methotrexate)
94. **Ans. (b) It is monoclonal antibody produced by injecting her-2 antigen.** (Ref: *Principles of Pharmacology*, 1st/882; *Katzung 11/e p978*)
Trastuzumab is a humanized (contain almost all human component except the complementarity determining region of variable chain) monoclonal antibody used against breast carcinoma. It is targeted against the protein of her-2/neu gene.
95. **Ans. (b) Characterized by enantiomeric interconversions** (Ref: *Goodman & Gilman 11/e p1370, 1371, Katzung 10th/919*)
- Thalidomide was used for morning sickness but later withdrawn due to severe teratogenic effects (phocomelia).
 - It is not extensively metabolized by microsomal enzymes.
 - Two isomers of thalidomide; S (teratogenic) and R (sedative) are present. But giving R isomer do not protect against teratogenic potential due to enantiomeric interconversions in the body.
 - It is now being used for multiple myeloma and has dose limiting adverse effect of peripheral neuropathy. It can also result in constipation.
96. **Ans. (c) Decitabine** (Ref: *Harrison's 17th/671*)
- DNA hypomethylating agents are used in the treatment of myelodysplastic syndromes. The agents in this group include:
 - Azacytidine
 - Decitabine
 - Homoharringtonine is a plant alkaloid that acts by inhibiting protein synthesis (inhibits peptide bond formation). It is used in CML.
97. **Ans. (c) Taxol** (Ref: *Katzung 10th/897, 903, 904; KDT 6/e p305, 306, 328*)
- Letrozole, anastrozole and exemestane are aromatase inhibitors useful for the treatment of tamoxifen resistant breast carcinoma.
 - Tamoxifen is a SERM. It is also used for breast cancer.
 - Taxol is commonly used term for paclitaxel. It is a cytotoxic drug (not hormonal).
98. **Ans. (b) Pancreatic cancer** (Ref: *Katzung 10th/891*)
Gemcitabine is an antimetabolite that is the drug of choice for pancreatic cancers.
99. **Ans. (a) Acute promyelocytic leukemia** (Ref: *Principles of pharmacology by HL Sharma and KK Sharma 2007, 576; Harrison 17th/389*)
- As_2O_3 promote the differentiation of APL cells and promote apoptosis by upregulating the genes involved in apoptosis. It is used for the treatment of acute promyelocytic leukemia.
100. **Ans. (c) Blocks the action of chimeric fusion protein of bcr-abl.** (Ref: *Principles of pharmacology by HL Sharma and KK Sharma 2007, 876, KDT 6/e p828*)
- In CML, fusion of bcr and abl genes result in the activation of a tyrosine kinase that is involved in the proliferation of myeloid cell lines.
 - Imatinib acts by inhibiting this tyrosine kinase by competitive inhibition of ATP-binding site.
 - Gefitinib and erlotinib are another tyrosine kinase inhibitors that are useful in non-small cell carcinoma of lung.
101. **Ans. (a) Tyrosine kinase** (Ref: *KDT 6/e p828*)
Imatinib acts by inhibiting the enzyme tyrosine kinase (activated by fusion of abl-bcr genes). It is useful in CML.
102. **Ans. (d) Antimetabolite** (Ref: *Katzung 10th/887*)
Pemetrexed acts by inhibiting DHFRase. It is an antimetabolite similar to methotrexate.
103. **Ans. (a) Thalidomide** (Ref: *KDT 6/e p84*)
104. **Ans. (d) Amifostine** (Ref: *internet*)
105. **Ans. (c) Non-Hodgkin lymphoma** (Ref: *Katzung 10th/589*)
Rituximab is a monoclonal antibody used for the treatment of non-Hodgkin lymphoma.
106. **Ans. (a) Hydroxyurea** (Ref: *Harrison 17th/638-639*)
- The most significant advance in the therapy of sickle cell anemia has been the introduction of hydroxyurea as a mainstay of therapy for patients with severe symptoms. Hydroxyurea (10–30 mg/kg per day) increases fetal hemoglobin and may also exert beneficial effects on RBC hydration, vascular wall adherence, and suppression of the granulocyte and reticulocyte counts.
 - The antitumor drug, 5-azacytidine, was the first agent found to elevate HbF. It never achieved widespread use because

of concerns about acute toxicity and carcinogenesis. However, low doses of the related agent, 5-deoxyazacytidine (decitabine) can elevate HbF with acceptable toxicity.

- Bone marrow transplantation can provide definitive cure but is known to be effective and safe only in children.

107. Ans. (a) Tamoxifen (Ref: *Katzung, 11/e p716, Goodman and Gilman, 11/e p1422*)

Tamoxifen is a selective estrogen receptor modulator and has antagonist action on estrogen receptors in breast whereas agonistic action at estrogen receptors in bone. It is indicated for treatment of breast carcinoma in patient with estrogen receptor positive breast tumors.

108. Ans. (a) Mitomycin-C (Ref: *J. Molecular Biology 2006; 360: 398-408*)

Mitomycin can be used for treatment of:

By intra-venous route	By Local route
• Esophageal carcinoma	• Superficial bladder cancer
• Breast cancer	• Eye surgery
	• Esophageal and tracheal stenosis

109. Ans. (c) Vincristine (Ref: *Katzung 10th/891*)

- Though surgery is the form of primary treatment in osteosarcoma but etoposide, cyclophosphamide, cisplatin and doxorubicin have been used.
- High dose methotrexate has been the drug of choice and is the only FDA approved agent for this condition.

110. Ans. (c) Cladribine (Ref: *Nelson 18th/2161*)

- Histiocytosis encompasses a group of diverse disorders with the common primary event of the accumulation and infiltration of monocytes, macrophages, and dendritic cells in the affected tissues.
- Localized skin lesions, especially in infants, can spontaneously regress. If treatment is required, topical corticosteroids may be tried. As a single agent, cyclosporine has been used in pretreated patients with advanced Langerhan Cell Histiocytosis. Most chemotherapy agents for the treatment of Langerhan Cell Histiocytosis are used in combination of **cytarabine arabinoside (Ara-C), vincristine, and prednisolone**.
- When patients do not have an early (ie, by 6 wk of therapy) response to vinblastine, corticosteroids, methotrexate, 6-mercaptopurine, or even etoposide, alternate therapies should be administered. Several studies demonstrated notable activity of cladribine. Cladribine is both lympholytic and monolytic, making it a potentially ideal drug to use in Langerhan Cell Histiocytosis.

111. Ans (d) Tretinoin (Ref: *Katzung 10th/899; KDT 6/e p853*)

Tretinoin causes chest pain, pleuritis, pulmonary infiltrates and pleural effusion. It is a known human teratogen. Daunorubicin and doxorubicin cause cardiotoxicity manifested as arrhythmias and CHF.

112. Ans. (a) Imatinib (Ref: *CMDT 2010/462*)

113. Ans. (a) Adriamycin (Ref: *KDT 6/e p828*)

- Doxorubicin (adriamycin) and daunorubicin are anthracycline derivatives.
- Daunorubicin is mainly used for hematological malignancies (acute leukemia) whereas doxorubicin is used for solid tumors and soft tissue sarcomas.

114. Ans. (b) Bleomycin (Ref: *KDT 6/e p827*)

Bleomycin can cause pulmonary fibrosis. It should be avoided in patients of lung disease.

115. Ans. (b) Cyclosporine (Ref: *KDT 6/e p839, 840*)

- All antimetabolites can be used as anticancer drugs except azathioprine.
- Cyclosporine acts by inhibiting the transcription of IL-2 gene. It has no anti-cancer property.

116. Ans. (c) Testosterone (Ref: *KDT 6/e p291*)

- Prostatic carcinoma results due to excessive testosterone.
- Testosterone is converted to dihydrotestosterone (DHT) by 5- α -reductase. DHT is responsible for prostatic growth.
- Flutamide is an androgen receptor antagonist whereas finasteride is 5 α reductase inhibitor. Both of these drugs can be used in prostatic cancer.
- Diethylstilbesterol is an estrogen. It will cause feedback inhibition of pituitary and hypothalamus. Decreased secretion of GnRH (LH and FSH) results in the decrease in testosterone. It was also used previously for prostatic carcinoma.

117. Ans. (b) Alkylating agents (Ref: *Goodman & Gilman 11/e p326, 1327*)

Sterility and secondary leukemias are distinctive adverse effects of alkylating agents.

118. Ans. (c) **Thyroid carcinoma** (Ref: CMDT-2010/667,1456,1469,1625)
- "Thyroid carcinomas are extra-ordinarily resistant to chemotherapy"
 - Neoadjuvant chemotherapy is administration of chemotherapy before surgery or radiation therapy whereas adjuvant chemotherapy is used after surgery/radiation.
- **Neoadjuvant chemotherapy is used in:**
 - Bladder cancer
 - Breast cancer
 - Colorectal cancer
 - Esophageal cancer
 - Gastric adenocarcinoma
 - Non-small cell lung cancer
119. Ans. (a) **Chondrosarcoma** (Ref: KDT 6/e p832)
120. Ans. (b) **Vincristine** (Ref: KDT 6/e p825)
121. Ans. (a) **Vincristine** (Ref: KDT 6/e p821, 882)
Proliferation independent means cell cycle nonspecific agents.
122. Ans. (a) **Tamoxifen** (Ref: KDT 6/e p304)
123. Ans. (c) **Doxorubicin** (Ref: CMDT 2010, 1466-1468)
124. Ans. (a) **Azathioprine** (Ref: KDT 6/e p208)
Allopurinol inhibits degradation of azathioprine and 6-mercaptopurine and thus potentiates their action.

ANSWERS OF RECENT QUESTIONS ASKED BY NATIONAL BOARD

1. Ans (b) **Doxorubicin** (Ref: KDT 7/e p858)
2. Ans (d) **Increased production of dihydrofolate reductase** (Ref: CMDT 2015/1638)
3. Ans (d) **It is excreted primarily in urine** (Ref: CMDT 2015 /1607)
4. Ans (a) **Inhibits mitotic spindle** (Ref: KDT 7/e p865)
5. Ans (a) **Hemorrhagic cystitis** (Ref: KDT 7/e p860)
6. Ans (a) **5- α reductase inhibitor** (Ref: KDT 7/e p302)
7. Ans (b) **Cisplatin** (Ref: KDT 7/e p861)
8. Ans (a) **Tubulin inhibitor** (Ref: KDT 7/e p865)
9. Ans. (a) **Methotrexate** (Ref: KDT 6/e p823)
10. Ans. (a) **Methotrexate** (Ref: KDT 6/e p823)
11. Ans. (b) **Vincristine** (Ref: KDT 7/e p 865)
12. Ans. (b) **Tyrosine kinase** (Ref: KDT 7/e p)
 - Imatinib inhibits tyrosine kinase linked with
 - abl-bcr fusion
 - PDGF receptor
 - c-kit receptor
13. Ans. (d) **All are true** (Ref: Goodman Gilman 7/e p1766)
14. Ans. (c) **Filgrastim** (Ref: KDT 7/e p876)
15. Ans. (a) **Bleomycin** (Ref: KDT 7/e p868)
16. Ans. (b) **Flutamide** (Ref: CMDT 2014 p715-717)
17. Ans. (c) **Doxorubicin** (Ref: KDT 7/e p867)
18. Ans. (c) **Causes upregulation of HER2/neu** (Ref: CMDT 2014, p716)
19. Ans. (a) **Increased concentrations of intracellular DHFR through gene amplification** (Ref: Goodman Gilman 12/e p1820)

20. Ans. (d) Vincristine (Ref: KDT 7/e p858)
21. Ans. (a) Alkylating agent (Ref: KDT 7/e p858)
22. Ans. (c) Cardiotoxicity (Ref: KDT 7/e p867)
23. Ans. (a) Antimetabolite (Ref: KDT 7/e p858)
24. Ans. (a) Bleomycin (Ref: KDT 7/e p868)
25. Ans. (a) Imatinib (Ref: KDT 7/e p869)
26. Ans. (d) Cladribine (Ref: KDT 7/e p858)
27. Ans. (a) Alkylating agent (Ref: KDT 7/e p858)
28. Ans. (a) 5-FU (Ref: KDT 7/e p858)
29. Ans. (d) Busulfan (Ref: KDT 7/e p86)
30. Ans. (a) Inhibiting angiogenesis (Ref: Goodman Gilman 12/e p1741)
31. Ans. (d) Cisplatin (Ref: CMDT 2014/ p736)
32. Ans. (c) Mitotane (Ref: Goodman and Gilman 12/e p1719)
33. Ans. (d) Cisplatin (Ref: KDT 7/e p861)
34. Ans. (b) Bleomycin (Ref: KDT 7/e p868)
35. Ans. (d) Lungs (Ref: KDT 7/e p868)
36. Ans. (b) Folinic acid (Ref: KDT 7/e p863)
37. Ans. (a) Vincristine (Ref: KDT 7/e p865)
38. Ans. (a) CHOP (Ref: KDT 7/e p875)
39. Ans. (a) Adriamycin, Bleomycin, Vincristine, Dacarbazine (Ref: KDT 7/e p875)
40. Ans. (c) Methotrexate (Ref: KDT 7/e p862)
41. Ans. (b) Methotrexate (Ref: KDT 7/e p858)
42. Ans. (a) Tamoxifen (Ref: KDT 7/e p872)
43. Ans. (a) Cyclophosphamide (Ref: KDT 7/e p860)
44. Ans. (c) Cisplatin (Ref: KDT 7/e p861)
45. Ans. (a) Aminoglutethimide (Ref: CMDT 2014 p1581)

IMMUNOSUPPRESSANTS

1. GLUCOCORTICOIDS

These are most commonly used immunosuppressant drugs and act by inhibiting the production of prostaglandins, leukotrienes, histamine, bradykinin and PAF.

- These drugs also *diminish chemotactic activity* of neutrophils and monocytes.
- Glucocorticoids cause *sequestration of lymphocytes* in lymphoid tissue resulting in lymphopenia.
- By *inhibiting IL-1 production*, these drugs cause a decrease in IL-2 and IFN γ production.
- Continuous administration of glucocorticoids can *increase the catabolism of IgG*. These are used as first line immunosuppressive drugs for solid organ as well as hematological stem cell transplant recipients. These are also used for the treatment of graft rejection and graft versus host disease (GVHD), treatment of ITP, rheumatoid arthritis and bronchial asthma.

2. CALCINEURIN INHIBITORS

Calcineurin is required for the activation of NFAT (nuclear factor of activated T cells) which in turn increases the transcription of IL-2 by activated T cells. Cyclosporine and tacrolimus (FK 506) inhibits the activation of NFAT by binding to immunophilins (cyclosporine binds to cyclophilin and tacrolimus binds to FKBP). Net result of administration of **cyclosporine and tacrolimus is inhibition of gene transcription of IL-2**. These are used as immunosuppressive agents for organ transplantation, GVHD and some autoimmune diseases like rheumatoid arthritis and psoriasis.

- Cyclosporine can cause *nephrotoxicity, hepatotoxicity, hypertension, hyperkalemia, hyperlipidemia, hyperuricemia, hyperglycemia, hirsutism, gum hyperplasia and neurotoxicity* (tremor, headache, motor disturbance and seizures).
- Incidence of *hyperglycemia and neurotoxicity are more with tacrolimus* than cyclosporine. Whereas **hirsutism, gum hyperplasia, hyperuricemia and hyperlipidemia are not caused by tacrolimus**.

Hirsutism, gum hyperplasia, hyperuricemia and hyperlipidemia are adverse effects of cyclosporine which are not caused by tacrolimus.

Note:

- Tacrolimus is more potent than cyclosporine.
- Tacrolimus is a macrolide antibiotic.
- **Nephrotoxicity** is the major indication for cessation or modification of cyclosporine therapy. Hypertension occurs in 50% of renal transplant and almost all cardiac transplant recipients.
- Sirolimus aggravates cyclosporine induced renal dysfunction whereas cyclosporine increases sirolimus induced hyperlipidemia and myelosuppression.

3. PROLIFERATION SIGNAL INHIBITORS

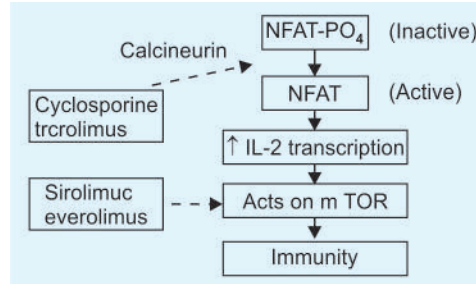
IL-2 stimulates immune system by activation of several T cells via activation of mammalian target of rapamycin (mTOR). **Sirolimus (rapamycin) binds to mTOR and inhibits the action of IL-2 without affecting its transcription**. It is used as immunosuppressive agent in organ transplantation and GVHD. It is **also incorporated in cardiac stents to decrease the chances of reocclusion**. Its major adverse effect is **thrombocytopenia** due to bone marrow suppression and hyperlipidemia. Sirolimus per se is not nephrotoxic. Lymphocyte is increased in a dose dependent fashion by sirolimus. **Everolimus** is a new drug in this category having

Tacrolimus is a macrolide antibiotic.

Everolimus has recently been approved for treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis.

Mycophenolate does not cause nephrotoxicity

shorter half life (43 hours as compared to 60 hours with sirolimus) and is **useful in cardiac transplantation**. These drugs increase the risk of *hemolytic uremic syndrome*. Everolimus has recently been approved for treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis.



4. PURINE SYNTHESIS INHIBITOR

Mycophenolate mofetil inhibits *inosine monophosphate dehydrogenase* after conversion to its active metabolite mycophenolic acid. This enzyme is necessary for *de novo* synthesis of purines. It is used as immunosuppressant in patients who are refractory to steroids. GI disturbances and myelosuppression are major adverse effects of this drug.

5. ANTIMETABOLITES

Azathioprine is the only antimetabolite that is used as immunosuppressant but not as an anticancer drug. It is a prodrug and is activated in the body to 6-mercaptopurine (anticancer drug). It lacks anticancer properties because conversion to active metabolite occurs only in lymphoid cells. Major toxic effect is bone marrow suppression. Its dose should be reduced if allopurinol is used concurrently because 6-MP is also metabolized by xanthine oxidase.

6. OTHER CYTOTOXIC AGENTS

Cyclophosphamide, chlorambucil and methotrexate are other anticancer drugs that can be used as immunosuppressants. Cyclophosphamide and chlorambucil are used in treating childhood nephrotic syndrome. Cyclophosphamide is also used for treatment of SLE and Wegner's granulomatosis.

7. LEFLUNOMIDE

Active metabolite of this prodrug inhibits **dihydro-orotate dehydrogenase** resulting in inhibition of pyrimidine synthesis. It is an orally active drug with long half life of several weeks. Liver and kidney damage are major toxicities. Cholestyramine increases its excretion. It is increasingly being used for polyoma virus nephropathy.

8. THALIDOMIDE

- It is a sedative drug that was withdrawn due to teratogenic (phocomelia) effects. It has come into market again due to its anti-angiogenic, immunomodulatory and anti-inflammatory effects.
- Currently, it is being used for multiple myeloma, erythema nodosum leprosum and skin manifestations of SLE.
- Important adverse effects of thalidomide include teratogenicity, peripheral neuropathy, constipation, hypothyroidism and increased risk of thrombosis particularly DVT. Immunomodulatory derivatives of thalidomide are termed IMiDs. **Lenalidomide** is an IMiD approved for myelodysplastic syndrome and multiple myeloma. Another group of thalidomide analogs, **SeleCIDs** (SElective Cytokine Inhibitory Drugs) are phosphodiesterase-4 (PDE 4) inhibitors with potent anti-TNF α activity.

9. ANTIBODIES

Polyclonal antibodies like anti-lymphocyte and anti-thymocyte antibodies, hyperimmune immunoglobulins and Rho (D) immunoglobulin are useful as immunosuppressive drugs. Recently, several **monoclonal antibodies** have been synthesized to produce this effect.

Monoclonal Antibody	Target	Indication
Abciximab	Gp II/IIIa	Antiplatelet
Adalimumab	TNF α	RA
Alefacept	LFA-3	Plaque psoriasis
Alemtuzumab	CD 52	B cell CLL Multiple sclerosis
Abatacept	CD-80, 86	RA
Aflibercept	VEGFR1,2	Neovascular Age related macular degeneration
Basiliximab	IL-2R (CD-25)	Immunosuppressant
Belimumab	BLyS	SLE
Bevacizumab	VEGF	Colorectal carcinoma, Glioblastoma, Renal cell carcinoma
Belatacept	CD 80, 86	Transplantation
Brentuximab	CD 30	Hodgkin lymphoma, Anaplastic large cell lymphoma
Cetuximab	EGFR	Colorectal carcinoma
Canakinumab	IL-1 β	Cryopyrin associated periodic syndrome (CAPS)
Certolizumab	TNF α	Crohn's disease
Daclizumab	IL-2R (CD-25)	Immunosuppressant
Denosumab	RANK ligand	Osteoporosis
Eculizumab	C5 complement component	Paroxysmal nocturnal hemoglobinuria, Atypical hemolytic uremic syndrome
Efalizumab	CD 11a chain of LFA	Psoriasis
Epratuzumab	CD 22	SLE
Etanercept	TNF α	RA (rheumatoid arthritis)
Gemtuzumab	CD 33	AML
Golimumab	TNF α	RA, Psoriasis, Ankylosing Spondylitis
Ibritumomab	CD 20	B-cell NHL
Infliximab	TNF α	RA, Crohn's disease, Psoriatic arthritis, Wegener's disease, Sarcoidosis
Ipilimumab	CTLA-4	Metastatic melanoma
Natalizumab	Integrin- α 4	Multiple sclerosis
Nimotuzumab	EGFR	Squamous cell carcinoma, Glioma
Nivolumab	PD-1	Non-small cell lung cancer
Obinutuzumab	CD-20	CLL
Ocrelizumab	CD-20	Breast cancer
Ofatumumab	CD 20	SLE
Omalizumab	Ig E	Bronchial asthma
Palivizumab	Fusion protein	RSV
Panitumumab	EGFR	Colorectal carcinoma
Pertuzumab	HER-2	Breast cancer

Contd...

Contd...

Ramucirumab	VEGFR-2	Non-small cell Lung cancer and cancer of gastroesophageal junction
Ranibizumab	VEGF	Neovascular Macular degeneration, Macular edema following retinal vein occlusion
Rituximab	CD 20	B-cell NHL
Rilonacept	IL-1	CAPS
Secukinumab	IL-17a	Plaque psoriasis
Siltuximab	IL-6	Castleman's disease
Tocilizumab	IL-6R	SLE, RA
Trastuzumab	her-2/neu	Breast cancer, Stomach and gastro-esophageal junction carcinoma
Ustekinumab	IL-12, IL-23	Plaque psoriasis
Vedolizumab	$\alpha_4\beta_7$	Ulcerative colitis Crohn's disease

Nomenclature of Monoclonal Antibodies

Name of the monoclonal antibody can be divided into four parts.

Prefix + Target subsystem + Origin subsystem + Suffix

- **Suffix** for all monoclonal antibodies is **mab**
- Depending on the source of origin, various names are given, e.g. u stands for human, xi for chimeric etc.
- Target is identified by specific letters, e.g. vi for virus, ci for circulation .
- *Previously, target consisted of three letters (first consonant, second vowel and third consonant) but third consonant can be deleted for ease of pronunciation. In 2009, new and shorter target subsystems were introduced.*
- Prefix is different for each monoclonal antibody.

Prefix	Target Subsystem			Source Subsystem		Suffix
	Old	New	Meaning		Meaning	
Variable	vi (r)	v (i)	Viral	u	human	mab
	ba (c)	b (a)	Bacterial	o	mouse	
	li (m)	l (i)	lower immunity	a	rat	
	fu (ng)	f (u)	fungal	i	primate	
	ne (r)	n (e)	nervous system	xi	chimeric	
	ki (n)	k (i)	Interleukin as target	zuaxo	humanizedrat mouse hybrid	
	mu (l)	-	musculoskeletal	xizu	chimeric humanized hybrid	
	o (s)	s (o)	Bone			
	co (l)		Colonic tumor			
	me (l)		Melanoma			
	ma (r)	- t(u)	Mammary tumor			
	go (t)		Testicular tumor			
	go (v)		Ovarian tumor			
	pr (o)		Prostate tumor			
	tu (m)		Miscellaneous tumor			

Examples of each target subsystem

Monoclonal antibody	Target subsystem	Indication
1. Abagovomab	gov	Ovarian cancer
2. Abciximab	ci	Antiplatelet
3. Adalimumab	lim	Rheumatoid Arthritis
4. Basiliximab	li	Transplantation
5. Canakinumab	kin (IL-1 β)	Rheumatoid Arthritis
6. Capromab	pro	Prostatic cancer
7. Cetuximab	tu	Colorectal cancer
8. Donesumab	s	Osteoporosis
9. Ecmoximab	me	Malignant melanoma
10. Edrocolomab	col	Colonic cancer
11. Efungumab	fung	Invasive candida infection
12. Ertumaxomab	ma	Mammary tumor (Breast cancer)
13. Infliximab	li	Rheumatoid arthritis
14. Nacolumab	col	Colonic cancer
15. Palivizumab	vi	Respiratory Syncytial Virus
16. Panobacumab	bac	Pseudomonas aeruginosa infection
17. Rituximab	tu	Non-Hodgkin lymphoma
18. Solanezumab	ne	Alzheimer's disease
19. Stamulumab	mul	Muscular dystrophy
20. Trastuzumab	tu	Breast cancer
21. Ustekinumab	kin (IL-12, IL-23)	Multiple sclerosis

10. CO-STIMULATION INHIBITOR

Certain costimulatory molecules are present on the surface of T cells as well as antigen presenting cells (APCs). Interaction of these molecules is necessary for the activation of T cells. **Abatacept** and **belatacept** act by inhibiting CD 80 and CD 86 costimulatory molecules present on APC. Abatacept is used for the treatment of severe rheumatoid arthritis resistant to DMARDs. **Belatacept** is used for preventing rejection of kidney transplants.

11. IL-1 INHIBITOR

Anakinra is an inhibitor of IL-1 being investigated for use in septic shock and RA.

12. OTHER DRUGS

Nintedanib is a small molecule kinase inhibitor that blocks multiple pathways involved in scarring of lung tissue. It is approved for oral treatment of **idiopathic pulmonary fibrosis**.

Apremilast is phosphodiesterase-4 inhibitor indicated for **severe plaque psoriasis** and **psoriatic arthritis**.

IMMUNOSTIMULANTS

1. LEVAMISOLE

It is used along with 5-FU for treatment of *colorectal carcinoma* after surgery. **Agranulocytosis** is major adverse effect. It is **also used for the treatment of pediculosis**. It was also used as an antihelminthic drug via stimulation of ganglionic nicotinic receptors.

2. BCG

Bacillus Calmette Guerin is a viable stain of *Mycobacterium bovis* and is useful as **intravesical therapy of superficial bladder cancer**.

3. CYTOKINES

These include **interferons**, colony stimulating factors (CSF) and various **interleukins**.

- Recombinant form of IL-2 is **Aldesleukin** and is **useful in malignant melanoma and renal cell carcinoma**
- **Filgrastim** (recombinant G-CSF) and **sargramostim** (recombinant GM-CSF) are **useful for chemotherapy induced myelosuppression**.

4. THALIDOMIDE

It is indicated for the treatment of ENL and multiple myeloma.

5. IMIQUIMOD

It is an immune response modifier shown to be effective against external genital and peri-anal warts (i.e., condyloma acuminata) by topical route. It act by releasing IFN α and cytokines like IL-1, IL-6 and TNF α etc. It has also been approved for basal cell carcinoma and actinic keratosis of the face and scalp.

DRUG OF CHOICE	
Clinical Diagnosis	Drug of Choice
• Rheumatoid arthritis	
- Pain relief	NSAIDs
- Bridge therapy	Corticosteroids
- DMARD	Methotrexate
• Psoriasis	
- Limited disease (<10% body surface area (BSA) involvement)	Topical steroid + Topical vitamin D analog (calcipotriene/calcitriol)
- Moderate (10-30% BSA)	UV phototherapy
- Severe (>30% BSA)	Narrow band UV-B (NB-UVB) Phototherapy
- Resistant to NB-UVB	PUVA
- Severe pustular	Methotrexate ¹
• Neovascular Age Related Macular Degeneration	Bevacizumab ²
• Crohn's disease	Corticosteroids
• Paroxysmal Nocturnal Hemoglobinuria	
- Mild	No treatment
- Severe hemolysis	Eculizumab
• Wegener's granulomatosis	Cyclophosphamide + corticosteroids
• Sarcoidosis	Corticosteroids
• Multiple sclerosis	Beta-interferons
• Antiphospholipid syndrome	Warfarin

1. Cyclosporine or infliximab may also be used
2. Ranivizumab or pegaptanib or aflibercept may also be used

MULTIPLE CHOICE QUESTIONS

1. All of the following are adverse effects of thalidomide except: (AI 2012)

- (a) Myocarditis
- (b) Constipation
- (c) Peripheral neuropathy
- (d) Sedation

2. A 5-year old child of severe nephrotic syndrome on treatment with tacrolimus, frusemide and prednisolone developed seizures. The investigations revealed:

- Serum Na⁺ = 136 mEq/L (AI 2012)
- Blood urea = 78 mg/dL
- Serum creatinine = 0.5 mg/dL,
- Serum albumin = 1.5 g/dL
- Serum total Ca = 7.5 mg/dL
- Urine albumin = 2g

What is the likely cause of symptoms in this baby?

- (a) Hypocalcemia
- (b) Tacrolimus toxicity
- (c) Uremia
- (d) Hyponatremia

3. Best treatment for kawasaki's disease is:

- (a) Aspirin (AIIMS Nov 2011)
- (b) I.V. immunoglobulins
- (c) Corticosteroids
- (d) Methotrexate

4. A pregnant woman of > 35 weeks gestation has SLE. All of the following drugs are used in treatment except:

- (a) Methotrexate (AIIMS May 2010)
- (b) Sulfasalazine
- (c) Prednisolone
- (d) Chloroquine

5. Which of the following antitumor agents works by impairing de novo purine synthesis? (Delhi PG - 2011)

- (a) Acycloguanosine
- (b) 5-Fluorouracil
- (c) Methotrexate (antifolate)
- (d) Allopurinol

6. All of the following statements about mycophenolate mofetil are true except: (AI 2010)

- (a) It is a prodrug
- (b) Gastrointestinal toxicity is common
- (c) It is used in transplant recipients where other drugs are not effective
- (d) It is highly nephrotoxic

7. Which of the following immunosuppressant drugs is nephrotoxic? (AIIMS Nov 2009)

- (a) Azathioprine

- (b) Cyclophosphamide
- (c) Mycophenolate mofetil
- (d) Tacrolimus

8. TNF- α inhibitors should not be used in:

(AIIMS Nov 2009)

- (a) Rheumatoid arthritis with HIV infection
- (b) Rheumatoid arthritis with hepatitis B
- (c) Rheumatoid arthritis with hepatitis C
- (d) Rheumatoid arthritis with pulmonary fibrosis

9. Treatment of choice for Kawasaki disease is:

- (a) Intravenous immunoglobulin (AIIMS May 2009)
- (b) Steroids
- (c) Azathioprine
- (d) Aspirin

10. A patient is given tacrolimus, which antibiotic should not be given to him? (AI 2009)

- (a) Gentamicin
- (b) Cisplatin
- (c) Rifampicin
- (d) Vancomycin

11. All are the side effects of tacrolimus EXCEPT: (AI 2009)

- (a) Hepatotoxic
- (b) Nephrotoxic
- (c) Ototoxic
- (d) Neurotoxic

12. All of the following drugs are used as immuno-suppressants EXCEPT: (AIIMS Nov 2008)

- (a) Glucocorticoids
- (b) Cyclosporine
- (c) Cephalosporin
- (d) Azathioprine

13. Thalidomide can be used in all of the following conditions EXCEPT: (AIIMS Nov 2008)

- (a) Behcet syndrome
- (b) HIV associated peripheral neuropathy
- (c) HIV associated mouth ulcers
- (d) Erythema nodosum leprosum

14. Anti-TNF alpha drugs are used for the treatment of all of the following diseases EXCEPT: (AIIMS Nov 2008)

- (a) Systemic lupus erythematosus
- (b) Seronegative arthritis
- (c) Psoriatic arthritis
- (d) Crohn's disease

15. Topical immunomodulator used for the treatment of genital warts is: (AI-2008)

- (a) Imiquimod

- (b) Podophylline
(c) Interferon
(d) Acyclovir
16. All of the following are the adverse effects of Tacrolimus EXCEPT: (AI-2008)
(a) Nephrotoxicity
(b) Neurotoxicity
(c) Hirsutism
(d) Hyperglycemia
17. All of the following statements about immunosuppressants are true EXCEPT: (AI 2007)
(a) Sirolimus acts by inhibiting the action of IL-2.
(b) Tacrolimus inhibits calcineurin pathway
(c) Mycophenolate acts by inhibiting GMP dehydrogenase
(d) Cyclosporine is an integral component of transplant rejection regimen
18. One of the following statements regarding mycophenolate mofetil is INCORRECT: (AI 2006)
(a) It is a prodrug
(b) It is a selective, uncompetitive and reversible inhibitor of IMP dehydrogenase
(c) It inhibits calcineurin
(d) Selectively inhibits lymphocytic proliferation
19. Which of the following statements is NOT TRUE about Tacrolimus? (AI 2004)
(a) It is a macrolide antibiotic
(b) It is indicated for the prophylaxis of organ transplant rejection
(c) Glucose intolerance is a well recognized side effect
(d) It can be safely administered with any nephrotoxic drug
20. Donesumab, a monoclonal antibody against RANK ligand is used for the treatment of: (AIIMS Nov 2006)
(a) Rheumatoid arthritis
(b) Osteoporosis
(c) Osteoarthritis
(d) Systemic lupus erythematosus
21. All of the following are immunosuppressive drugs EXCEPT: (AIIMS May, 2004)
(a) Cyclosporine
(b) Cefaclor
(c) Azathioprine
(d) Steroids
22. Which of the following pairs are incorrectly matched: (PGI Dec. 2007)
(a) Abciximab – Antiplatelet
(b) Omalizumab – Colon carcinoma
(c) Rituximab – Rheumatoid arthritis
(d) Trastuzumab – her/2/neu +ve breast carcinoma
(e) Palivizumab – Psoriasis
23. Thalidomide can be used in: (AIIMS May, 2004)
(a) Myocardial infarction
(b) Erythema nodosum leprosum
(c) Wernicke's encephalopathy
(d) Epilepsy
24. FK 506 is a type of: (AIIMS May, 2007)
(a) Immunoglobulin antibody
(b) Non-depolarizing muscle relaxant
(c) Macrolide antibiotic
(d) Opioid anaesthetic
25. Complications of cyclosporine therapy are: (PGI June, 2006)
(a) Hypertension
(b) Pulmonary fibrosis
(c) Hirsutism
(d) Nephrotoxicity
(e) Hyperkalemia
26. Drugs inhibiting the formation of IL-2 are: (PGI June, 2004)
(a) Cycloserine
(b) Cyclosporine
(c) OKT-3
(d) Tacrolimus
27. A 50 year old male, Ram Lal suffering from renal failure, underwent kidney transplant. He was prescribed a nucleotide derivative following the organ transplant. The nucleotide derivative of therapeutic importance in this organ transplant is: (AIIMS Nov, 2003) (DPG 2008)
(a) Azathioprine
(b) 5-Fluorouracil
(c) Cytarabine
(d) Allopurinol
28. The immunosuppressant action of cyclosporine appears to be due to:
(a) Activation of NK cells
(b) Blockade of tissue responses to inflammatory mediators
(c) Inhibition of gene transcription of interleukins
(d) Interference with antigen recognition
29. Sirolimus is more likely than cyclosporine to cause:
(a) Hypertension
(b) Osteoporosis
(c) Renal insufficiency
(d) Thrombocytopenia
30. An agent that activates natural killer cells and is useful in renal cell carcinoma is:
(a) Aldesleukin
(b) Etanercept
(c) Leflunomide
(d) Thalidomide
31. Which of the following monoclonal antibodies is a humanized antibody?
(a) Rituximab
(b) Palivizumab
(c) Infliximab
(d) Basiliximab

32. Which of the following drugs is used as an immuno-suppressant but lacks anticancer activity?
- Methotrexate
 - 6-Mercaptopurine
 - Azathioprine
 - 5-Fluorouracil
33. Most commonly used immunosuppressants are:
- Glucocorticoids
 - Cyclosporine
 - Tacrolimus
 - Methotrexate
34. Which metabolic abnormality is caused by cyclosporine?
- Hyperkalemia
 - Hypokalemia
 - Hypercalcemia
 - Hypocalcemia
35. Which of the following is NOT an adverse effect of cyclosporine?
- Hirsutism
 - Nephrotoxicity
 - Hypertension
 - Hypoglycemia
36. Immunosuppressant drug inhibiting the action of IL-2 without inhibiting its transcription is:
- Prednisolone
 - Cyclosporine
 - Tacrolimus
 - Sirolimus
37. Which of the following drugs inhibits de novo synthesis of purines?
- Cyclosporine
 - Tacrolimus
 - Mycophenolate
 - Infliximab
38. Which of the following drug is an Immunostimulant?
- Prednisolone
 - Levamisol
 - Cyclosporine
 - Thalidomide
39. BCG is used for:
- Treatment of tuberculosis
 - Treatment of superficial bladder cancer
 - Treatment of anthrax
 - All of the above
40. Route of administration of BCG for bladder cancer is:
- Oral
 - Subcutaneous
 - Intravenous
 - None of the above
41. Immunostimulant used for the treatment of malignant melanoma is:
- Levamisol
 - BCG
 - Aldesleukin
 - Methotrexate
42. A widely used drug that suppresses cellular immunity, inhibits prostaglandin and leukotriene synthesis and increases the catabolism of IgG antibody is:
- Cyclophosphamide
 - Prednisone
 - Cyclosporine
 - Infliximab
43. Mrs Reeta Wardhan, A 50-year-old female with rheumatoid arthritis is being considered for infliximab therapy. Which of the following tests should be performed before beginning treatment?
- Liver function tests
 - PPD skin test
 - Pulmonary function tests
 - Visual examination
44. All are true about levamisole EXCEPT: (DPG-2008)
- Act as an immunostimulator
 - Act as an immunodepressor in high doses
 - Single dose is sufficient for the treatment of psoriasis
 - Acts as antihelminthic by causing depolarization
45. Cyclosporine inhibits: (DPG 2006) (AIIMS 1997) (TN 2000)
- T lymphocyte proliferation
 - B lymphocyte proliferation
 - Both T and B lymphocyte proliferation
 - NK cells only
46. Cyclosporine acts by decreasing the production of: (DPG 2005)
- IL-1
 - IL-2
 - IL-6
 - IL-8
47. Not true about thalidomide: (DPG 2004)
- Causes phocomelia
 - Not tested in pregnant animals before introduction
 - Still has restricted clinical use
 - Has no antiangiogenesis action against tumour
48. Side effects of cyclosporine are all, EXCEPT: (DPG 2002)
- Nephrotoxicity
 - Bone marrow suppression
 - Hypertension
 - Hirsutism
49. Which of the following antineoplastic and immunosuppressant drugs is a dihydrofolate reductase inhibitor? (DPG 2001)
- Methotrexate
 - Adriamycin
 - Vincristine
 - Cyclophosphamide
50. Which of the following act through helper T cells? (MPPG 2004)
- Cyclosporine
 - Azathioprine

- (c) Cytarabine
(d) Cycloserine
51. All are true about cyclosporine-A-EXCEPT: (UP 2008)
(a) Given orally as too toxic by intravenous route
(b) Given in renal transplant
(c) Selectively inhibit T-lymphocytes proliferation
(d) It causes renal toxicity
52. All of the following are side effects of cyclosporine EXCEPT: (TN 2005)
(a) Post-transplant lymphoproliferative disorders (PTLDs)
(b) Hypotension
(c) Nephrotoxicity
(d) Tremors
53. Infliximab is: (RJ 2008)
(a) IgG1 chimeric monoclonal antibody against TNF α
(b) IgG1 fully human monoclonal antibody against TNF α
(c) IgG4 chimeric monoclonal antibody against TNF α
(d) P75 TNF receptor fusion protein
54. Monoclonal antibody to IL-5 is: (RJ 2008)
(a) Mepolizumab
(b) Omalizumab
(c) Keliximab
(d) Altrakincept
55. Anti IgE monoclonal antibody used in bronchial asthma is: (RJ 2008)
(a) Mepolizumab
(b) Omalizumab
(c) Keliximab
(d) Altrakincept
56. Etanercept used in rheumatoid arthritis act by the inhibition of: (RJ 2009)
(a) TNF alpha
(b) TFG beta
(c) IL-2
(d) IL-6
57. Tacrolimus acts by inhibiting: (MH 2007)
(a) DNA and RNA synthesis
(b) Anti-lymphocyte antibody formation
(c) T-Cell proliferation
(d) All of the above
58. Fully humanized antibodies used in treatment of rheumatoid arthritis? (MH 2007)
(a) Anakira
(b) Adalimumab
(c) Infliximab
(d) Leflunomide
59. The only FDA approved radioactive antibody that can be used for treatment of lymphoma: (MH 2006)
(a) Trastuzumab
(b) Ibritumomab
(c) Rituximab
(d) Imatinib
60. All are TNF- α antagonists used in rheumatoid arthritis except: (Bihar 2005)
(a) Ifosfamide
(b) Infliximab
(c) Etanercept
(d) Adalimumab
61. Tacrolimus level is increased by all EXCEPT: (MP 2009)
(a) Erythromycin
(b) Itraconazole
(c) Danazole
(d) Rifampicin
62. Bevacizumab is used in: (Kolkata 2009)
(a) Diabetic retinopathy
(b) Glaucoma
(c) Diabetic nephropathy
(d) Neuropathy
63. All of the following is true about "Imiquimod" EXCEPT: (AP 2006)
(a) Direct antiviral activity
(b) Indirect antiviral activity
(c) Antitumor activity
(d) It release cytokines
64. Which of the following immuno-suppressive agents acts selectively by inhibiting helper T-cells? (MPPG 2007)
(a) Cyclophosphamide
(b) Azathioprine
(c) Cyclosporine
(d) Cytosine arabinoside

RECENT QUESTIONS ASKED BY NATIONAL BOARD

- Which of the following drug does not cause renal toxicity?
(a) Cisplatin
(b) Tacrolimus
(c) Mycophenolate mofetil
(d) Naproxen
- Anti IgE monoclonal antibody is -
(a) Certolizumab
(b) Rifampicin
(c) Omalizumab
(d) Canakinumab
- Mechanism of action of bevacizumab is
(a) Acts on VEGF
(b) EGFR antagonist
(c) PDGF monoclonal antibody
(d) Tyrosine kinase inhibitor
- Which of the following is a calcineurin inhibitor?
(a) Cyclophosphamide
(b) Cyclosporine
(c) Etanercept
(d) Sirolimus

5. **Basiliximab acts by antagonism against:**
 - (a) CD 25
 - (b) CD 11a
 - (c) TNF
 - (d) IL-2
6. **Bevacizumab is:**
 - (a) Monoclonal antibody against VEGF
 - (b) Anti-IL-2 monoclonal antibody
 - (c) Monoclonal antibody against FGFR
 - (d) Monoclonal antibody against EGFR
7. **Rituximab is antibody against:**
 - (a) CD 20
 - (b) VEGF
 - (c) EGER
 - (d) IL-2
8. **True about azathioprine is:**
 - (a) It has more anti tumor effect than immunosuppressant effect
 - (b) It is not a prodrug
 - (c) It selectively affects differentiation of T cells
 - (d) It is a pyrimidine antimetabolite
9. **Thalidomide is not used in:**
 - (a) HIV related neuropathy
 - (b) Erythema nodosum leprosum
 - (c) HIV related oral ulcer
 - (d) Behcet's disease
10. **All of the following are tumor necrosis factor blocking agents, except:**
 - (a) Adalimumab
 - (b) Eterncept
 - (c) Infliximab
 - (d) Abciximab
11. **Which of the following immunosuppressive agent requires monitoring of renal function on regular basis?**
 - (a) Azathioprine
 - (b) Mycophenolate mofetil
 - (c) Methotrexate
 - (d) Cyclosporine A
12. **A topical retinoid recently introduced for the treatment of psoriasis is:**
 - (a) Adapalene
 - (b) Tazarotene
 - (c) Alitretinoin
 - (d) Bexarotene
13. **Immunostimulant agent among the following is:**
 - (a) Pirenzepine
 - (b) Levamisol
 - (c) Albendazole
 - (d) Methotrexate
14. **Anthelmintic also acting as immunomodulator is:**
 - (a) Albendazole
 - (b) Levamisole
 - (c) Mebendazole
 - (d) Piperazine
15. **Cyclosporin-A acts on:**
 - (a) CD4 cells
 - (b) CD3 cells
 - (c) CD8 cells
 - (d) B lymphocytes

EXPLANATIONS

1. Ans. (a) **Myocarditis** (Ref: Goodman Gilman 12/e p1742)

- Thalidomide was banned because of teratogenic effects (phocomelia). Now it has come again in the market for use as an anticancer drug in **multiple myeloma and melanoma**.
- **Lenalidomide** is its more potent and non-teratogenic derivative.
- *Thalidomide most commonly causes sedation and constipation* in cancer patients. It can also cause *peripheral sensory neuropathy*.
- Two enantiomers of thalidomide (R and S) are present but these are interconvertible in body, therefore racemic mixture is used.

2. Ans. (b) **Tacrolimus toxicity** (Ref: Harrison 18/e p2272, 361, 347, 2308)

To get to the answer, we will look at the options one by one.

Hypocalcemia: Serum calcium in this boy is 7.5 mg/dL. Hypocalcemia can result in seizures but the level should be very low. Further, if we correct calcium with serum albumin, it will come in normal range. Corrected calcium level in the serum can be calculated by adding 0.8 mg/dL With every 1.0 g/dL decrease in serum albumin below the normal value of 4.0 g/dL. Hence, in this patient, corrected serum calcium level will be

$$7.5 + 0.8 \times (4.0 - 1.5) = 9.5 \text{ mg/dL}$$

It is in normal range (8.5-10.5 mg/dL) and thus cannot be the cause of seizures in this person.

Uremia: Although blood urea is elevated (78 mg/dL as compared to normal value of 15-40 mg/dL) but serum creatinine is normal (0.5 mg/dL). For diagnosis of uremia, serum creatinine must be 3 times the normal value. Thus, uremia cannot be the answer.

Hyponatremia: Serum sodium is at lower normal value (136-152 mEq/L). For causing seizures, serum sodium should be less than 125 mEq/L. Therefore, this option can also be ruled out.

Tacrolimus toxicity: This child is on tacrolimus therapy. It is a known neurotoxin and can cause seizures. It also can cause renal failure. Further by ruling out other options, the most likely cause seem to be tacrolimus toxicity.

3. Ans. (b) **I.V. immunoglobulins** (Ref: CMDT 2012/1378-1379)

- Every patient with a clinical diagnosis Kawasaki disease should be treated.
- IVIG is given within the first 10 days of illness.
- Concomitant aspirin should be started until the patient is afebrile
- If fever persist beyond 36 hours after the initial IVIG infusion, a new dose of IVIG should be given if no other source of fever is found.
- Methylprednisolone should follow if the disease persists after the second IVIG administration.
- Further options for refractory cases include TNF blockers (eg, infliximab), cyclophosphamide, methotrexate, and plasmapheresis.

4. Ans. (b) **Sulfasalazine** (Ref: Harrison 17/e p2083)

Sulfasalazine is one of the drugs implicated in causing SLE, therefore obviously it will not be used in its treatment.

Do not get confused by seeing pregnancy in the question. Other drugs given in the question are used for treatment of SLE but sulfasalazine is not used at all.

5. Ans. (c) **Methotrexate (antifolate)** (Ref: Goodman and Gilman 12/e p1691)

De novo synthesis refers to the synthesis of complex molecules from simple molecules such as sugars or amino acids, as opposed to their being recycled after partial degradation.

Methotrexate and pemetrexed are the inhibitors of dihydrofolate reductase (DHFRase). These drugs also inhibit Thymidylate synthase (TS) and the enzymes involved in early purine synthesis like glycylamide ribonucleotide formyltransferase (GART). These drugs are thus involved in inhibiting the denovo purine synthesis.

6. Ans. (d) **It is highly nephrotoxic** (Ref: Katzung 11/e p973)

- Mycophenolate mofetil is a prodrug, its active metabolite is mycophenolic acid.
- It is used as an immunosuppressant drug in solid organ transplant patients for refractory rejection and as an alternative to cyclosporine / tacrolimus in patients who do not tolerate these drugs.

- Major toxicity is gastrointestinal (nausea, vomiting, diarrhea, abdominal pain). It can also cause hypertension and reversible neutropenia.
- Unlike cyclosporine and tacrolimus, it does not cause nephrotoxicity.

7. **Ans. (d) Tacrolimus** (Ref: *Katzung 11/e p972; KDT 6/e p204, 728, 840-841*)

- **Tacrolimus and cyclosporine** toxicity include nephrotoxicity, neurotoxicity, hyperglycemia, hypertension, hyperkalemia and GI complaints. Cyclosporine also cause hirsutism, which is not seen with tacrolimus use.

8. **Ans. (b) Rheumatoid arthritis with hepatitis B** (Ref: *Katzung 11/e p634*)

- Anti-TNF α drugs should be avoided in
 - Pulmonary tuberculosis
 - Multiple sclerosis
 - Hepatitis B
 - Congestive heart failure
- Anti-TNF- α drugs like infliximab, etanercept and adalimumab are used in rheumatoid arthritis and increase the risk of bacterial infections. These can lead to reactivation of latent tuberculosis. Infliximab rarely, result in leucopenia, activation of hepatitis B and vasculitis.

9. **Ans. (a) Intravenous immunoglobulin** (Ref: *CMDT-2010/1288*)

- All patients of Kawasaki's disease should be treated with intravenous immunoglobulin (IVIG).
- Aspirin should be used for fever and inflammation. It should be continued if coronary aneurysm develops.
- Methyl prednisolone should follow if disease symptoms persist after two injections of IVIG.
- Drugs for refractory cases include infliximab, cyclophosphamide and methotrexate.

10. **Ans. (c) Rifampicin** (Ref: *KDT 6/e p840*)

- Rifampicin is a potent enzyme inducer. The drug has the chance of inducing the metabolism. This might reduce the efficacy of tacrolimus and graft rejection may occur.
- Gentamicin, cisplatin and vancomycin have additive nephrotoxic effect with tacrolimus, but dose reduction may protect from these adverse effects.

11. **Ans. (c) Ototoxic** (Ref: *Principles of Pharmacology by Dr. KK Sharma & Dr. HL Sharma 1/e p914; KDT 6/e p840*)

- Ototoxicity is not a side effect of tacrolimus.
- Tacrolimus can cause nephrotoxicity, neurotoxicity, hepatotoxicity and diabetes mellitus.
- Unlike cyclosporine, it does not cause hirsutism.

12. **Ans. (c) Cephalosporin** (Ref: *Principles of Pharmacology, 1/e p912; KDT 6/e p837*)

Cephalosporins are β -lactam antibiotics whereas other drugs are immunosuppressants.

13. **Ans. (b) HIV Associated Peripheral Neuropathy** (Ref: *P 876, Indian Journal of Pharmacology 2003; 35: 204-212*)

Peripheral neuropathy is an adverse effect of thalidomide, therefore it is not indicated for HIV induced peripheral neuropathy.

Clinical uses of thalidomide

- AIDS related aphthous ulcers
- AIDS related wasting syndrome
- Multiple myeloma and other solid tumors like AIDS-related Kaposi's sarcoma
- Prevention of graft versus host disease (GVHD) after transplantation
- Rheumatoid arthritis
- Ankylosing spondylitis
- Crohn's disease and Behcet's syndrome

Adverse reactions to thalidomide

- Teratogenicity
- Peripheral neuropathy
- Drowsiness
- Skin rashes
- Constipation

14. Ans. (a) **Systemic Lupus Erythematosus** (Ref: Harrison 17/e p2039)

There is already under-expression of TNF- α in SLE, therefore we cannot use anti-TNF drugs for this condition. It is further strengthened by the fact that anti-TNF alpha drugs like infliximab cause SLE as the adverse effect.

Indications for TNF- α inhibitors

- Rheumatoid arthritis
- Juvenile arthritis
- Psoriatic arthritis
- Psoriasis
- Ankylosing spondylitis
- Crohn's disease

15. Ans. (a) **Imiquimod** (Ref: Katzung 10/e p816, Goodman & Gilman 11/e p1690)

Drugs used for viral warts (condyloma acuminata) are

- **Imiquimod**: It is an immune response modifier, useful in the treatment of external genital and peri-anal warts topically. Mechanism of action against these HPV-induced lesions is unknown. 5% cream is applied 3 times weekly and washed off 6-10 hours after each application. Recurrences appear to be less common than with ablative therapies. Local skin reactions and pigmentary skin lesions are the important side effects.
- **Resiquimod** is another immunomodulator, which is used topically for HSV.
- **Podophyllin** acts by inhibiting the polymerization of tubulin monomers in mitotic spindle.
- Interferons α -2b may be used intralesional for condyloma acuminata.
- Acyclovir is used for HSV-1, HSV-2 and varicella zoster virus. It is not useful for CMV infections.

16. Ans. (c) **Hirsutism** (Ref: Harrison 17/e p1987-23, Katzung, 11/e p972)

- Tacrolimus produces same adverse effects like cyclosporine but unlike latter it does not cause hirsutism and gum hypertrophy. (Harrison)
- Toxicity of cyclosporine includes nephrotoxicity, hypertension, hyperglycemia, liver dysfunction, hyperkalemia, altered mental status, seizures and hirsutism.

17. Ans. (c) **Mycophenolate acts by inhibiting GMP dehydrogenase** (Ref: KDT 6/e p837, 841)

- Mycophenolate mofetil acts by blocking IMP dehydrogenase.
- Cyclosporine and tacrolimus are calcineurin inhibitors that act by decreasing the transcription of IL-2 gene. Cyclosporine is commonly used to prevent rejection in transplant recipients.
- Sirolimus acts by inhibiting mTOR (a tyrosine kinase) that is the target of IL-2.

18. Ans. (c) **It inhibits calcineurin** (Ref: KDT 6/e p841)

- Mycophenolate mofetil is a prodrug. It is converted to mycophenolic acid that inhibits the enzyme, IMP dehydrogenase. It selectively inhibits the proliferation of lymphocytes and acts as an immunosuppressant agent.
- Calcineurin inhibitors are cyclosporine and tacrolimus.

19. Ans. (d) **It can be safely administered with any nephrotoxic drug** (Ref: KDT 6/e p840)

- Tacrolimus is a nephrotoxic agent. Like cyclosporine, it should be administered cautiously in patients receiving other nephrotoxic drugs.
- In its structure, tacrolimus contains a large macrocyclic ring. It is therefore a macrolide in nature.
- It is an immunosuppressant agent and is used to prevent the rejection of transplanted organ.
- Nephrotoxicity, hyperglycemia and neurotoxicity are well recognized adverse effects of this drug.

20. Ans. (b) **Osteoporosis** (Ref: Principles of pharmacology by HL Sharma and KK Sharma 2007/641)

- Receptor for activated nuclear factor κ B (RANK) is present on osteoclast progenitors. Binding of RANK-ligand to these receptors causes differentiation and activation of osteoclast progenitors to mature osteoclasts. Denosumab is a monoclonal antibody that prevents the binding of RANK-ligand with RANK. This prevents activation of osteoclasts and it can therefore be used in osteoporosis.
- Osteoblasts synthesize and release osteoprotegerin (OPG), identical with RANK, which functions as a 'decoy receptor'. OPG, thus inhibits the binding of RANK-L to RANK. Hence OPG analogs can be the potential therapeutic agents of osteoporosis.

21. Ans. (b) **Cefaclor** (Ref: KDT 6/e p837)

- Cefaclor is a cephalosporin

22. Ans. (b) Omalizumab – Colon carcinoma; (c) Rituximab – Rheumatoid arthritis; (e) Palivizumab – Psoriasis (Ref: KDT 6/e p610)

- Abciximab is a monoclonal antibody against Gp IIb/IIIa receptors. It is used as an antiplatelet drug in PTCA and cardiac transplants.
- Omalizumab is a monoclonal antibody against IgE. It is used for bronchial asthma.
- Rituximab is a monoclonal antibody against CD 20. It is mainly used for non-Hodgkin's lymphoma. It can also be used for rheumatoid arthritis.
- Trastuzumab is a monoclonal antibody against her 2/neu gene. It is used for breast carcinoma.
- Palivizumab is a monoclonal antibody used against respiratory syncytial virus.

23. Ans. (b) Erythema nodosum leprosum (Ref: KDT 6/e p756)

24. Ans. (c) Macrolide antibiotic (Ref: Katzung 11/e p972)

- Tacrolimus is also known as FK-506. It is an immunosuppressant macrolide antibiotic produced by *Streptomyces tsukubaensis*.
- Muromonab CD3 is also known as OKT3. It is a monoclonal antibody against CD3 cells.

25. Ans. (a) Hypertension; (c) Hirsutism; (d) Nephrotoxicity (e) Hyperkalemia (Ref: KDT 6/e p840)

Adverse effect of cyclosporine are :

- **Nephrotoxicity**
- **Increased BP**
- Hyperglycemia
- Anorexia
- **Hyperkalemia**
- **Hirsutism**
- Gum hyperplasia
- Tremors and seizures

26. Ans. (b) Cyclosporine; (d) Tacrolimus (Ref: KDT 6/e p838)

- Cyclosporine and tacrolimus inhibits antigen stimulated activation and proliferation of helper cells as well as expression of IL-2.
- Cycloserine is an antitubercular drug that acts by inhibiting bacterial cell wall synthesis.
- OKT3 – is monoclonal antibody. It activates T cells non specifically and releases cytokines, specially TNF- α

27. Ans. (a) Azathioprine (Ref: KDT 6/e p840)

- Immunosuppressants are used in organ transplantation to prevent the rejection. Most commonly used agents for this purpose are glucocorticoids.
- Azathioprine is a nucleotide derivative that can be used as an immunosuppressant.
- 5-Fluorouracil and cytarabine are also nucleotide derivatives but these are used for the treatment of cancers.
- Allopurinol is used to decrease the production of uric acid. It has no role in renal transplantation.

28. Ans. (c) Inhibition of gene transcription of interleukins (Ref: KDT 6/e p838, 839, 840)

- Cyclosporine and tacrolimus acts by inhibiting calcineurin, which is involved in the activation of NFAT. Final result of this process is increased transcription of IL-2 gene.
- Sirolimus does not inhibit the transcription of IL-2 but interferes with its action. It inhibits the enzyme tyrosine kinase, known as mTOR (which is activated by IL-2).

29. Ans. (d) Thrombocytopenia (Ref: KDT 6/e p840)

- Cyclosporine and tacrolimus cause nephrotoxicity as an adverse effect.
- Sirolimus (rapamycin) results in bone marrow suppression and thus may cause anemia, thrombocytopenia and leukopenia.

30. Ans. (a) Aldesleukin (Ref: Katzung 10/e p906)

Recombinant IL-2 (aldesleukin) is used for the treatment of malignant melanoma and renal cell carcinoma.

31. Ans. (b) Palivizumab (Ref: Katzung 10/e p816)

For nomenclature of monoclonal antibodies, refer to text.

32. Ans. (c) Azathioprine (Ref: KDT 6/e p819, 820, 838)

Azathioprine is an antimetabolite that is used as an immunosuppressant but not as an anti-neoplastic drug. It is a prodrug and is converted to its active metabolite (6-mercaptopurine) in the lymphoid cells only.

33. **Ans. (a) Glucocorticoids** (Ref: KDT 6/e p828)
34. **Ans. (a) Hyperkalemia** (Ref: KDT 6/e p840)
35. **Ans. (d) Hypoglycemia** (Ref: KDT 6/e p840)
Cyclosporine causes hyper and not hypoglycemia
36. **Ans. (d) Sirolimus** (Ref: Katzung 10/e p918)
37. **Ans. (c) Mycophenolate** (Ref: KDT 6/e p841)
By inhibiting the enzyme IMP dehydrogenase, mycophenolate inhibits the de novo synthesis of purines.
38. **Ans. (b) Levamisol** (Ref: Goodman & Gilman 11/e p1422)
All other drugs listed in the options possess immunosuppressant properties.
39. **Ans. (b) Treatment of superficial bladder cancer** (Ref: Goodman & Gilman 11/e p1422)
BCG is used for immunization against TB. It is also used for the treatment of superficial bladder cancers. It is directly instilled in the urinary bladder for this purpose.
40. **Ans. (d) None of the above** (Ref: Goodman & Gilman 11/e p1422)
Intravesical route is used for BCG in the treatment of bladder carcinoma.
41. **Ans. (c) Aldesleukin** (Ref: Katzung 10/e p906)
It is a recombinant IL-2 used for the treatment of renal cell carcinoma and malignant melanoma.
42. **Ans. (b) Prednisone** (Ref: KDT 6/e p828, 838)
Glucocorticoids are powerful immunosuppressants. These inhibit both cellular and humoral immunity by:
- Decreasing the recruitment of immune cells.
 - Catabolism of immunoglobulins.
 - Inhibiting the enzyme phospholipase A₂ resulting in decreased production of PGs, LTs and TXs.
43. **Ans. (b) PPD skin test** (Ref: Katzung 11/e p633)
Infliximab is a monoclonal antibody against TNF- α . It is commonly used to treat moderate to severe rheumatoid arthritis particularly in patients who have failed methotrexate therapy. TNF- α inhibitors can cause serious adverse effects, including reactivation of latent tuberculosis. All patients being considered for TNF- α inhibitor therapy should have a baseline PPD skin test to screen for latent tuberculosis.
44. **Ans. (c) Single dose is sufficient for the treatment of psoriasis** (Ref: Goodman & Gilman 11/e p1422)
- Levamisole is an immunomodulator acting as immunostimulant at low doses and immunodepressant at high doses.
 - It was used as anti-helminthic and causes depolarization by stimulating nicotinic receptors.
 - It is used for treatment of colorectal carcinoma in combination with 5-FU.
 - It is slow to act in psoriasis and requires two day therapy per week for prolonged periods.
45. **Ans. (a) T lymphocyte proliferation** (Ref: KDT 6/e p837-839)
Cyclosporine profoundly and selectively inhibits 'T' lymphocyte proliferation, IL-2 and other cytokine production.
46. **Ans. (b) IL-2** (Ref: KDT 6/e p837)
47. **Ans. (d) Has no antiangiogenesis action against tumour** (Ref: KDT 6/e p84, 834)
- Thalidomide was banned in 1960 because of its teratogenic effect of phocomelia (seal like limbs). It has anxiolytic, adjuvant analgesic/antipyretic properties and has been found to counteract cancer associated cachexia.
 - Its mechanism of action is by suppressing TNF and or by modulating IL-2.
 - Recently it has been reintroduced as antineoplastic drug due to its anti-angiogenesis action.
48. **Ans. (b) Bone marrow suppression** (Ref: KDT 6/e p840)
49. **Ans. (a) Methotrexate** (Ref: KDT 6/e p823)
50. **Ans. (a) Cyclosporine** (Ref: KDT 6/e p837)

Mechanism of action of:

- (a) Cyclosporine – Through T helper cells (by inhibiting calcineurin)
- (b) Azathioprine – Inhibits de novo purine synthesis and damages DNA. It selectively affects cytolytic T lymphocytes.

- (c) *Cytarabine* – Inhibits DNA synthesis in S-phase.
- (d) *Cycloserine* – Inhibits bacterial cell wall synthesis.

51. Ans. (a) Given orally as too toxic to intravenous (Ref: KDT 6/e p839-840)
52. Ans. (b) Hypotension (Ref: KDT 6/e p840)
53. Ans. (a) IgG₁ chimeric monoclonal antibody against TNF α (Ref: KDT 6/e p205)
54. Ans. (a) Mepolizumb (Ref: www.wikipedia.org)
55. Ans. (b) Omalizumab (Ref: KDT 6/e p226)
56. Ans. (a) TNF alpha (Ref: KDT 6/e p203)
57. Ans. (c) T-Cell proliferation (Ref: KDT 6/e p837)
58. Ans. (b) Adalimumab (Ref: Katzung 11/e p633)
59. Ans. (b) Ibritumomab (Ref: Katzung 11/e p978)
60. Ans. (a) Ifosfamide (Ref: KDT 6/e p633-634)
61. Ans. (d) Rifampicin (Ref: KDT 6/e p840, www.medscape.com/druginfo)
Erythromycin, itraconazol and danazol inhibit the metabolism of tacrolimus and thus increase the plasma concentration whereas rifampicin is an enzyme inducer and decrease its plasma level.
62. Ans. (a) Diabetic retinopathy (Ref: Katzung 11//977; Harrison 17/e p512)
Bevacizumab is a monoclonal antibody against VEGF and is used as an anti-angiogenic drug. It is mainly used for colorectal carcinoma and is used off-label by intravitreal injection to slow progression of neovascular macular degeneration.
63. Ans. (a) Direct antiviral activity (Ref: Katzung 11/e p1053)
64. Ans. (c) Cyclosporine (Ref: KDT 6/e p838)
Cyclosporine inhibits helper T cells (CD4) cells by inhibiting the transcription of IL-2 (via calcineurin inhibition).

ANSWERS OF RECENT QUESTIONS ASKED BY NATIONAL BOARD

1. Ans (c) Mycophenolate mofetil (Ref: KDT 7th/883)
2. Ans (c) Omalizumab (Ref: KDT 7th/231)
3. Ans (a) Acts on VEGF (Ref: KDT 7th/871)
4. Ans (b) Cyclosporine (Ref: KDT 7th/878)
5. Ans. (a) CD 25 (Ref: KDT 7th/884)
6. Ans. (a) Monoclonal antibody against VEGF (Ref: KDT 7th/871)
7. Ans. (a) CD 20 (Ref: KDT 7th/872)
8. Ans. (c) It selectively affects differentiation of T cells (Ref: KDT 7th/863-864)
9. Ans. (a) HIV related neuropathy (Ref: KDT 7th/786)
10. Ans. (d) Abciximab (Ref: KDT 7th/631, 883-884)
11. Ans. (d) Cyclosporine A (Ref: KDT 7th/880-881)
12. Ans. (b) Tazarotene (Ref: KDT 7th/891)
13. Ans. (b) Levamisol (Ref: KDT 7th/852)
14. Ans. (b) Levamisole (Ref: KDT 7th/812)
15. Ans. (a) CD4 cells (Ref: KDT 7th/838-39)

DRUGS USED IN DERMATOLOGY

1. Glucocorticoids

Potency of these agents is traditionally measured using vasoconstrictor assay (area of skin blanching). *Betamethasone, clobetasol, diflurasone, halobetasol, amcinonide, desoximetasone, fluocinonide, halcinonide, triamcinolone, flurandrenolide, hydrocortisone, mometasone, aclo-metasone, dexamethasone and desonide* formulations can be used topically. **Betamethasone dipropionate is most potent and hydrocortisone is least potent topically steroid.** Skin atrophy (cigarette paper skin), striae, telengictasia, purpura and acneiform eruptions are the side effects occurring by chronic use.

Betamethasone dipropionate is most potent and hydrocortisone is least potent topically steroid.

Skin atrophy (cigarette paper skin), striae, telengictasia, purpura and acneiform eruptions are the side effects occurring by chronic use of topical steroids.

2. Retinoids

These may be **first generation** (*retinol, tretinoin, isotretinoin and alitretinoin*), **second generation** (*acitretin*), **third generation** (*tazarotene and bexarotene*) and **retinoid-like** (*adaplene*) compounds. These are potent **teratogens** (contra-indicated in pregnancy) and may cause dry skin, nose bleeds, conjunctivitis, alopecia, muscular pain, pseudotumor cerebri and mood alterations.

- Tretinoin is used for acne vulgaris and as an adjunctive agent for treating photoaging.
- Tazarotene is approved for psoriasis and acne vulgaris.
- Alitretinoin is approved only for treatment of skin manifestations of Kaposi's sarcoma.
- Isotretinoin is indicated for the treatment of severe nodulocystic acne vulgaris. It may result in hyperlipidemia, myalgia and arthralgia.
- Acitretin (major metabolite of etretinate) was used for psoriasis but was withdrawn due to very long half life (2-3 days).
- Bexarotene is used for cutaneous T-cell lymphoma. It may cause lipid abnormalities, hypothyroidism and gastrointestinal symptoms.

3. Photochemotherapy

Ultraviolet radiations may be classified into UV-A (320-400 nm), UV-B (290-320 nm) and UV-C (100-290 nm) according to wavelength. *UV-B is most erythrogenic and melanogenic radiation.*

- **PUVA:** 8-Methoxypsoralen (oral) followed by UV-A is approved for treatment of *vittiligo, psoriasis and cutaneous T-cell lymphoma*. Major side effects include nausea, blistering and painful erythema. It increases the risk of melanoma and squamous cell carcinoma.
Photopheresis: After oral methoxypsoralen, leucocytes are separated from whole blood using extracorporeal pheresis (ECP) device and then exposed to UV-A radiation. Irradiated cells are then returned to the patient. ECP is effective for *cutaneous T-cell lymphoma*.
- **Photodynamic therapy:** It combines photosensitizing drugs (mostly porphyrins) with visible light for the treatment of *non-melanoma skin cancers and actinic keratosis*.

4. Antimetabolites

- **Methotrexate** is used for moderate to severe *psoriasis, pemphigus vulgaris, pityriasis rubra, SLE, dermatomyositis and cutaneous T-cell lymphoma*. Pregnancy and lactation are absolute contra-indications.

- **Azathioprine** is steroid sparing agent for pemphigus vulgaris, bullous pemphigoid, dermatomyositis, atopic dermatitis, SLE, psoriasis and Behcet's disease.
- **5-FU** is used for actinic keratoses and superficial basal cell carcinoma.

5. Calcineurin inhibitors

Cyclosporine is used for atopic dermatitis, psoriasis, alopecia areata, pemphigus vulgaris, bullous pemphigoid, lichen planus and pyoderma gangrenosum. **Tacrolimus** and **pimecrolimus** are other agents in this group.

6. Biological agents

- **Alefacept** and **efalizumab** are approved for moderate to severe *psoriasis*.
- **Etanercept** is approved for psoriasis, rheumatoid arthritis and ankylosing spondylitis.
- **Infliximab** is approved for Crohn's disease and rheumatoid arthritis and is in phase III trials for treatment of psoriasis.
- **Denileukin diftitox** is indicated for advanced cutaneous T cell lymphoma.

7. Sunscreens

These may protect from UV-A (avobenzone, oxybenzone, titanium oxide and zinc oxide) or UV-B (cinnamates, salicylates etc.). **Sun protection factor (SPF)** defines a ratio of minimal dose of sunlight that produce erythema on skin with sunscreens to that without sunscreen. It provides valuable information regarding UVB protection but is *useless for UVA efficacy*.

8. Other agents

- *Cholestasis associated pruritis* may respond to *cholestyramine, ursodeoxycholic acid, ondansetron, rifampicin and nalmefene* (opioid antagonist).
- *Pruritis of uremia* is most effectively treated with *UVB radiation*. It may also respond to *naltrexone and omeprazole*.
- *Capsaicin* is approved for the treatment of *post herpetic neuralgia and painful diabetic neuropathy*.
- **Masoprocol** is a potent 5-LOX inhibitor with antitumor activity effective for topical treatment of actinic keratosis.

AGE-RELATED MACULAR DEGENERATION

- It is of two types Dry and wet. Dry form is most common but untreatable. Vitamin supplements with zinc, lutein and zeaxanthin may delay its progression. Wet form or neovascular ARMD is amenable to therapy.
- Photodynamic therapy with verteporfin (a radiosensitizer) is the approved therapy of neovascular ARMD.
- New strategies include intravitreal administration of anti-VEGF compounds. These include pegaptanib, ranibizumab, aflibercept and bevacizumab.
- Anecorvate is an angiogenesis inhibitor indicated for ARMD.

TREATMENT OF POISONINGS

Poisoning	Treatment
1. Ergot Alkaloids	Nitroprusside
2. β -blockers	Glucagon and Calcium
3. Organophosphates	Atropine
4. Carbamates	Atropine
5. Benzodiazepines	Flumazenil
6. Zolpidem	Flumazenil

Contd...

Sun protection factor (SPF) defines a ratio of minimal dose of sunlight that produce erythema on skin with sunscreens to that without sunscreen.

Contd...

	Poisoning	Treatment
7.	Cyanide	O ₂ + Amyl nitrite + Sodium Thiosulphate
8.	Hydrogen Sulfide	Amyl nitrite
9.	Carbon Monoxide	Hyperbaric Oxygen
10.	Methemoglobinemia	High Dose O ₂ + Methylene Blue
11.	Ethylene Glycol	Fomepizole
12.	Iron	Desferrioxamine
13.	Methanol	Fomepizole or ethanol
14.	Salicylates	Alkaline diuresis with sodium bicarbonate
15.	Isoniazid	Pyridoxine
16.	Lithium	Hemodialysis
17.	Serotonin syndrome	Cyproheptadine or chlorpromazine
18.	Opioids	Naloxone
19.	Scorpion sting	Prazosin
20.	Acetaminophen	N-acetylcysteine
21.	Atropine	Physostigmine
22.	Calcium channel blockers	Calcium
23.	Theophylline/caffeine	Esmolol

CHELATING AGENTS

	Drug	Uses in poisoning of
1.	Dimercaprol (BAL)	As, Pb, Hg, Au (contra-indicated in Fe and Cd poisoning)
2.	Succimer	Pb, As, Cd, Hg
3.	Unithiol	Hg, As, Pb
4.	Calcium disodium EDTA	Pb, Zn, Cd, Mn, Hg, Fe
5.	DTPA	Uranium, plutonium
6.	Dicobalt EDTA	Cyanide
7.	D-penicillamine	Cu, Wilson disease, Pb, Hg, cystinuria, scleroderma
8.	Trientine	Cu
9.	Desferrioxamine	Fe
10.	Deferiprone (oral)	Fe
11.	Deferasirox (oral)	Fe

STREET NAMES OF SOME DRUGS OF ABUSE

DRUG OF ABUSE	STREET NAME
Gamma Hydroxy butyrate (GHB)	Liquid ecstasy
	Grievous bodily harm
Phencyclidine and Ketamine	Angel dust
	Hog
	Special K
Cocaine	Crack (vapour to be smoked)

Contd...

Contd...

DRUG OF ABUSE	STREET NAME
	Rush
	Coke
	Snow
	Blow
	Peruvian marching Powder
Methylene dioxymethamphetamine (MDMA)	Ecstasy
	Rave drug
Lysergic acid diethylamide (LSD)	Windowpane
	Twenty-five

ADVERSE EFFECTS**1. Gingival hyperplasia**

Phenytoin	Lamotrigine
Calcium antagonists	Cyclosporine
Sirolimus	

2. Pancreatitis

Asparaginase	Didanosine
Stavudine	Zalcitabine
Azathioprine	Ethacrynic acid
Sulfonamides	Furosemide
Corticosteroids	Opioids
Thiazides	Estrogens
Mercaptopurine	Pentamidine
Valproic acid	Oral contraceptives

3. Cholestatic jaundice

Erythromycin estolate	Acetohexamide
Anabolic Steroids	Androgens
Chlorpropamide	Phenothiazines
Nitrofurantoin	Gold salts
Oral contraceptives	Flucloxacillin
Cyclosporine	Methimazole
Co-amoxycylav	

4. Altered taste

ACE inhibitors	Acetazolamide
Biguanides	Griseofulvin
Lithium	Metronidazole
Rifampicin	

5. Metallic taste

Metronidazole	Acetazolamide
Disulfiram	Auranofin
Vincristine	

6. Pulmonary fibrosis

Bleomycin	Mitomycin
Amiodarone	Busulfan
Chlorambucil	Cyclophosphamide
Methysergide	Vinblastine
Methotrexate	

7. Pulmonary eosinophilia

Amiodarone	Bleomycin
Captopril	Gold salts
GM-CSF	Nitrofurantoin
Contrast media	L-tryptophan
Phenytoin	Iodine
Carbamazepine	Aspirin
Sulfasalazine	Nilutamide
Propylthiouracil	Penicillamine
Methotrexate	Minocycline

8. Sedation

Clonidine	Methyldopa
Antihistaminics	Barbiturates
Benzodiazepines	Reserpine
TCAs	

9. Extraparasympathetic reactions

Metoclopramide	Methyldopa
Phenothiazines	Reserpine
Amitriptyline	L-dopa
Butyrophenones e.g., haloperidol	

10. Seizures

INH	Nalidixic acid
Amphetamines	Imipenem
Local Anaesthetics	Pethidine

Contd...

Contd...

Penicillins	Phenothiazines
TCA	Vincristine
Bupropion	Clozapine
Physostigmine (IV)	Quinolones
Theophylline	
11. Tremors	
TCAs	
Theophylline	
Lithium	
Sympathomimetics (β_2 -agonists)	
12. Peripheral neuropathy	
INH	Didanosine
Stavudine	Zalcitabine
Paclitaxel	Nitrofurantoin
Cisplatin	TCAs
Ethambutol	Nalidixic acid
Chlorpropamide	Demeclocycline
Ethionamide	Hydralazine
Metronidazole	Polymyxin B
Procarbazine	Phenytoin
Tolbutamide	Vincristine
Chloroquine	Chloramphenicol
Amiodarone	Clofibrate
Methysergide	
Aminoglycosides e.g. streptomycin	
13. Pseudotumor cerebri (Raised ICT)	
Sympathomimetics	Nalidixic acid
Oral contraceptives	Tetracyclines
Hypervitaminosis A	Glucocorticoids
Amiodarone	
14. Hypertension	
Cocaine	MAO inhibitors
Cyclosporine	Glucocorticoids
Oral contraceptives	TCAs
Rofecoxib	Valdecoxib
Clonidine withdrawal	Sympathomimetics
15. Hypotension	
Theophylline	Adenosine
Morphine	Quinidine
Fosphenytoin (I.V.)	Amiodarone
IL-2	Levo-dopa
Alpha blockers	Guanethidine
Bretylium	β -blockers (I.V.)
Glyceryl trinitrate	Chlorpromazine

Diuretics	Clonidine
Calcium channel blockers	
16. Congestive heart failure	
Minoxidil	CCBs
β -blockers	Carbenoxolone sodium
Diazoxide	Estrogens
Indomethacin	Mannitol
Phenylbutazone	Corticosteroids
Verapamil	
17. First dose phenomenon	
Prazosin	Murumonab CD3
Sargramostim	
ACE inhibitors esp. captopril	
18. Exacerbation of angina	
α -blockers	Withdrawal of β -blockers
Ergotamine	Thyroxine excess
Methysergide	Sumatriptan
Minoxidil	Hydralazine
Vasopressin	Oxytocin
Nifedipine	
19. Cardiomyopathy	
Daunorubicin	Emetine
Lithium	Phenothiazines
Sympathomimetics	Trastuzumab
Doxorubicin (Adriamycin)	
20. Hyperglycemia	
Thiazides	Furosemide
Glucocorticoids	Oral contraceptives
Diazoxide	L-asparaginase
Glucagon	Cyclosporine
Phenytoin	Propranolol
Tacrolimus	Protease inhibitors
Niacin	Encainide
Pentamidine (late in therapy)	
21. Hypoglycemia	
Oral hypoglycemics	Quinine
Insulin	β -blockers
Ethanol	Octreotide
Salicylates (late in over dose)	
Pentamidine (early in therapy)	

Contd...

Contd...

22. Hypertriglyceridemia

Corticosteroids	Protease inhibitors
β -blockers (non ISA)	Ethanol
Estrogens	Oral contraceptives
Thiazides	

23. Hyperkalemia

NSAIDs	SCh
ACE inhibitors	
Potassium sparing diuretics (spironolactone, amiloride and triamterene)	
Salt substitutes	ARBs (Losartan)
Lithium	Pentamidine
Digoxin overdose	Cyclosporine
Heparin	β -blockers (initially)
Cytotoxics	Trimethoprim

24. Hypokalemia

Thiazides	Furosemide
Carbenoxolone	Lithium
Corticosteroids	Amphotericin B
Gentamicin	Insulin
Mannitol	Theophylline
Carbonic anhydrase inhibitors	

25. Hyperuricemia

Cyclosporine	Diuretics
Pyrazinamide	Low dose salicylates
Nicotinic acid	Cytotoxics

26. Hypercalcemia

Cholecalciferol	Thiazides
Calcium (IV)	

27. Hypocalcemia

Calcitonin	Bisphosphonates
Plicamycin	Phenytoin
Gallium nitrate	

28. Lactic acidosis

Phenformin	Metformin
Zidovudine	Zalcitabine
Spironolactone	Acetazolamide
Salicylates	

29. Gynaecomastia

Digitalis	Spironolactone
Testosterone	Ketoconazole
Ethionamide	Calcium antagonists

Estrogens	Griseofulvin
INH	Methyldopa
Reserpine	Phenytoin
Cimetidine	Flutamide
Cyproterone acetate	Goserelin

Clomiphene

30. Hyperprolactinemia

Phenothiazines	Butyrophenones
TCAs	Reserpine
Methyldopa	Metoclopramide
Domperidone	

31. Hyperthyroidism

Amiodarone	Iodides

32. Hypothyroidism

Lithium	Iodides
Sulfonamides	Amiodarone
Phenylbutazone	Carbimazole
Acetazolamide	Phenytoin

33. Nephrogenic diabetes insipidus

Lithium	Demeclocycline
Methoxyflurane	

34. Colour vision alteration

Sulfonamides	Thiazides
Barbiturates	Digitalis
Ethambutol	Quinine
Streptomycin	

35. Glaucoma

Mydriatics	TCAs
Synpathomimetics	Corticosteroids

36. Ototoxicity (Vestibular)

Aminoglycosides	Mustine
Quinidine	Quinine
Chloroquine	Vancomycin
Furosemide	Ethacrynic acid
Salicylates (high dose)	

37. Ototoxicity (Auditory)

NSAIDs	Vancomycin
Ethacrynic acid	Aminoglycosides

38. Aplastic anaemia

Chloramphenicol	Phenytoin
Gold Salts	Carbamazepine
Phenylbutazone	Sulfonamides
Zidovudine	Colchicine
Carbimazole	Quinacrine

Contd...

Contd...

Felbamate	Cytotoxics
Thioamides	
Trimethadione	
39. Haemolytic Anaemia in G-6-PD deficiency	
Primaquine	Furazolidone
Chloramphenicol	Dapsone
Aspirin	Quinidine
Procainamide	Nalidixic acid
Quinine	Cotrimoxazole
Nitrofurantoin	Sulfonamides
Phenazopyridine	
40. Megaloblastic anaemia	
Pentamidine	Methotrexate
Trimethoprim	Cotrimoxazole
N ₂ O	Oral contraceptives
Metformin	Primidone
Phenobarbitone	Phenytoin
Triamterene	
41. SLE-like syndrome	
Hydralazine	Acebutolol
Asparaginase	Barbiturates
Bleomycin	Cephalosporins
Iodides	Sulfonamides
Thiouracil	Methyldopa
Phenytoin	INH
Quinidine	Procainamide
42. Myopathy	
Statins	Clofibrate
Daptomycin	Amphotericin B
Carbenoxolone	Chloroquine
Cimetidine	Oral contraceptives
Corticosteroids	
43. Skeletal muscle tremors	
β ₂ -agonists	Zaleplon
44. Erythema Multiforme/Stevens-Johnson syndrome/Toxic epidermal necrolysis	
Sulphones	Allopurinol
Cephalosporins	Chlorpropamide
Codeine	Ethosuximide
Lamotrigine	Nalidixic acid
Phenylbutazone	Piroxicam

Quinolones	Tocainide
Valproic acid	Penicillins
Tetracyclines	Salicylates
Barbiturates	Carbamazepine
Phenytoin	Thiazides
45. Hirsutism	
Anabolic steroids	Minoxidil
Cyclosporine	Phenytoin
46. Decreased libido/Impotence	
β-blockers	Antipsychotics
Lithium	Clonidine
Diuretics	Methyl dopa
Oral contraceptives	Sedatives
TCAs	
47. Interstitial nephritis	
Cephalosporins	Ciprofloxacin
Allopurinol	Furosemide
NSAIDs	Methicillin
Phenindione	Rifampicin
Sulfonamides	Thiazides
48. Syndrome of inappropriate ADH secretion	
Vinca alkaloids	Cyclophosphamide
Desmopressin	Oxytocin
49. Disulfiram-like reaction	
Metronidazole	Cefamandole
Cefotetan	Cefoperazone
Moxalactam	Chlorpropamide
Procarbazine	
50. Osteoporosis	
Glucocorticoids	Heparin
Thyroxine	
51. Prolonged QT_c interval	
Terfenadine	Astemizole
Cisapride	Sparfloxacin
Gatifloxacin	Grepafloxacin
Amiodarone	Bretylium
Disopyramide	Procainamide
Quinidine	Sotalol
Mefloquine	Pentamidine
Thioridazine	Ziprasidone

MULTIPLE CHOICE QUESTIONS

1. Ocreplasmin is the newer drug used in which of the following conditions?
 - (a) Retinal break
 - (b) Vitreomacular adhesion
 - (c) Submacular bleed
 - (d) Diabetic macular bleed
2. Which of the following drug is implicated in the causation of osteomalacia of the bone? (AI - 2012)
 - (a) Phenytoin
 - (b) Steroids
 - (c) Heparin
 - (d) Estrogen
3. All of the following drugs cause tachycardia except? (AI - 2012)
 - (a) Amphetamine
 - (b) Nifedipine
 - (c) Theophylline
 - (d) Clonidine
4. Which of the following drugs can result in cyanide poisoning? (AI - 2012)
 - (a) Sodium Nitroprusside
 - (b) Amyl nitrite
 - (c) Hydroxycobalamin
 - (d) Sodium thiosulphate
5. Bremelanotide is used for: (AIIMS Nov - 2011)
 - (a) Erectile dysfunction
 - (b) Lower urinary tract symptoms
 - (c) Prostate Cancer
 - (d) Metastatic renal cancer
6. Drug used for non infectious uveitis in LUMINATE clinical trial program: (AIIMS Nov - 2011)
 - (a) Steroid/Infliximab
 - (b) Cyclosporin
 - (c) Methotrexate
 - (d) Voclosporin
7. ECG of a patient showed tall T waves with normal rhythm. Laboratory examination showed serum potassium levels to be 7.5 mEq/ L. Which of the following therapies will lead to fastest reduction in the serum potassium levels? (AIIMS May 2011, 2010)
 - (a) Insulin glucose IV
 - (b) Calcium gluconate
 - (c) Cation exchange resin
 - (d) NaHCO_3
8. Which among the following does not cause hyperpyrexia? (AI - 2011)
 - (a) MAO Inhibitors
 - (b) Alcohol
 - (c) Atropine
 - (d) Amphetamine
9. All of the following drugs can cause SLE like syndrome except? (AIIMS Nov 2010)
 - (a) INH
 - (b) Penicillin
 - (c) Hydralazine
 - (d) Sulphonamide
10. Hyperkalemia without ECG changes may be treated with all except: (AIIMS Nov 2009) (AIIMS May & Nov 2010)
 - (a) Calcium gluconate
 - (b) Salbutamol
 - (c) Na bicarbonate
 - (d) Insulin with dextrose
11. All are true about neuropeptide Y except: (AIIMS Nov 2010)
 - (a) Consist of 36 amino acids
 - (b) Decreased in starvation
 - (c) Decrease thermogenesis
 - (d) Regulated by melanocortin
12. All of the following can increase appetite except: (AIIMS May 2010)
 - (a) Agouty Related Protein
 - (b) Neuropeptide Y
 - (c) Melanocyte stimulating hormone
 - (d) Agouti related peptide
13. PUVA therapy is used in: (Delhi PG - 2011)
 - (a) Psoriasis
 - (b) Lichen planus
 - (c) Freckles
 - (d) Melasma
14. Hypomagnesemia due to increased excretion by the kidney is caused by all except: (AIIMS May 2010)
 - (a) Furosemide
 - (b) Digitalis
 - (c) Aminoglycoside
 - (d) Cisplatin
15. Savlon contains: (AIIMS May 2010)
 - (a) Cetrimide and cetavlon
 - (b) Cetrimide and Chlorhexidine
 - (c) Cetrimide, Chlorhexidine and butyl alcohol
 - (d) Cetrimide and butyl alcohol
16. Which of the following drug produce neutrophilia? (Delhi PG 2011)
 - (a) Chlorambucil
 - (b) Glucocorticoids
 - (c) Sulfonamides
 - (d) Chloramphenicol

17. A 2 years old child without fever develops bone pain, vomiting and features of increased intracranial pressure following excessive medication. The drug most likely to be responsible for this is: (Delhi PG - 2011)
 - (a) Vitamin A
 - (b) Phenothiazine
 - (c) Phenytoin
 - (d) Vitamin D
18. All of the following are causes of "lupus", except: (Delhi PG - 2011)
 - (a) Hydralazine
 - (b) Clofibrate
 - (c) Penicillamine
 - (d) Chlorpromazine
19. All of the following drugs can cause hirsutism except: (AI 2010)
 - (a) Phenytoin
 - (b) Flutamide
 - (c) Norethindrone
 - (d) Danazol
20. A 17 year old girl had been taking a drug for treatment of acne for the last 2 years, which has lead to pigmentation. Which drug could it be? (AI 2010)
 - (a) Doxycycline
 - (b) Minocycline
 - (c) Azithromycin
 - (d) Chlorpromazine
21. Which of the following is incorrectly matched? (AI 2010)
 - (a) Phenytoin: Cleft lip and palate
 - (b) Zidovudine: Cardiomyopathy
 - (c) Valproate: Neural tube defect
 - (d) ACE inhibitors: Renal defects
22. Skin pigmentation occurs with which of the following drugs? (PGI Dec. 2001)
 - (a) Clofazimine
 - (b) Minocycline
 - (c) Sulfonamides
 - (d) Gold
 - (e) Rifampicin
23. Drug not used for treatment of acute Hyperkalemia is: (AIIMS May 2009)
 - (a) Insulin + glucose
 - (b) Potassium exchange resins
 - (c) Calcium carbonate
 - (d) Sodium bicarbonate
24. Appetite suppressors are all EXCEPT: (AI 2009)
 - (a) Melanocyte stimulating hormone
 - (b) Melanocyte corticotrophic releasing hormone
 - (c) Neuropeptide Y
 - (d) Leptin
25. Which teratogen causes deafness? (AIIMS May 2008)
 - (a) Isotretinoin
 - (b) Chloroquine
 - (c) Alcohol
 - (d) Warfarin
26. Which of the following drugs is NOT used in scabies? (AIIMS May 2008)
 - (a) Benzene hexachloride
 - (b) Permethrin
 - (c) Ciclopirox oleamine
 - (d) Crothamiton
27. A female has hypopigmented leison on centre of forehead. Drug responsible is? (AIIMS Nov 2008)
 - (a) Hydroquinone
 - (b) Ether metabolite of hydroquinone
 - (c) Para tertiary butyl catechol
 - (d) Para tertiary butyl phenol
28. Prostaglandin analogs have therapeutic utility in the following EXCEPT: (DPG 2009)
 - (a) Palliative treatment of patent ductus arteriosus
 - (b) Pulmonary hypertension
 - (c) Impotence
 - (d) Inflammatory bowel disease
29. Psoralen-A is used in the treatment of: (DPG 2009)
 - (a) Pemphigus
 - (b) Vitiligo
 - (c) Pityriasis alba
 - (d) Ichthyosis
30. Tactile sensations over the body are a characteristic of which poisoning? (DPG 2009)
 - (a) Cocaine
 - (b) Opium
 - (c) Cannabis
 - (d) Barbiturate
31. The erectile disorder in males is more specifically treated with which of the following agents? (DPG 2009)
 - (a) Sildenafil
 - (b) Diazepam
 - (c) Fluoxetine
 - (d) Zolpidem
32. All of the following drugs cause discolouration of urine EXCEPT: (AI-2008)
 - (a) Nitrofurantoin
 - (b) Digoxin
 - (c) Azo dyes
 - (d) Rifampicin
33. Probiotics are useful for: (AI-2008)
 - (a) Necrotizing enterocolitis
 - (b) Breast milk jaundice
 - (c) Hospital acquired pneumonia
 - (d) Neonatal seizures
34. Which of the following drugs is NOT used for erectile dysfunction? (AI 2007)
 - (a) Phenyelphrine
 - (b) Apomorphine
 - (c) Yohimbine
 - (d) Vardenafil

35. All of the following agents are used in obesity EXCEPT: (AI 2007)
 (a) Orlistat
 (b) Sibutramine
 (c) Olestra
 (d) Neuropeptide Y analogues
36. All of the following can induce methemoglobinemia EXCEPT: (AIIMS May, 2004)
 (a) Nitroglycerine
 (b) Procaine
 (c) Prilocaine
 (d) Phenytoin
37. Hypertension is not seen with: (AIIMS May, 2007)
 (a) Cyclosporine
 (b) NSAIDs
 (c) Erythropoietin
 (d) L-dopa
38. Interstitial nephritis is seen in all EXCEPT: (AIIMS May, 2007)
 (a) Diuretics
 (b) Beta lactams
 (c) Allopurinol
 (d) Isoniazid
39. Bone marrow aplasia is not seen with: (AIIMS May, 2007)
 (a) Chloramphenicol
 (b) Methicillin
 (c) Alpha methyl hydantoin
 (d) Chlorpromazine
40. Hyperglycemia is caused by all EXCEPT: (AIIMS Nov., 2007)
 (a) Beta blockers
 (b) Steroids
 (c) Diuretics
 (d) Indomethacin
41. Hypercalcemia is caused by all EXCEPT: (AIIMS Nov., 2007)
 (a) Loop diuretics
 (b) Lithium
 (c) Vitamin D intoxication
 (d) Thiazides
42. Which of the following is not used as a sedative, but causes sedation as a side effect: (AIIMS Nov., 2007)
 (a) Digitalis, anti-arrhythmics
 (b) Antihistaminics, antidepressants
 (c) Macrolides
 (d) Benzodiazepines
43. Which of the following characterizes Atkins diet?
 (a) Severely reduced fat content (AIIMS May, 2007)
 (b) Severely reduced carbohydrate content
 (c) Severely reduced protein content
 (d) Reduced mineral content
44. Drugs causing metallic taste are: (PGI Dec. 2006)
 (a) Antimicrobials
 (b) Angiotensin receptor blockers
 (c) Anticancer drugs
 (d) NSAIDs
 (e) Gold
45. Mucositis is caused by: (PGI Dec. 2006)
 (a) 5-Fluorouracil
 (b) Methotrexate
 (c) Paclitaxel
 (d) Cisplatin
 (e) Etoposide
46. Drugs causing pericarditis are all EXCEPT: (PGI Dec. 2006)
 (a) Methysergide
 (b) Hydralazine
 (c) Amiodarone
 (d) Bretylium
 (e) Minoxidil
47. Drugs which cause fetal renal anomalies are: (PGI Dec. 2006)
 (a) Enalapril
 (b) Frusemide
 (c) Angiotensin receptor blocker
 (d) Amlodipine
 (e) Phenytoin
48. Drugs causing hypokalemia are: (PGI Dec. 2006)
 (a) Amphotericin B
 (b) Insulin
 (c) Cyclosporine
 (d) Carbenoxolone
 (e) NSAIDs
49. Hyperkalemia is caused by: (PGI Dec. 2006)
 (a) Amphotericin B
 (b) ACE Inhibitors
 (c) Cyclosporine
 (d) GM-CSF
 (e) Succinylcholine
50. Drugs causing osteoporosis are: (PGI June, 2005)
 (a) Vit K
 (b) Lithium
 (c) Dilantin
 (d) Heparin
 (e) Etidronate
51. Neurochemical mechanism of analgesia involves: (PGI Dec. 2004)
 (a) VR-1
 (b) Nicotinic cholinergic
 (c) Nocistatin pattern
 (d) Nociceptin pattern
 (e) Anandamide
52. Drugs causing nephrotoxicity are: (PGI Dec. 2002)
 (a) Gentamicin
 (b) Cloxacillin
 (c) Phenacetin
 (d) Erythromycin
 (e) Doxycycline
53. Drugs causing cholestatic jaundice are: (PGI Dec. 2002)
 (a) Estrogen
 (b) Cyclosporine
 (c) INH
 (d) Phenothiazine
 (e) Ethambutol

54. **Isotretinoin is:** (PGI June, 2002)
 (a) A vitamin A analogue
 (b) Used in cystic acne
 (c) Safe in pregnancy
 (d) Used in psoriasis
 (e) Bony hyperostosis is a safe effect
55. **Motor neuropathy is caused by:** (PGI June, 2002)
 (a) Dapsone
 (b) Cisplatin
 (c) Arsenic
 (d) Lead
 (e) Hypothyroidism
56. **Urine discolouration is caused by:** (PGI June, 2002)
 (a) Thiamine
 (b) Rifampicin
 (c) Mepacrine
 (d) INH
 (e) Riboflavin
57. **Drugs which can cause malformation in the fetus if used during pregnancy include:** (PGI Dec. 2001)
 (a) Heparin
 (b) Warfarin
 (c) Valproic acid
 (d) Steroids
 (e) Phenytoin
58. **Which drugs are implicated in the causation of nephrotic syndrome:** (PGI Dec. 2001)
 (a) Gold
 (b) Amphoterecin B
 (c) Rifampicin
 (d) Ibuprofen
 (e) Captopril
59. **Drugs which cause pericarditis are:** (PGI Dec. 2001)
 (a) Hydralazine
 (b) Procainamide
 (c) Bretylium
 (d) Methysergide
 (e) Amiodarone
60. **Free radical scavengers are:** (PGI June, 2001)
 (a) Vit-C
 (b) Vit-E
 (c) Vit-A
 (d) Glutathione
 (e) Iron
61. **Treatment of choice in solar keratosis is:** (DPG 2010)
 (a) Methotrexate
 (b) Topical 5 FU
 (c) Topical mechlorethamine
 (d) Topical steroids
62. **All drugs cause interstitial lung disease, except:** (DPG 2010)
 (a) Phenytoin sodium
 (b) Sulphonamides
 (c) Busulphan
 (d) Alpha methyl dopa
63. **Constipation is caused by all of the following drugs EXCEPT:** (DPG 2008)
 (a) Neostigmine
 (b) Atropine
 (c) Morphine
 (d) Fentanyl
64. **Hirsutism is caused by which drug:** (DPG 2008)
 (a) Minoxidil
 (b) Dactinomycin
 (c) Cycloserine
 (d) Valsartan
65. **Which of the following drugs can cause lipodystrophy?** (DPG 2007)
 (a) Atorvastatin
 (b) Probucol
 (c) Saquinavir
 (d) Gentamicin
66. **Which of the following drugs is not used for the treatment of hyperkalemia?** (DPG 2007)
 (a) Salbutamol
 (b) Calcium gluconate
 (c) Sodium bicarbonate
 (d) Magnesium sulphate
67. **Gastric lavage is contra-indicated in:** (DPG 2007) (Karnataka 2004)
 (a) Salicylate poisoning
 (b) Kerosene poisoning
 (c) Morphine poisoning
 (d) Organophosphate poisoning
68. **Astringents are substances that:** (DPG 2006)
 (a) Irritate sensory nerve endings
 (b) Precipitate proteins
 (c) Penetrate target cell nucleus for their action
 (d) All of the above
69. **All of the following drugs can cause cholestatic jaundice EXCEPT:** (DPG 2005)
 (a) Erythromycin estolate
 (b) INH
 (c) OC pills
 (d) Chlorpromazine
70. **All of the following drugs cause hirsutism EXCEPT:** (DPG 2005)
 (a) Phenytoin
 (b) Minoxidil
 (c) Corticosteroids
 (d) Heparin
71. **Correctly matched pair of heavy metals and their chelating agents is:** (MPPG 2001)
 (a) Iron-BAL
 (b) Mercury-Calcium disodium edetate
 (c) Copper-d-penicillamine
 (d) Aresenic-Desferrioxamine

72. All are true about nitric oxide EXCEPT:
(a) Vasodilation (AIIMS Nov., 2007)
(b) Smooth muscle relaxation
(c) Beneficial in ARDS
(d) cAMP mediated
73. Which of the following drugs are used for smoking cessation? (DPG 2007)
(a) Bupropion
(b) Buspirone
(c) Venlafaxine
(d) Fluoxetine
74. Which one of the following is a cholestatic drug? (TN 2005)
(a) Erythromycin
(b) Phenothiazines
(c) Oral contraceptives
(d) All of the above
75. Which one of the following is not a cause for hyperkalemia: (TN 2008)
(a) Digoxin
(b) Potassium sparing diuretic
(c) Renin angiotensin system blockers
(d) Cyclosporine
76. Vitamin, which acts as a hormone is: (RJ 2000)
(a) A
(b) C
(c) D
(d) E
77. Which of the following drug has disulfide groups? (RJ 2001)
(a) BAL
(b) EDTA
(c) Penicillin
(d) Penicillamine
78. In nodulocystic acne treatment is: (RJ 2004)
(a) Steroids
(b) Antibiotics
(c) Isotretinoin
(d) Antifungal
79. Iron poisoning in 4 year child is treated by: (RJ 2007)
(a) Stomach lavage
(b) Desferrioxamine IV 100 mg
(c) X-ray abdomen
(d) Blood transfusion
80. Drug therapy used in treatment of Wernicke's encephalopathy: (JIPMER 2000) (MH 2005)
(a) Diazepam
(b) Disulfiram
(c) Thiamine
(d) Cynocobalamine
81. Which of the following chelating agent is the degradation product of Penicillin? (MH 2008)
(a) EDTA
(b) Dimercaprol
(c) Penicillamine
(d) Desferrioxamine
82. Pulmonary fibrosis occurs most commonly by:
(a) Clindamycin (Jharkhand 2003)
(b) Amiodarone (AP2004)
(c) Nikkomycin (AP2001)
(d) Kanamycin
83. Scleromatous skin changes are seen in all except: (Jharkhand 2003)
(a) Adriamycin
(b) Bleomycin
(c) Steroid
(d) Busulphan
84. Pulmonary fibrosis is noted with all except: (Jharkhand 2006)
(a) Busulfan
(b) Bleomycin
(c) Nitrofurantoin
(d) Bumetanide
85. Vitamin-B6 deficiency is seen with the use of all of the following drugs except: (AP 2002)
(a) Cycloserine
(b) Cyclosporine
(c) INH
(d) d-Penicillamine
86. Severe myopathy commonly is a side effect of (MP 2009)
(a) Rosuvastatin
(b) Nicotinic acid
(c) Ezetimibe
(d) Colesevelam
87. The following drugs can produce ototoxicity except: (MP 2009)
(a) Ethacrynic acid
(b) Aztreonam
(c) Gentamicin
(d) Frusemide
88. Gynaecomastia is an adverse effect of all of the following drugs except: (Kolkata 2008)
(a) Spironolactone
(b) Finasteride
(c) Cortisol
(d) Cimetidine
89. Drug not causing hyperuricemia: (Kolkata 2008)
(a) Probenecid
(b) Thiazide
(c) Pyrazinamide
(d) Ethambutol
90. Drugs which produce gynaecomastia are all EXCEPT: (Karnataka 2007)
(a) Cimetidine
(b) Digoxin
(c) Cortisol
(d) Spironolactone
91. The appearance of markedly vacuolated, nucleated red cells in the marrow, anemia and reticulocytopenia are characteristic dose-dependent side effects of: (Karnataka 2007)
(a) Azithromycin
(b) Chloramphenicol

- (c) Clindamycin
(d) Doxycycline
92. The following drugs cause methemoglobinemia: (Karnataka 2004)
(a) Aniline
(b) Dapsone
(c) Nitrates
(d) All of the above
93. Iodophores are mixtures of the following: (Karnataka 2002)
(a) Iodine and alcohol
(b) Iodine and aldehyde
(c) Iodine and surface active agents
(d) Iodine and phenol
94. Flushing with alcohol is seen in all EXCEPT: (MPPG 2001)
(a) Amoxicillin
(b) Co-trimoxazole
(c) Furazolidone
(d) Chlorpropamide
95. Which of the following drug causes hemolytic anemia in glucose-6-phosphate dehydrogenase deficient individual? (DNB 2002)
(a) Chloramphenicol
(b) Acetaminophen
(c) Prednisolone
(d) Griseofulvin
96. Pleural fibrosis is caused by: (PGI June, 2002)
(a) Phenytoin
(b) Methysergide
(c) Amiodarone
(d) Ergotamine
(e) Ranitidine
5. Nicotine replacement therapy is available in all forms except:
(a) Chewing gum
(b) Lozenges
(c) Patch
(d) Tablets
6. A person on anti-tubercular drugs complained of deafness and tinnitus in one ear. Drug implicated is:
(a) Streptomycin
(b) Isoniazid
(c) Ethambutol
(d) Rifampicin
7. Drug of choice for malaria in pregnancy is:
(a) Proguanil
(b) Chloroquine
(c) Artemisinin
(d) Halofantrine
8. Regarding sildenafil, all of the following statements are correct except:
(a) Should not be used with nitrates
(b) Inhibitor of phosphodiesterase V
(c) Increases libido and prolongs orgasm
(d) Its side effects are potentiated by inhibition of CYP 3A4
9. Warm antibody haemolytic anemia is seen in:
(a) Methyldopa (b) Penicillin
(c) Quinine (d) Stibophen
10. Which drug does not cause thyroid dysfunction?
(a) Amiodarone (b) Lithium
(c) PAS (d) Paracetamol
11. Highly vestibulotoxic drug is:
(a) Cisplatin
(b) Streptomycin
(c) Dihydrostreptomycin
(d) Quinine
12. Which of the following drug can cause thyroid dysfunction?
(a) Amiodarone
(b) Ampicillin
(c) Ibutilide
(d) Acyclovir
13. Drug causing peripheral neuropathy is:
(a) Zalcitabine
(b) Isoniazid
(c) Nitrofurantoin
(d) All of the above
14. Which of the following drugs does not cause gynaecomastia:
(a) Ketoconazole
(b) Cimetidine
(c) Digitalis
(d) Pyrazinamide
- RECENT QUESTIONS ASKED BY NATIONAL BOARD**
1. Which of the following drug causes hirsutism?
(a) Phenytoin
(b) Valproate
(c) Carbamazepine
(d) Phenobarbitone
2. Sildenafil acts by inhibiting
(a) Phosphodiesterase -2
(b) Phosphodiesterase -5
(c) Adenyl cyclase
(d) Guanyl cyclase
3. Drug contraindicated in a diabetic patient is:
(a) Mannitol
(b) Steroids
(c) Enalapril
(d) Glycerol
4. Drugs used in the treatment of obesity is/are:
(a) Orlistat
(b) Sibutramine
(c) Rimonabant
(d) All of the above

EXPLANATIONS

1. **Ans. (b) -Vitreomacular adhesion** (Ref: http://www.revophth.com/content/d/retinal_insider/c/40601/)

Ocriplasmin is a recombinant protease with activity against fibronectin and laminin, components of the vitreoretinal interface. It is approved by FDA for treatment of symptomatic vitreomacular adhesion (VMA). It works by dissolving the proteins that link the vitreous to the macula, resulting in posterior detachment of the vitreous from the retina.

There are two primary indications for ocriplasmin. The first is for patients who have mild to moderate symptomatic VMA, and also have good visual acuity. Vitrectomy surgery would not be a viable option for this group, because their vision is too good to risk the complications associated with surgery. The FDA approval of ocriplasmin provided surgeons with a minimally invasive means of treating these patients who previously had no viable option.

The second set of patients are those with more moderate VMA whose visual acuity has deteriorated to 20/80 or worse, sufficient to justify surgery. Ocriplasmin is the ideal first choice in these patients.

2. **Ans. (a) Phenytoin** (Ref: *CMDT 2012/1120*)

Phenytoin inhibit the hepatic production of 25 hydroxy vitamin D and also directly inhibit bone mineralization and thus may result in osteomalacia. Steroids and heparin result in osteoporosis not osteomalacia.

Important drugs causing osteomalacia are:

- Phenytoin
- Carbamazepine
- Valproate
- Phenobarbitone
- Bisphosphonates

3. **Ans. (d) Clonidine** (Ref: *KK Sharma 2/e p174*)

- Clonidine is α_2 agonist and decreases the central sympathetic outflow. It decreases blood pressure as well as heart rate.

4. **Ans. (a) Sodium Nitroprusside** (Ref: *CMDT 2012/1533*)

5. **Ans. (a) Erectile dysfunction** (Ref: *Internet*)

- **Bremelanotide** functions by activating the melanocortin receptors.
- It was shown to be effective in treating sexual dysfunction in both men (erectile dysfunction or impotence) and women (sexual arousal disorder).

6. **Ans. (d) Voclosporin** (Ref: *Internet*)

Friends, it is very unfortunate that AIIMS people are asking such type of questions. How can a medical student be expected to know about the trials about a drug which we are sure even many ophthalmology resident are not aware of. So we will suggest just to remember the answer and do not go for details.

The LUMINATE (Lux Uveitis Multicenter Investigation of a New Approach to Treatment) clinical development program was initiated in 2007 to assess the safety and efficacy of voclosporin for the treatment, maintenance, and control of all forms of noninfectious uveitis.

7. **Ans (a) Insulin glucose IV** (Ref: *CMDT 2010/799*)

Severe hyperkalemia requires emergent treatment directed at minimizing membrane depolarization, shifting K^+ into cells, and promoting K^+ loss.

- Administration of calcium gluconate decreases membrane excitability. The effect begins within minutes but is short-lived (30–60 min), and the dose can be repeated if no change in the electrocardiogram is seen after 5–10 min.
- Insulin causes K^+ to shift into cells and will temporarily lower the plasma K^+ concentration. Although glucose alone will stimulate insulin release from normal pancreatic beta cells, a more rapid response generally occurs when exogenous insulin is administered (with glucose to prevent hypoglycemia). The plasma K^+ concentration will fall by 0.5–1.5 mmol/L in 15–30 min, and the effect will last for several hours.
- Alkali therapy with intravenous $NaHCO_3$ can also shift K^+ into cells. This should be reserved for severe hyperkalemia associated with metabolic acidosis. Patients with end-stage renal disease seldom respond to this intervention and may not tolerate the Na^+ load and resultant volume expansion.
- When administered parenterally or in nebulized form, beta 2-adrenergic agonists promote cellular uptake of K^+ . The onset of action is 30 min and the effect lasts 2–4 h.

- Therefore, from the above discussion, fastest acting drug in hyperkalemia is calcium gluconate but it does not reduce potassium level and only counteracts the ECG changes induced by K^+ . For reducing the potassium level quickly, the drug is glucose insulin.
- Ans. (b) Alcohol** (Ref: *Modi's Medical Jurisprudence and Toxicology*, 23/e p313)
 - Ethyl alcohol** causes vasodilatation and peripheral circulation increases, resulting in a feeling of warmth, but at the same time there will be **loss of body heat from the skin**.
 - In **atropine** poisonin, **Pyrexia** (hot as a hare) is a common event and the temperature may be raised by 1 to 6 ° F.
 - When taken in excess, **Amphetamine** produces a dry mouth, loss of appetite, irritability, dizziness, loss of sleep, dilated pupils, severe chest pain, restlessness, tachycardia, hypertension, **rise of temperature** and death.
 - MAOI** toxicity may present as opisthotonus, muscle rigidity, diaphoresis, hypertension, chest pain, diarrhea, hallucinations, combativeness, confusion, **marked hyperthermia** and trismus.
 - Ans. (b) Penicillin** (Ref: *Harrison*, 17/2083)
 - Ans. (a) Calcium gluconate** (Ref: *CMDT-2010/798-799*)
Calcium antagonizes the cardiac conduction abnormalities induced by potassium. In the given question, patient has no ECG changes; therefore calcium gluconate will not be useful. Use of calcium gluconate should be restricted to life-threatening hyperkalemia.
 - Ans. (b) Decreased in starvation** (Ref: *Ganong*, 21/e p115, 354)
Neuropeptide secretion increases during starvation, the other actions are true regarding neuropeptide Y.
Neuropeptide Y is a polypeptide containing 36 amino acid residues that is closely related to pancreatic polypeptide. It is present in many parts of the brain and the autonomic nervous system. In the autonomic nervous system, although not in the brain, much of it is located in noradrenergic neurons, from which it is released by high-frequency stimulation. It augments the vasoconstrictor effects of norepinephrine. Circulating neuropeptide Y from sympathetic nerves increases with severe exercise in humans. In the hypothalamus, it mediates increased appetite. Y1, Y2, Y4, Y5, and Y6 receptors for this polypeptide have been cloned.
 - Ans. (c) Melanocyte stimulating hormone** (Ref: *Harrison* 17/e p472-473)
MSH causes loss of appetite and thus agonists to this agent can be used for treatment of obesity
 - Ans (a) Psoriasis** (Ref: *Goodman and Gilman* 12/e p1814)
FDA approved indications of PUVA are vitiligo and psoriasis.
 - Ans (b) Digitalis** (Ref: *Harrison* 17/e p2372)
Digitalis toxicity is precipitated by hypomagnesemia but it itself do not cause this metabolic abnormality.
Drugs and toxins causing hypomagnesemia are:

• Ethanol	• Diuretics (Loop, Thiazide, osmotic)
• Cisplatin	• Pentamidine
• Foscarnet	• Cyclosporine
• Aminoglycosides	• Amphotericin B
 - Ans (b) Cetrime and Chlorhexidine** (Ref: *KDT* 6/e p861)
Savlon is a very popular disinfectants in the hospitals and it contains of chlorhexidine and cetrime.
 - Ans. (b) Glucocorticoids** (Ref: *KDT* 6/e p278)
Glucocorticoids cause sequestration of lymphocytes, eosinophils, monocytes and basophils in tissues (and thus decrease circulating levels of these cells) whereas circulating neutrophils are increased due to release from bone marrow.
 - Ans (a) Vitamin A** (Ref: *KDT* 6/e p871)
Hypervitaminosis A result in nausea, vomiting, itching, erythema, dermatitis, exfoliation, hair loss, bone and joint pains, loss of appetite, irritability, bleeding, increased intracranial pressure and chronic liver disease.
 - Ans (b) Clofibrate** (Ref: *CMDT* 2010, 752)
Drugs associated with Lupus Erythematosus.

Definite association	Possible association	Unlikely association
Chlorpromazine	Beta-Blockers	Allopurinol
Hydralazine	Captopril	Chlorthalidone
Isoniazid	Carbamazepine	Gold Salts

Contd...

Contd...

Definite association	Possible association	Unlikely association
Quinidine	Cimetidine	Griseofulvin
Procainamide	Ethosuximide	Methysergide
Methyldopa	Levodopa	Oral contraceptives
	Lithium	Tetracyclines
	Trimethadione	Phenylbutazone
	Nitrofurantoin	Reserpine
	Penicillamine	Streptomycin
	Phenytoin	Penicillin
	Propylthiouracil	
	Sulfasalazine	
	Sulfonamides	
	Methimazole	

19. **Ans. (b) Flutamide** (Ref: CMDT-2010/1055; Katzung 11/e p718)
 'Flutamide is an anti-androgen and is used for treatment of hirsutism'
20. **Ans. (b) Minocycline** (Ref: Harrison 17/e p327-328, CMDT-2010/121)
 Both minocycline as well as chlorpromazine can cause pigmentation on long-term use.
 However, as the patient in question is being treated for acne, the answer should be minocycline. Antibiotics used in acne are erythromycin, clindamycin, tetracycline, doxycycline and minocycline.
21. **Ans. (b) Zidovudine - Cardiomyopathy** (Ref: Katzung 11/e p1028-1029)
 'Zidovudine do not cause teratogenicity, rather it is used during pregnancy to prevent vertical transmission. The major toxicity of zidovudine is bone marrow suppression.'
22. **Ans. (a) Clofazimine; (b) Minocycline; (d) Gold** (Ref: KDT 6/e p713,752, 204)
- **Drugs causing pigmentation of skin are:**
 - OCP
 - Minocycline
 - Chloroquine
 - Chlorpromazine and related phenothiazines
 - Heavy metals (Ag, Au, Bi, As)
 - Clofazimine
 - Amiodarone
 - Quinacrine

Note:

- Chloroquine causes blue-black pigmentation of nails and palate and depigmentation of hair.
- Zidovudine, hydroxyurea causes brown discolouration of nails.
- Sulphonamides cause fixed drug eruptions.
- Rifampicin cause redish discolouration of secretions.
- Vancomycin cause *Redman Syndrome*.

23. **Ans. (b) Potassium exchange resins** (Ref: CMDT-2010/798-799)

Drugs used for emergency treatment of hyperkalemia are:

- Insulin (with glucose)
- β -agonists
- Sodium bicarbonate
- Calcium gluconate

Drugs used as non-emergency measure in hyperkalemia are:

- Loop diuretics
- K^+ exchange resins [Sodium polystyrene sulfate]

24. **Ans. (c) Neuropeptide Y** (Ref: Katzung 10/e p386-88)

- Alpha-Melanocyte-Stimulating Hormone (alpha-MSH) and corticotropin-releasing hormone (CRH) both suppress food intake.

- NPY is known to be an extremely potent stimulator of feeding behavior.
- Leptin appears to act, at least in part, by inhibiting NPY synthesis and release in the hypothalamus.

25. Ans. (a) **Isotretinoin** (Ref: *Williams obstetrics* 22/e p346, 347, 348; KDT 6/e p854)

- Isotretinoin can cause microtia or anotia.
- These defects are frequently associated with agenesis or stenosis of the external ear canal and may lead to deafness.
- Isotretinoin is one of the most potent teratogen in common use.
- Abnormalities commonly occur after 1st Trimester.
- Any organ system can be affected by isotretinoin exposure but malformations typically involve the cranium, face, heart, central nervous system and thymus.
- Facial defects include *cleft palate* and *maldevelopment of the facial bones* and cranium.
- Cardiac anomalies include *conotruncal or outflow tract* defects.
- *Hydrocephalus* is the most common central nervous system defect.
- Thymic abnormalities include *aplasia, hypoplasia or malposition*.

Features of Fetal Alcohol syndrome

- Behaviour disturbances
- Brain defects
- Cardiac defects
- Spinal defects
- *Craniofacial anomalies*

Warfarin

- *First trimester* → Hypoplastic nasal bridge, chondrodysplasia
- *Second trimester* → C.N.S. malformations
- *Third trimester* → Risk of bleeding, Discontinue the use one month before delivery.
- Chloroquine is not teratogenic.

26. Ans. (c) **Ciclopirox oleamine** (Ref: *Neeta Khanna* 1/e p265; KDT 6/e p863)

Scabicides used in the t/t of scabies are

- *Permethrin* (5%)
- *Benzyl benzoate* (25%)
- *Gamma benzene hexachloride (BHC)* (1%)
- *Crotamiton* (10%)
- *Ivermectin*

27. Ans. (d) **Para Tertiary Butyl Phenol** (Ref: *Handbook of Occupational Dermatology by Lasse Kanerva*/289)

- This is a characteristic chemical leukoderma caused by the use of bindi due to its characteristic location (centre of forehead).
- Para tertiary butylphenol (PTBP) is present in the adhesives of bindi and result in leukoderma.

REMEMBER: Most potent agent causing chemical leukoderma is **Monobenzyl ether of hydroquinone**.

28. Ans. (a) **Palliative treatment of patent ductus arteriosus** (Ref: *Katzung* 10/e p305; KDT 6/e p182)

Prostaglandin analogs are useful for

- Pulmonary hypertension
- Impotence
- Peptic ulcer
- Bronchial asthma
- Inflammatory bowel disease

Remember, For PDA, indomethacin (drug decreasing PGs) is used.

29. Ans. (b) **Vitiligo** (Ref: *Katzung* 10/e p998; KDT 6/e p851)

- Psoralens (like trioxsalen and methoxsalen) along with UV-A are used to induce pigmentation in vitiligo.

30. Ans (a) **Cocaine** (Ref: *Goodman & Gilman* 11/e p621; KDT 6/e p356-357)

Cocaine characteristically causes tactile hallucinations (feeling of worms running on skin), which is known as Magnon phenomenon.

31. Ans. (a) **Sildenafil** (Ref: *Katzung* 10/e p188; KDT 6/e p295-296)

Sildenafil, vardenafil and tadalafil are phosphodiesterase V inhibitors indicated for erectile dysfunction.

32. Ans. (b) Digoxin (Ref: Principles of Pharmacology by Dr KK Sharma and Dr HL Sharma p105-107, 735, 779, 837)

33. Ans. (a) Necrotizing enterocolitis (Ref: Clinical Microbiology Reviews, Vol. 16, No. 4, October 2003, 658-672)

Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.

Bacterial colonization or infection of the intestine by pathogens such as *Clostridium*, *Escherichia*, *Klebsiella*, *Salmonella*, *Shigella*, *Campylobacter*, *Pseudomonas*, *Streptococcus*, *Enterococcus*, *Staphylococcus aureus*, and coagulase-negative staphylococci increases the risk of necrotizing enterocolitis.

Other potential uses of probiotics are

- Managing lactose intolerance
- Cholesterol lowering
- Improving immune function and preventing infections
- Antibiotic-associated diarrhea
- Improving mineral absorption
- Irritable bowel syndrome and colitis
- Prevention of colon cancer
- Lowering blood pressure
- *Helicobacter pylori*
- Reducing inflammation
- Prevents harmful bacterial growth under stress

34. Ans. (a) Phenylephrine (Ref: Katzung 9/e p189, Ahuja 6/e p194)

Drugs used for the treatment of erectile dysfunction are:

- **Oral therapy**
 - Phosphodiesterase-5 inhibitors, e.g. sildenafil, tadalafil
 - α_2 blocker, e.g. yohimbine.
 - α_1 and α_2 blocker, e.g. Phentolamine.
 - D_1 agonist, e.g. Apomorphine (sublingual).
 - Antidepressants, e.g. trazodone.
 - NO precursor, e.g. L-arginine.
- **Intracavernosal injection therapy**
 - PGE₁ analogue, e.g. alprostadil.
 - Non-selective PDE inhibitor, e.g. Papaverine.
 - Non-selective α blocker, e.g. phentolamine.
 - VIP analog, e.g. aviptadil.
 - 5HT₂ and α blocker, e.g. ketanserin.
 - Thymoxamine (α blocker with vasodilatory property).

35. Ans. (d) Neuropeptide Y analogues (Ref: KDT 6/e p130-131)

Drugs used for the treatment of obesity are:

- Fenfluramine
- Sibutramine (serotonin and NA reuptake inhibitor)
- Sucrose polyester (olestra)
- β_3 agonists
- Dexfenfluramine
- Orlistat (Pancreatic lipase inhibitor)
- Neuropeptide Y antagonists

36. Ans. (d) Phenytoin (Ref: Harrison 16/e p640; KDT 6/e p357, 524)

37. Ans. (d) L-dopa (Ref: KDT 6/e p416)

- Levo-dopa may form dopamine in the periphery. It can act on receptors in the blood vessels but increase in BP is not seen. Rather, postural hypotension is quite common with L-dopa therapy. It may be due to its central action resulting in the decrease in central sympathetic outflow.
- Cyclosporine can produce nephrotoxicity, ototoxicity, hyperkalemia, hyperglycemia, hypertension and hyperlipidemia.
- Erythropoietin produces symptoms due to sudden rise in hematocrit. It may cause hypertension.
- NSAIDs blunt the antihypertensive and diuretic effects of thiazides and loop diuretics and may result in salt and water retention.

38. Ans. (b) Beta lactamase inhibitors (Ref: <http://www.aafp.org/afp/20030615/2527.html>)

- **Drugs causing interstitial nephritis are**
 - **Antibiotics:** Cephalosporins, penicillins, ciprofloxacin, ethambutol, isoniazid, macrolides, rifampicin, sulfonamides, tetracyclines and vancomycin.
 - All NSAIDs.
 - **Diuretics:** Thiazides, furosemide, triamterene.
 - **Others:** Allopurinol, acyclovir, amlodipine, azathioprine, carbamazepine, captopril.

39. Ans. (b) Methicillin (Ref: Clinical Pharmacology and applied therapeutics by P.V. Rataboli/479, Harrison's 15/e p426)
- Drugs causing aplastic anemia or bone marrow aplasia are:

Chloramphenicol	Felbamate	Phenylbutazone
Hydantoin	Indomethacin	Sulfonamides
Gold salts	Chlorpromazine	Zidovudine
Carbamazepine	Penicillamine	Zidovudine
Ticlopidine		

40. Ans. (d) Indomethacin (See below)

41. Ans. (a) Loop diuretics (Ref: Katzung 10/e p244)

LOOP LOOSES CALCIUM. Loop diuretics cause hypocalcemia by more excretion whereas thiazides cause hypercalcemia by decreasing its excretion.

42. Ans. (b) Antihistaminics, antidepressants (Ref: Goodman & Gilman 10/e p452)

- First generation antihistaminics cause sedation and anticholinergic side effects.
- Sedative action of TCAs appears immediately and these drugs (particularly clomipramine, maprotiline and bupropion) lower the seizure threshold.
- Benzodiazepines are used as sedative drugs

43. Ans. (b) Severely reduced carbohydrate content (Ref: Harrison's 17/e p470)

- Recent data suggests that very low carbohydrate "Atkins" style diets are more effective for short term weight loss when compared with standard caloric restriction. However, these diets have not been shown to be effective in maintaining weight loss.

44. Ans. (a) Antimicrobials; (c) Anticancer drugs; (e) Gold

- Drugs causing metallic taste:
 - Antibiotics - Metronidazole
 - Anticancers - Cisplatin, Dacarbazine
 - Anti-arrhythmatics - Amiodarone, Adenosine
 - Anti-diabetics - Phenformin
 - TCA - Nortryptiline
 - Anti-convulsants
 - Anti-thyroid drugs
 - Gold

45. Ans. (a) 5-Fluorouracil; (b) Methotrexate; (c) Paclitaxel; (e) Etoposide (Ref: Harrison 15/e p471-474)

- Drugs that frequently cause mucositis are
 - Bleomycin - Actinomycin-D - Daunorubicin
 - Fluorouracil - Methotrexate - Paclitaxel
 - Mithramycin - Etoposide - Amasacrine
 - Hydroxyurea - Cytosine arabinoside - Topotecan

46. Ans. (c) Amiodarone; (d) Bretylium (Ref: Harrison's 17/e p1493)

- Drugs causing pericarditis
 - Procainamide - Hydralazine - Phenytoin
 - Isoniazid - Minoxidil - Anticoagulants
 - Methysergide - Minoxidil - Penicillins

47. Ans. (a) Enalapril; (c) Angiotensin receptor blocker (Ref: KDT 6/e p488)

- Both ACEIs and ARBs are contraindicated in pregnancy. They affect growth and development of fetus. ACEI cause hypoplasia of organs specially Lungs and kidneys.
- Furosemide can be used in pregnancy. No such fetal anomalies mentioned.
- Phenytoin produces fetal hydantoin syndrome characterised by hypoplastic phalanges, cleft palate, hare lip and microcephaly when used in pregnancy. (Ref: KDT 5/e p373)

48. Ans. (a) Amphotericin B; (b) Insulin; (d) Carbenoxolone (Ref: Harrison's 16/e p259, 262)

- Drugs causing hypokalemia Hyperkalemia
 - Insulin Digitalis toxicity
 - β_2 adrenergic agonists ACEI, ARB, NSAIDs

- β -Adrenergic antagonists - Trimethoprim
- GM-CSF - Pentamidine
- Diuretics - Spironolactone
- Osmotic diuretics - Amiloride
- Carbenoxolone - Heparin
- Amphotericin B - Salt substitutes
- Penicillin derivatives - Succinylcholine
- Licorice-Cyclosporine

49. Ans. (b) ACE inhibitors; (c) Cyclosporine; (e) Succinylcholine (Ref: Harrison's 16/e p259)

50. Ans. (b) Lithium; (c) Dilantin; (d) Heparin (Ref: Harrison 16/e p2271)

Drugs causing osteoporosis:

- Glucocorticoids • Cyclosporine • Cytotoxic drugs
- Anticonvulsants • Excessive alcohol intake • Excessive thyroxine
- Aluminum • Gonadotropin releasing hormone agonists
- Heparin • Lithium

Etidronate is used in osteoporosis.

51. Ans. (a) VR-1 (b) Nicotinic cholinergic; (d) Nociceptin pattern (e) Anandamide (Ref: Ganong 21/e p124, 143, 144, 148)

- VR-1 (vanilloid receptor-1) and VRL-1 are new receptors that are associated with pain mechanism. VR-1 produces pain with capsaicin but VRL-1 doesn't. VR-1 is clearly a nociceptor while VRL-1 is probably a nociceptor. Nociceptors mediate potentially harmful stimuli such as pain, extreme heat and extreme cold.
- Nicotinic cholinergic mechanism is involved in the regulation of pain as the analgesic effect of nicotine is reduced in mice lacking α_4 and β_2 nicotinic cholinergic receptor subunits.
- There are anandamide containing neurons in the parabrachial grey matter and other areas concerned with pain. Anandamide have definite analgesic effects.

52. Ans. (a) Gentamicin; (c) Phenacetin (Ref: KDT 5/e p465, 732)

- Aminoglycosides and phenacetin cause nephrotoxicity while cloxacillin, doxycycline and erythromycin does not have nephrotoxic potential.

53. Ans. (a) Estrogen; (b) Cyclosporine; (d) Phenothiazine (Ref: Harrison 15/e p434)

- Drugs causing cholestatic jaundice are:
 - Oral contraceptives - Phenothiazines - Erythromycin
 - Chlorpropamide - Nitrofurantoin - Cyclosporine
 - Anabolic steroids - Androgens - Acetohexamide
 - Gold salts - Flucloxacillin - Clavulanic acid/amoxicillin
 - Methimazole
- INH cause hepatitis and peripheral neuritis.
- Ethambutol cause optic neuritis and hyperuricemia.

54. Ans. (a) A vitamin A analogue; (b) Used in cystic acne; (e) Bony hyperostoses is a side effect (Ref: KDT 6/e p854)

- Isotretinoin (Accutane) is a vitamin A analogue for treatment of severe cystic acne that has not responded to conventional therapy.
- It is absolutely contraindicated in pregnancy, as it is highly teratogenic; upto 25% exposed fetuses had birth defects manifested as craniofacial, heart, and CNS abnormalities (Accutane embryopathy).
- Adverse effects on isotretinoin are:
 - Dry skin and mucous membrane
 - Pseudotumor cerebri
 - Depression
 - Hypertiglyceridemia
 - Hypercholesterolemia
 - Minor alteration of LFT
 - $\uparrow$ Fasting blood sugar
 - Miscellaneous: decreased night vision, musculoskeletal or bowel symptoms, rash, thinning of hair, exuberant granulation tissue in lesions, bony hyperostoses (seen only with very high doses or with long duration of therapy), moderate to severe myalgias.
- Etretinate, a synthetic second generation retinoid is used in severe refractory psoriasis, especially that associated with inflammation, and in psoriatic arthritis.

55. Ans. (a) Dapsone; (c) Arsenic; (d) Lead (Ref: Harrison/2067, 2068, 2503, 2504)
- Dapsone, a dermatologic agent used for leprosy, causes dose related *pure motor* neuropathy.
 - Arsenic causes *both motor and sensory* neuropathy.
 - Inorganic lead causes *selective motor* neuropathy with prominent wrist drop.
 - Cisplatin causes *severe sensory sensory* neuropathy.
 - In hypothyroidism, carpal function with stiffness, cramps and pain. Myopathy, with muscle swelling, is more common.
56. Ans. (b) Rifampicin; (e) Riboflavin (Ref: KDT 6/e p742)
- Rifampicin causes discolouration of urine and other body secretions which becomes orange-red.
 - Riboflavin (vit. B₂) is a yellow coloured flavone compound. In high doses, it is excreted unchanged in urine, giving urine a yellow colour.
 - Mepacrine is an antimalarial drug which is also active against Giardia and tape worms. It is a yellow powder; long term use discolours skin and eye, but not urine.
 - Thiamine (vit. B₁) is a colourless compound and does not discolour urine.
 - INH metabolites are excreted in urine, but do not discolour urine.
57. Ans. (b) Warfarin; (c) Valproic acid; (d) Steroids; (e) Phenytoin (Ref: KDT 5/e p76)
- Heparin does not cross placental barrier.
 - Fetal malformation with different drugs are given below:
 - Warfarin → 'Chondrodysplasia punctata' – Craniofacial abnormality known as contradi syndrome.
 - Valproic acid → Neural tube defect, spina bifida
 - Phenytoin → 'Fetal hydantoin syndrome': hypoplastic phalanges, cleft lip, cleft palate, microcephaly.
 - Steroid → Maternal and fetal adrenal hypoplasia, cleft palate/lip, cardiac defects.
58. Ans. (a) Gold; (d) Ibuprofen; (e) Captopril (Ref: Harshmohan 5/e p435)
- Drugs causing nephrotic syndrome – Gold, penicillamine, captopril, NSAIDs (here ibuprofen), phenindione, probenecid, ketoprofen.
 - Amphotericin causes renal tubular acidosis with hypokalemia.
 - Rifampicin can be safely used in renal failure.
59. Ans. (a) Hydralazine; (b) Procainamide; (d) Methysergide (Ref: Harrison 17/e p1493)
- Drugs causing pericarditis are:
 - Procainamide – Hydralazine – Phenytoin
 - Isoniazid – Methysergide – Minoxidil
 - Anti coagulants
 - Amiodarone causes myocardial depression.
60. Ans. (a) Vit-C; (b) Vit-E; (c) Vit-A; (d) Glutathione (Ref: Harper/649)
- The free radical scavengers along with the free radical are given below:

	Reactive species	Anti-oxidants
O ₂	Singlet oxygen	Vit. A, β-carotene, Vit. E
O ₂ ⁻	Superoxide radical	Superoxide dismutase, Vit. E, β-carotene
OH	Hydroxyl free radical	
RO	Alkoxyl free radical	Vit. E, Vit. C
ROO	Peroxyl free radical	Catalase, glutathione peroxidase
H ₂ O ₂	Hydrogen peroxide	Glutathione peroxidase
LOOH	Lipid peroxides	

61. Ans. (b) Topical 5FU (Ref: CMDT-2010/113)
- Solar (actinic) keratosis is treated by application of liquid nitrogen. Alternative treatment is 5-FU. Imiquimod cream can also be used.
62. Ans. (d) Alpha methyl dopa (Ref: CMDT-2010/262, Katzung 11/e p943)

Drugs causing interstitial lung disease are:

• Amiodarone	• Methotrexate	• Nitrofurantoin
• Nitrosoureas	• Sulfonamides	• Gold salts

- Busulfan
- Phenytoin
- Penicillamine
- Cyclophosphamide
- Bleomycin

63. Ans. (a) **Neostigmine** (Ref: KDT 6/e p101, 455)

- Neostigmine is an inhibitor of acetylcholinesterase and thus acts like a cholinergic drug. Therefore, it can produce diarrhea (not constipation).
- Atropine is an anti-cholinergic drug, thus can cause constipation.
- Morphine and fentanyl are opioids. These can also result in constipation.

64. Ans. (a) **Minoxidil** (Ref: KDT 6/e p548)

- Minoxidil is a potassium channel opener, useful as antihypertensive drug. It can cause hirsutism in females and is used for the treatment of alopecia in males.

65. Ans. (c) **Saquinavir** (Ref: Goodman & Gilman 11/e p1301)

- All protease inhibitors are associated with HIV-lipodystrophy. Saquinavir is a protease inhibitor.
- All NRTIs are associated with lactic acidosis. Stavudine can also cause lipoatrophy (maximum among NRTIs).
- Insulin can also result in lipodystrophy.

66. Ans. (d) **Magnesium sulphate** (Ref: Harrison 16/e p262-263)

- Calcium gluconate decreases membrane excitability and reverses ECG changes of severe hyperkalemia.
- Insulin and bicarbonate can shift potassium inside the cells. Glucose is added to prevent hypoglycemia due to insulin.
- β_2 agonists like salbutamol can also move potassium inside the cells.

67. Ans. (b) **Kerosene poisoning** (Ref: KDT 6/e p81)

Gastric lavage is contra-indicated in kerosene and acid or alkali i.e. corrosive poisonings.

68. Ans. (b) **Precipitate proteins** (Ref: KDT 6/e p846)

- Astringents are substances that precipitate proteins, but do not penetrate cells, thus affect the superficial layer only.

69. Ans. (b) **INH** (Ref: Harrison 17/e p765)

- Drugs causing cholestatic hepatitis:

- Acetohexamide	- Anabolic steroids	- Androgens
- Chlorpropamide	- Clavulanic acid/amoxicillin	- Cyclosporine
- Erythromycin estolate	- Flucloxacillin	- Gold salts
- Methimazole	- Nitrofurantoin	- Oral contraceptives
- Phenothiazines		
- **INH does not produce cholestatic jaundice, rather it causes diffuse hepatocellular damage.**

70. Ans. (d) **Heparin** (Ref: Harrison 17/e p01)

- Drugs causing hirsutism:
 - Androgens
 - Oral contraceptives containing androgenic progestins
 - Minoxidil
 - Phenytoin
 - Diazoxide
 - Cyclosporine (Not tacrolimus)
- **Heparin produces transient and reversible alopecia.**

71. Ans. (c) **Copper-d penicillamine** (Ref: KDT 6/e p807)

72. Ans. (d) **cAMP mediated** (Ref: Katzung 10/e p309, 310)

- NO acts through cGMP and not through cAMP
- Nitric oxide (NO) is a signaling molecule having important role in various pathophysiological conditions. It is also known as endothelium derived relaxing factor (EDRF).
- NO formed from the action of NOS binds to iron in heme and causes an increase in the concentration of cGMP by stimulating guanylyl cyclase. This cGMP is responsible for its vasodilatory actions.
- It is beneficial in ARDS and pulmonary artery hypertension.

73. Ans. (a) **Bupropion** (Ref: Harrison 16/e p2575; Katzung 11/e p521, 1110)

Drugs used for smoking cessation are:

- Nicotine (gum, patch, nasal inhaler, oral inhaler)
- Clonidine (oral, patch)
- Varenicilline
- Nortriptyline
- Amfebutamone
- Bupropion
- Rimonabant
- Mecamylamine

74. Ans. (d) All of the above (Ref: Harrison 16/e p434)

75. Ans. (a) Digoxin (Ref: Harrison 15/e p432)

76. Ans. (c) D (Ref: KDT 6/e p330)

77. Ans. (a) BAL (Ref: KDT 6/e p865)

78. Ans. (c) Isotretinoin (Ref: KDT 6/e p854)

79. Ans. (b) Desferrioxamine IV 100 mg (Ref: KDT 6/e p587)

80. Ans. (c) Thiamine (Ref: KDT 6/e p873)

81. Ans. (c) Penicillamine (Ref: KDT 6/e p867)

82. Ans. (b) Amiodarone (Ref: KDT 6/e p516)

83. Ans. (c) Steroid (Ref: KDT 6/e p286)

84. Ans. (d) Bumetanide (Ref: Harrison 15/e p430-432)

85. Ans. (b) Cyclosporine (Ref: KDT 6/e p876)

86. Ans. (a) Rosuvastatin (Ref: KDT 6/e p615)

87. Ans. (b) Aztreonam (Ref: Dhingra's Ent 4/e p34)

88. Ans. (c) Cortisol (Ref: CMDT 2010/1064)

89. Ans. (a) Probenecid (Ref: KDT 6/e p191)

90. Ans. (c) Cortisol (Ref: KDT 6/e p498,571,629)

Drugs causing gynaecomastia are

- D Digitalis
- I Isoniazid
- S Spironolactone
- C Cimetidine and Ketoconazole
- O Oestrogens

91. Ans. (b) Chlormaphenicol (Ref: KDT 6/e p717)

The features given are of bone marrow suppression which a very significant adverse effect of chlormaphenicol.

92. Ans. (d) All of the above (Ref: KDT 6/e p524,752, Harrison 17/e p35.4)

Drugs causing Methemoglobinemia are

- Aniline derivatives
- Nitrites
- Nitro- and nitrosohydrocarbons
- Sulfonamides
- Dapsone
- Nitrites
- Phenazopyridine
- Primaquine
- Prilocaine
- Nitrogen oxides

93. Ans. (c) Iodine and surface active agents (Ref: Katzung 11/e p880)

94. Ans. (a) Amoxicillin (Ref: KDT 6/e p383; Niraj Ahuja 5/e p43)

DRUGS CAUSING DISULFIRAM LIKE REACTION

- Metronidazole
- Cefamandole
- Chlorpropamide
- Sulfonamides (Co-trimoxazole)
- Furazolidone
- Cefotetan
- Procarbazine
- Phenylbutazone
- Cefoperazone
- Moxalactam
- Griseofulvin

95. Ans. (a) Chloramphenicol (Ref: Harrison 15/e p433)

96. Ans. (b) Methysergide; (c) Amiodarone (Ref: KDT 6/e p167,516)

- Methysergide and amiodarone causes pleural fibrosis
- Others drugs mentioned here, donot cause pleural fibrosis.

ANSWERS OF RECENT QUESTIONS ASKED BY NATIONAL BOARD

1. Ans. (a) Phenytoin (Ref: KDT 7th/414)
2. Ans. (b) Phosphodiesterase – 5 (Ref: KDT 7th/303)
3. Ans. (b) Steroids (Ref: KDT 7th/294)
4. Ans. (d) All of the above (Ref: KDT 7/e p139)
5. Ans. (d) Tablets (Ref: CMDT 2014 p8)
 - Nicotine replacement is available as
 - Patch
 - Gum
 - Lozenges
 - Nasal sprays
 - Inhalers
6. Ans. (a) Streptomycin (Ref: KDT 7/e p770)
7. Ans. (b) Chloroquine (Ref: KDT 7/e p823)
8. Ans. (c) Increases libido and prolongs orgasm (Ref: KDT 7/e p303-304)
 - Sildenafil inhibits PDE-5 and result in erection. It is not an aphrodisiac, do not increase libido.
9. Ans. (a) Methyldopa (Ref: KDT 7/e p566)
10. Ans. (d) Paracetamol (Ref: KDT 7/e p533)
11. Ans. (b) Streptomycin (Ref: KDT 7/e p769-770)
12. Ans. (a) Amiodarone (Ref: KDT 7/e p533)
13. Ans. (d) All of the above (Ref: KDT 7/e p760, 767, 808)
14. Ans. (d) Pyrazinamide (Ref: KDT 7/e p793, 650, 516, 769)

	Drug of choice	Reference
Acetaminophen poisoning	ACETYLCYSTEINE	CMDT 2015/1553
Acute bronchial asthma	SALBUTAMOL	CMDT 2015/251
Acute gout	NSAIDS (EXCEPT ASPIRIN)	CMDT 2015/813
Acute hyperkalemia	CALCIUM GLUCONATE	CMDT 2015/872
Acute mania	NEUROLEPTICS (E.G. OLANZAPINE) $\pm$ LITHIUM	CMDT 2015/1061
Acute severe digitalis toxicity	DIGIBIND	CMDT 2015/1556
Acute severe migraine	SUMATRIPTAN	CMDT 2015/955
ADHD	METHYLPHENIDATE	KDT 6th/470
Alzheimer's disease	DONEPEZIL/RIVASTIGMINE/GALLANTAMINE	CMDT 2015/59
Ameobiasis		
– Asymptomatic intestinal	DILOXANIDE FUROATE	CMDT 2015/1495
– Symptomatic intestinal	METRONIDAZOLE + DILOXANIDE	CMDT 2015/1495
– Extraintestinal (e.g. hepatic)	METRONIDAZOLE + DILOXANIDE	CMDT 2015/1495
Anaphylactic shock	ADRENALINE (s.c./i.m.)	CMDT 2015/487
Anti thyroid in pregnancy and breast feeding	PROPYLTHIOURACIL	CMDT 2015/1104
Anticoagulant for HIT	ARGATROBAN/BIVALIRUDIN	CMDT 2015/542
Atonic seizures	VALPROATE	Harrison 18th/3262
Atropine poisoning	PHYSOSTIGMINE	CMDT 2015/1553
Atypical pneumonia	TETRACYCLINE/ ERYTHROMYCIN	Katzung 11th/797
Babesiosis	QUININE + CLINDAMYCIN	CMDT 2015/1490
Benzodiazepine poisoning	FLUMAZENIL	CMDT 2015/1553
Beta blocker poisoning	GLUCAGON	CMDT 2015/1562
Bipolar disorder	LITHIUM	Harrison 18th/3540
Brucella	DOXYCYCLINE + RIFAMPICIN	CMDT 2015/1442
Carbamate poisoning	ATROPINE	CMDT 2015/1574
Cheese reaction	PHENTOLAMINE	KDT 6th/440, 545
Chemotherapy induced vomiting (Early phase)	PALONOSETRON	CMDT 2015/1645
Chloroquine resistant malaria	ARTEMISININ COMBINATION THERAPY	CMDT 2015/1484
Cholera	TETRACYCLINE	CMDT 2015/1440
Chronic lymphocytic leukemia	FLUDARABINE + RITUXIMAB $\pm$ CYCLOPHOSPHAMIDE	CMDT 2015/520
Cisplatin induced vomiting (Delayed Phase)	APREPITANT	CMDT 2015/1645
Clonidine withdrawal	PHENTOLAMINE	KDT 6th/545
Coccidiosis		
– Cryptosporidiosis	PAROMOMYCIN/NITAZOXANIDE	CMDT 2015/1498
– Isosporiasis	COTRIMOXAZOLE	CMDT 2015/1498
– Cyclosporiasis	COTRIMOXAZOLE	CMDT 2015/1498
– Microsporidiosis	ALBENDAZOLE	CMDT 2015/1498

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Complicated Malaria	ARTESUNATE	CMDT 2015/1484
Cyanide toxicity	AMYL NITRITE/HYDROXOCOBALAMIN	CMDT 2015/1564
Cytomegalovirus (CMV)	GANCICLOVIR	CMDT 2015/1353
Depression	FLUOXETINE	Harrison 18th/3538
Diabetes insipidus		
– Central	DESMOPRESSIN	CMDT 2015/1088
– Nephrogenic	THIAZIDES	CMDT 2015/1088
– Lithium-induced	AMILORIDE	CMDT 2015/1088
Diabetes mellitus		
– Type 1	INSULIN	CMDT 2015/1209
– Type 2	METFORMIN	CMDT 2015/1211
– Ketoacidosis	REGULAR INSULIN + IV FLUIDS	CMDT 2015/1224
– Pregnancy	INSULIN	CMDT 2015/1221
DMARD	METHOTREXATE	CMDT 2015/819
Drug induced Parkinsonism	BENZHEXOL (TRIHENYPHENYDIL)	KDT 6th/421
Echinococcosis	ALBENDAZOLE	CMDT 2015/1506
Muscle relaxant for Endotracheal intubation	SUCCINYLCHOLINE	KDT 6th/346
Enteric fever	CEFTRIAXONE/CIPROFLOXACIN	CMDT 2015/1438
Enterobiasis	ALBENDAZOLE	CMDT 2015/1509
Ethylene glycol poisoning	FOMEPIZOLE	CMDT 2015/1571
Fasciola hepatica	TRICLABENDAZOLE	CMDT 2015/1502
Febrile seizures	DIAZEPAM	KDT 6th/413
Fibrinolytics overdose	EACA	Katzung 11th/602
Filariasis	DIETHYLCARBAMAZINE	CMDT 2015/1514
Flukes (except fasciola)	PRAZIQUANTAL	Katzung 11th/924
Generalized anxiety disorder		
– Acute treatment	BENZODIAZEPINES	CMDT 2015/1031-1032
– Sustained treatment	ANTIDEPRESSANTS (VENLAFAXINE/DULOXETINE)	CMDT 2015/1031-1032
Giardiasis	METRONIDAZOLE/	CMDT 2015/1499
Gonorrhoea	CEFTRIAXONE + AZITHROMYCIN/DOXYCYCLINE	CMDT 2015/1444
Grand mal epilepsy	VALPROATE	Harrison 18th/3262
Graves Ophthalmopathy	I.V. METHYLPREDNISOLONE	CMDT 2015/1107
Hairy cell leukemia	CLADRIBINE	CMDT 2015/521
Heparin overdose	PROTAMINE	Katzung 11th/593
Herpes simplex		
– Mucocutaneous	ACYCLOVIR/VALACYCLOVIR	CMDT 2015/118, 1343
– Keratitis	TOPICAL TRIFLURIDINE/VIDARABINE/ACYCLOVIR	CMDT 2015/118, 1343
– Neonatal	ACYCLOVIR	CMDT 2015/118, 1343
– Encephalitis/Meningitis	ACYCLOVIR	CMDT 2015/118, 1343
– Bell palsy	PREDNISOLONE	CMDT 2015/118, 1343
Hookworm	ALBENDAZOLE	CMDT 2015/1507
Hypertension in pregnancy	α - METHYL DOPA/BETA BLOCKERS	CMDT 2015/801
Hypertension with BHP	PRAZOSIN	Katzung 11th/154

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Hypertensive emergencies in pregnancy	LABETALOL	CMDT 2015/460
Hypertensive emergencies	NICARDIPINE + LABETALOL	CMDT 2015/460
Hypertriglyceridemia	FIBRATES	Harrison 18th/1067
Hypothyroidism	LEVO-THYROXINE	CMDT 2015/1097
Hypovolemic shock	I.V. FLUIDS (CRYSTALLOIDS)	CMDT 2015/486-487
Infantile spasms	ACTH	Katzung 11th/418
Iron toxicity	DESFERRIOXAMINE	CMDT 2015/1567
Kala azar	LIPOSOMAL AMPHOTERICIN B	CMDT 2015/1479
Malaria (P. Vivax)	CHLOROQUINE	CMDT 2015/1484
Malaria (P. falciparum)	ARTEMISININ COMBINATION THERAPY	CMDT 2015/1484
Malignant hyperthermia	DANTROLENE	Harrison 18th/147
Methanol poisoning	FOMEPIZOLE	CMDT 2015/1571
MRSA	VANCOMYCIN	Harrison 18th/1070
Multiple myeloma	DEXAMETHASONE + LENALIDOMIDE AND/OR BORTEZOMIB	CMDT 2015/526
Mydriatic in adults	TROPICAMIDE	Katzung 11th/119
Mydriatic in children	ATROPINE	Katzung 11th/119
Myoclonic seizures	VALPROATE	Harrison 18th/3262
Neurocysticercosis	ALBENDAZOLE + CORTICOSTEROIDS	CMDT 2015/1505
Neurolept anaesthesia	FENTANYL+DROPERIDOL+NITROUS OXIDE	Katzung 11th/495
Neurolept analgesia	FENTANYL + DROPERIDOL	Katzung 11th/495
Neurolept malignant syndrome	DANTROLENE	Harrison 18th/147
Nocturnal enuresis	DESMOPRESSIN	KDT 6th/577
NSAID induced PUD	PROTON PUMP INHIBITORS	CMDT 2015/612
OCD	FLUOXETINE	CMDT 2015/1034
OHA in obese patients	METFORMIN	CMDT 2015/1199-1200
Onchocerciasis (river blindness)	IVERMECTIN	CMDT 2015/1515
Opioid poisoning	NALOXONE	CMDT 2015/1533
Organophosphate poisoning	ATROPINE	CMDT 2015/1574
P/O Chloroquine resistant malaria	MEFLOQUINE	CMDT 2015/1488
P/O Influenza A [H5N1 and H1N1]	OSELTAMIVIR	CMDT 2015/1388
P/O Malaria in pregnancy	CHLOROQUINE	CMDT 2015/1488
P/O Malaria	CHLOROQUINE	CMDT 2015/1488
P/O Mycobacterium avium complex	CLARITHROMYCIN/ AZITHROMYCIN	CMDT 2015/1451
P/O Plague	DOXYCYCLINE	CMDT 2015/1443
P/O Pneumocystis jiroveci pneumonia	COTRIMOXAZOLE	CMDT 2015/1323
P/O Rheumatic fever	BENZATHINE PENICILLIN	CMDT 2015/418
P/O Toxoplasmosis	COTRIMOXAZOLE	CMDT 2015/1492
P/O Whooping cough	ERYTHROMYCIN	CMDT 2015/1393
Panic attack (Acute treatment)	BENZODIAZEPINES	CMDT 2015/1032
Panic disorder (sustained treatment)	SSRI (SERTRALINE)	CMDT 2015/1033
Partial seizures (Temporal Lobe Epilepsy)	CARBAMAZEPINE	Harrison 18th/3262
Peptic ulcer disease	PPIs	CMDT 2015/610

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Performance anxiety	PROPRANOLOL	Harrison 17th/2713
Petit mal epilepsy in >3 yrs	VALPROATE	Harrison 18th/3262
Petit mal epilepsy in children	ETHOSUXIMIDE	Harrison 18th/3266
Phobias	SSRI (SERTRALINE)	CMDT 2015/1033
Pneumocystis jiroveci pneumonia	COTRIMOXAZOLE	CMDT 2015/1323
POAG	LATANOPROST	CMDT 2015/179
Post menopausal osteoporosis	ALENDRONATE	Harrison 18th/2405
Post prandial hyperglycemia	NATEGLINIDE	KDT 6th/269
Post traumatic stress disorder	SSRI (SERTRALINE/PAROXETINE)	CMDT 2015/1032
Prevention of DVT	WARFARIN	Katzung 11th/600
Prophylaxis of mania	LITHIUM	Katzung 11th/502
Prophylaxis of MI	ASPIRIN	Katzung 11th/600
Pseudomonas	PIPERACILLIN-TAZOBACTAM/CEFTAZIDIME+ AMINOGLYCOSIDES	CMDT 2015/1288
Roundworm (Ascariasis)	ALBENDAZOLE	CMDT 2015/1507
Secondary Shock	α - BLOCKERS	KDT 6th/136
Shock with oliguria	DOPAMINE	CMDT 2015/487
SMR in asthmatics	CURONIUMS LIKE VECURONIUM	Katzung 11th/460
SMR in liver and kidney disease	CIS-ATRACURIUM	Katzung 11th/453
Steroid induced osteoporosis	ALENDRONATE	CMDT 2015/1136
Status epilepticus	LORAZEPAM (I.V.)	CMDT 2015/966
Streptococcus	PENICILLIN	CMDT 2015/1287
Strongyloidiasis	IVERMECTIN	CMDT 2015/1509
Surgical prophylaxis	CEFAZOLIN	Katzung 11th/896
Syphilis		
– Primary	BENZATHINE PENICILLIN G	CMDT 2015/1459
– Secondary	BENZATHINE PENICILLIN G	CMDT 2015/1459
– Latent	BENZATHINE PENICILLIN G	CMDT 2015/1459
– Tertiary except neurosyphilis	BENZATHINE PENICILLIN G	CMDT 2015/1459
– Neurosyphilis	PENICILLIN G (AQUEOUS)	CMDT 2015/1459
– In pregnancy	PENICILLIN G (AS ABOVE)	CMDT 2015/1459
Tapeworms (except Echinococcus)	PRAZIQUANTAL	CMDT 2015/1503-1505
Termination of acute angina	S.L. NITROGLYCERINE	CMDT 2015/355
Termination of PSVT	ADENOSINE	CMDT 2015/381
Tetanus	METRONIDAZOLE	Harrison 18th/1199
To keep ductus patent	ALPROSTADIL (PGE_1)	Katzung 11th/326
Toxoplasmosis in pregnancy	SPIRAMYCIN	CMDT 2015/1492
Toxoplasmosis	PYRIMETHAMINE + SULFADIAZINE + FOLINIC ACID	CMDT 2015/1492
Treatment of PDA	INDOMETHACIN	Katzung 11th/326
Treatment of PPH	OXYTOCIN	Katzung 11th/289
Trichomoniasis	METRONIDAZOLE	CMDT 2015/1500
Trichinosis	MEBENDAZOLE/ALBENDAZOLE	CMDT 2015/1511
Trichuris	ALBENDAZOLE	CMDT 2015/1507
Trigeminal neuralgia	OXCARBAZEPINE/CARBAMAZEPINE	CMDT 2015/958

Contd...

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VRSA	LINEZOLID/STREPTOGRAMINS	Harrison 18th/1169
Warfarin overdose	VITAMIN K ₁	CMDT 2015/1560
Wegener's granulomatosis (now known as granulomatosis with polyangitis)	CYCLOPHOSPHAMIDE	CMDT 2015/841

Full form of Abbreviations

ADHD	:	Attention deficit hyperkinetic disorder
DI	:	Diabetes insipidus
DVT	:	Deep vein thrombosis
EACA	:	Epsilon amino caproic acid
HIT	:	Heparin induced thrombocytopenia
IDN	:	Isosorbide dinitrate
MRSA	:	Methicillin resistant <i>Staphylococcus aureus</i>
NTG	:	Nitroglycerine
OCD	:	Obsessive compulsive disorder
OHA	:	Oral hypoglycemic agent
P/O	:	Prophylaxis of
PDA	:	Patent ductus arteriosus
POAG	:	Primary open angle glaucoma
PPI	:	Proton pump inhibitor
PSVT	:	Paroxysmal supraventricular tachycardia
PUD	:	Peptic Ulcer Disease
VRSA	:	Vancomycin resistant <i>Staphylococcus aureus</i>

NOTES

This image shows a single page of white paper with horizontal blue or grey ruling lines. The lines are evenly spaced and run across the width of the page, leaving small margins at the top and bottom. There are no vertical margin lines, text, or other markings on the page.

1. **Abatacept:** Co-stimulation inhibitor useful for the treatment of DMARD resistant **rheumatoid arthritis**.
2. **Abiraterone acetate:** It is converted in vivo to abiraterone, an androgen biosynthesis inhibitor that inhibits 17 α -hydroxylase/C 17, 20-lyase (CYP17) It is indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant **prostate cancer** who have received prior chemotherapy containing docetaxel.
3. **AbobotulinumtoxinA:** An acetylcholine release inhibitor and a neuromuscular blocking agent for the treatment of **cervical dystonia** in adults to reduce the severity of abnormal head position and neck pain, and for the temporary improvement in the appearance of moderate to severe glabellar lines.
4. **Acetyl-carnitine:** Apart from increasing the cholinergic transmission, it also possesses antioxidant property It is useful in slowing the progression of **Alzheimer's disease**.
5. **Acridinium bromide:** An anticholinergic with specificity for muscarinic receptors. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation. It has been recently approved for **COPD**.
6. **Ado-trastuzumab emtansine:** It is a HER2-targeted antibody (trastuzumab) and microtubule inhibitor (mertansine) conjugate indicated for the treatment of patients with HER2-positive, **metastatic breast cancer**. Trastuzumab alone stops growth of cancer cells by binding to the HER2/neu receptor, whereas mertansine enters cells and destroys them by binding to tubulin. Because the monoclonal antibody targets HER2, and HER2 is only over-expressed in cancer cells, the conjugate delivers the toxin specifically to tumor cells. Its major adverse effects include hepatotoxicity, cardiotoxicity (reduction in left ventricular ejection fraction), and teratogenicity.
7. **Afatinib:** It is a tyrosine kinase inhibitor of EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4). It is specifically indicated for the first-line treatment of patients with metastatic **non-small cell lung cancer** whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.
8. **Aflibercept:** It is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration It is specifically approved for **neovascular (wet) age-related macular degeneration**.
9. **Alcaftadine:** It is a topical H1 histamine receptor antagonist indicated for the prevention of itching associated with **allergic conjunctivitis** as an ophthalmic solution.
10. **Aldesleukin:** Recombinant IL-2 useful for **renal cell carcinoma** and **malignant melanoma**.
11. **Alefacept:** Fusion protein against LFA- used for **plaque psoriasis**.
12. **Alemtuzumab:** Monoclonal antibody against CD 2 useful for **B-cell CLL**.
13. **Aliskiren, Remikiren and Enalkiren:** Oral renin inhibitors useful for the treatment of **hypertension**.
14. **Alogliptin:** It is a dipeptidyl peptidase-4 (DPP-4) inhibitor (like sitagliptin and vildagliptin) for the treatment of **type 2 diabetes**.
15. **Alosetron:** 5-HT₃ antagonist used to reduce pain and diarrhoea in **irritable bowel syndrome**.
16. **Altretamine:** Anticancer drug useful for **ovarian carcinoma**.
17. **Alvimopan:** Peripheral μ opioid receptor antagonist useful for **postoperative paralytic ileus**.
18. **Amineptine:** Serotonin reuptake enhancer similar to tianeptin for **depression**.
19. **Anakinra:** Inhibitor of IL-1 useful in **septic shock** and **rheumatoid arthritis**.
20. **Anecorvate:** Angiogenesis inhibitor for **neovascular age related macular degeneration**.
21. **Apafant and Lexipafant:** PAF antagonists being investigated for the treatment of **acute pancreatitis**.
22. **Apixaban:** A factor Xa inhibitor anticoagulant indicated to reduce the risk of stroke and systemic embolism in patients with **non-valvular atrial fibrillation**.
23. **Aprepitant:** Neurokinin NK1 (substance P) receptor antagonist useful for the treatment of **chemotherapy induced vomiting**.
24. **Asenapine:** An atypical antipsychotic used sublingually for the treatment of **schizophrenia and acute mania or mixed episodes associated with bipolar I disorder**.
25. **Asoprisnil:** Selective progesterone receptor modulator being tried for **leiomyoma**.
26. **Atosiban:** Oxytocin receptor antagonist used to **delay premature labour**.
27. **Avanafil:** It is a phosphodiesterase 5 (PDE5) inhibitor like sildenafil and is specifically indicated for the treatment of **erectile dysfunction**.

28. **Avasimibe:** Hypolipidemic drug acting as ACAT-1 inhibitor.
29. **Aviptadil:** VIP analog useful for **erectile dysfunction**.
30. **Axitinib:** It inhibits receptor tyrosine kinases including vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2, and VEGFR-3. It is specifically approved for the oral treatment of **advanced renal cell carcinoma** after failure of one prior systemic therapy.
31. **Azilsartan medoxomil:** An angiotensin II receptor blocker (ARB) for the treatment of **hypertension**.
32. **Basiliximab and Daclizumab:** Monoclonal antibodies used as **immunosuppressants**.
33. **Bazedoxifene:** It is a selective estrogen receptor modulator (**SERM**) indicated for the **treatment** of moderate to severe **vasomotor symptoms** associated with menopause and the **prevention of postmenopausal osteoporosis** in combination with estrogen.
34. **Bedaquiline:** An inhibitor of mycobacterial ATP synthase indicated as a part of combination therapy in adults with pulmonary **MDR and XDR tuberculosis**. It increases QT interval and thus should not be combined with any other drug causing QT prolongation.
35. **Belatacept:** It is a selective T-cell (lymphocyte) costimulation blocker. It binds to CD 80 and CD 86 on antigen-presenting cells, thereby blocking CD 28 mediated costimulation of T lymphocytes. It is specifically indicated for the prophylaxis of organ rejection in adult patients receiving a **kidney transplant**. It is approved for use in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids.
36. **Belimumab:** It is a B-lymphocyte stimulator (BLyS)-specific inhibitor indicated for the treatment of adult patients with active, autoantibody-positive, **systemic lupus erythematosus**.
37. **Bendamustine:** A purine alkylator hybrid chemotherapy agent indicated for the treatment of patients with **chronic lymphocytic leukemia (CLL)** and relapsed indolent **non-Hodgkin's lymphoma**.
38. **Beractant and Poractant:** Surfactants for **neonatal RDS**.
39. **Besifloxacin ophthalmic suspension:** A topical quinolone antimicrobial for the treatment of **bacterial conjunctivitis**, commonly referred to as "pink eye".
40. **Bevacizumab:** A monoclonal antibody against vascular endothelial growth factor (VEGF) used as angiogenesis inhibitor recently approved for **glioblastomas** and **metastatic renal cell carcinoma**. It is also indicated for treatment of **metastatic colorectal cancer**.
41. **Bicalutamide and Nilutamide:** Androgen receptor blockers similar to flutamide for **prostate cancer**.
42. **Bimatoprost:** Indicated for the treatment of **hypotrichosis** (or reduced amount of hair) of the eyelashes. Growth of the eyelashes is a well documented side effect of bimatoprost which is currently approved for the treatment of **glaucoma**.
43. **Bortezomib:** Proteasome inhibitor useful in refractory and relapsing **multiple myeloma**. Proteasome normally inhibits the apoptosis and inhibition of this protein by bortezomib results in accelerated apoptosis.
44. **Bosentan and sitaxentan:** Endothelin receptor antagonists useful for **primary pulmonary hypertension**.
45. **Bosutinib:** It is specifically indicated for the treatment of adults with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) **chronic myelogenous leukemia** with resistance or intolerance to prior therapy. It inhibits the Bcr-Abl kinase that promotes CML and also inhibits the Src-family kinases.
46. **Brentuximab vedotin:** It is a CD 30-directed antibody-drug conjugate (ADC) consisting of three components: 1) the chimeric IgG 1 antibody cAC10, specific for human CD 30, 2) the microtubule disrupting agent monomethyl auristatin E (MMAE) and 3) a protease-cleavable linker that covalently attaches MMAE to cAC 10. Brentuximab vedotin is designed to be stable in the bloodstream, but to release MMAE upon internalization into CD-30 expressing tumor cells, resulting in a targeted cell-killing effect. It is specifically approved for 1) **Hodgkin lymphoma** after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates and 2) **systemic anaplastic large cell lymphoma** after failure of at least one prior multi-agent chemotherapy regimen. It is administered intravenously.
47. **Brimonidine:** An alpha-2 adrenergic agonist with potent vasoconstrictive activity. Its once daily topical gel formulation is specifically indicated for the topical **treatment of persistent** (nontransient) **erythema of rosacea** in adults 18 years of age or older.
48. **Cabazitaxel:** A microtubule inhibitor indicated in combination with prednisone for treatment of patients with hormone-refractory metastatic **prostate cancer**.
49. **Cabozantinib:** It is a tyrosine kinase inhibitor approved for treatment of patients with progressive, metastatic **medullary thyroid cancer**. It acts as a small molecule inhibitor of the tyrosine kinases activated by c-Met and VEGFR2, and has been shown to reduce tumor growth, metastasis, and angiogenesis.
50. **Calcitriol Ointment:** Vitamin D analog indicated for the topical treatment of mild to moderate **plaque psoriasis** in adults 18 years and older.
51. **Canagliflozin:** A sodium-glucose co-transporter 2 (**SGLT2**) **inhibitor**. Inhibiting SGLT2 is believed to reduce blood glucose levels by increasing the amount of glucose excreted in the urine. It is specifically indicated as an adjunct to diet and exercise to improve glycemic control in adults with **type 2 diabetes mellitus**.

52. **Canakinumab:** A human monoclonal antibody against IL-1 β for the treatment of children and adults with **cryopyrin-associated periodic syndrome (CAPS)**.
53. **Canakinumab:** A human monoclonal **anti-human IL-1 β antibody** (it does not bind IL-1 α), indicated for the treatment of active **Systemic Juvenile Idiopathic Arthritis (SJIA)** in patients aged 2 years and older.
54. **Carbetocin:** Long acting oxytocin analog to **prevent uterine atony after LSCS**.
55. **Carfilzomib:** It is a proteasome inhibitor like bortezomib. is specifically indicated for the treatment of **multiple myeloma** in patients who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.
56. **Caspofugin and Anidulafungin:** Drugs of echinocandin group inhibiting cell wall synthesis by inhibition of β 1, 3 glycan production. These are approved for **invasive aspergillosis**.
57. **Ceftaroline fosamil:** A fifth generation cephalosporin with activity against both gram-positive and gram-negative microorganisms, approved for the treatment of **community-acquired bacterial pneumonia (CABP)**, including cases caused by *Streptococcus pneumoniae* bacteremia, and **acute bacterial skin and skin structure infection**, including cases caused by methicillin-resistant *Staphylococcus aureus* (MRSA).
58. **Certolizumab:** PEGylated anti-TNF (tumor necrosis factor) biologic therapy for the treatment of moderate to severe **Crohn's disease** in adults.
59. **Cetuximab:** Monoclonal antibody against epidermal growth factor receptor (EGFR) useful for **colorectal carcinoma**.
60. **Ciclesonide:** Inhaled corticosteroid indicated for the maintenance treatment of **asthma** and as prophylactic therapy in adult and adolescent patients aged 12 years and older.
61. **Cilastazole:** PDE-III inhibitor useful as an **antiplatelet drug for intermittent claudication**.
62. **Cilomilast and Roflumilast:** PDE IV inhibitors useful in **bronchial asthma**.
63. **Cinacalcet:** Calcimimetic drug that acts by decreasing the release of PTH It is useful in **osteoporosis**.
64. **Clevidipine butyrate:** An intravenous, ultrashort-acting calcium channel blocker for the **treatment of severely elevated blood pressure** in the hospital setting when oral therapy is not feasible or desirable.
65. **Clonidine hydrochloride:** It is a centrally acting α 2-adrenergic agonist recently indicated for the treatment of **attention deficit hyperactivity disorder (ADHD)** as monotherapy or as adjunctive therapy to stimulant medications.
66. **Cobicistat:** Is a licenced drug for use in the treatment of infection with the **HIV**. Like ritonavir, cobicistat is of interest not for its anti-HIV properties, but rather its ability to inhibit liver enzymes that metabolize other medications used to treat HIV, notably elvitegravir, an HIV integrase inhibitor. By combining cobicistat with elvitegravir, higher concentrations of elvitegravir are achieved in the body with lower dosing, enhancing elvitegravir's viral suppression while diminishing its adverse side-effects. In contrast with ritonavir, the only currently approved booster, cobicistat has no anti-HIV activity of its own. It is a component of the four-drug, fixed-dose combination HIV treatment elvitegravir/cobicistat/emtricitabine/tenofovir (known as the "Quad Pill").
67. **Collagenase clostridium histolyticum:** An injectable formulation of purified collagenase (an enzyme that causes collagen to degrade within the connective tissue), specifically indicated for the treatment of adult men with **Peyronie's disease** with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy. It is supplied as a powder for reconstitution into a solution for intralesional injection.
68. **Crizotinib:** It is an oral selective, ATP-competitive small molecule dual inhibitor of mesenchymal epithelial transition growth factor (c-Met or hepatocyte growth factor) and ALK tyrosine kinases It is specifically approved for the treatment of locally advanced or metastatic **non-small cell lung cancer**.
69. **Crofelemer:** An oral proanthocyanidin oligomer indicated to relieve symptoms of **diarrhea in HIV/AIDS** patients taking antiretroviral therapy. It acts by voltage-independently blocking two structurally unrelated chloride channels in the gut, namely the cystic fibrosis transmembrane conductance regulator (CFTR) and the calcium activated channel anoctamin 1. As a result of the channel inhibition, fewer chloride ions are excreted into the gut, which also decreases the excretion of sodium ions and water, improving stool consistency and reducing duration of the diarrhoea. It is not absorbed from the gut and is consequently excreted with the stool.
70. **Cysteamine bitartrate:** The delayed-release capsules of this drug is a cystine depleting agent that lowers the cystine content of cells in patients with nephropathic cystinosis, an inherited defect of lysosomal transport. It is specifically indicated for the management of **nephropathic cystinosis** in adults and children ages 6 years and older.
71. **Cysteamine hydrochloride:** It is a cystine-depleting agent by converting cystine to cysteine and cysteine-cysteamine mixed disulfides and reduces corneal cystine crystal accumulation. It thus lowers the cystine content of cells in patients with cystinosis, a rare genetic disorder. It is specifically approved for the treatment of corneal cystine crystal accumulation in adults and children with **cystinosis**. It is supplied as an ophthalmic solution for topical administration.
72. **Dabrafenib:** It is an inhibitor of some mutated forms of BRAF kinases, as well as wild-type BRAF and CRAF kinases. It is indicated for the treatment of patients with **unresectable or metastatic melanoma** with BRAF V600E mutation as detected by an FDA-approved test. It is not indicated for treatment of patients with wild-type BRAF melanoma.

73. **Dalfampridine:** An oral potassium channel blocker indicated **to improve walking ability in people with multiple sclerosis.**
74. **Daltroban and Sultroban:** TXA2 receptor antagonists Possess **anti-aggregatory effects on platelets.**
75. **Dapagliflozin:** An orally active sodium glucose cotransporter type 2 (SGLT-2) inhibitor. Inhibiting SGLT2 activity modulates reabsorption of glucose in the kidney, resulting in excretion of glucose in the urine. It is specifically indicated as an adjunct to diet and exercise to improve glycemic control in adults with **type II diabetes mellitus.** It is given orally. Renal function should be assessed before initiating this drug.
76. **Daptomycin:** New bactericidal drug effective against streptogramin and linezolid resistant **Staphylococcus aureus.**
77. **Darifenacin and solefenacin:** Selective M3 blocker useful for **irritable bowel syndrome** and **overactive bladder.**
78. **Dasatinib:** Tyrosine kinase inhibitor approved for the treatment of adults in all phases of **chronic myeloid leukemia (CML)** (chronic, accelerated, or myeloid or lymphoid blast phase) with resistance or intolerance to prior therapy including imatinib mesylate.
79. **Deferipirone and Deferasirox:** Oral iron chelating agent useful in thalassemia patients.
80. **Degarelix:** An injectable gonadotropin-releasing hormone (GnRH) receptor antagonist indicated for patients with **advanced prostate cancer.**
81. **Denileukin defitox:** Combination of IL-2 with diphtheria toxin for **cutaneous T cell lymphoma.**
82. **Denosumab:** Monoclonal antibody against RANKL being used in osteoporosis is now approved for the treatment of adults and skeletally mature adolescents with **giant cell tumor** of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
83. **Denosumab:** Monoclonal antibody against RANK-L for **osteoporosis.**
84. **Desvenlafaxine:** Serotonin-norepinephrine reuptake inhibitor (SNRI) approved for the treatment for adult patients with **major depressive disorder.** It is also currently under review as a treatment for moderate-to-severe vasomotor symptoms associated with menopause.
85. **Dexlansoprazole:** Proton pump inhibitor with a novel delivery system approved for the treatment of **erosive esophagitis** and heartburn associated with symptomatic non-erosive **gastroesophageal reflux disease (GERD).**
86. **Dexmedetomidine:** Selective α_2A agonist useful for **preanaesthetic medication to provide preoperative sedation, analgesia, antianxiety effects and reduction in bronchial secretions.**
87. **Dextromethorphan hydrobromide and quinidine sulfate combination:** It is a combination product containing dextromethorphan hydrobromide (an uncompetitive NMDA receptor antagonist and sigma-1 agonist) and quinidine sulfate (a CYP 450 2D6 inhibitor) indicated as the first line treatment of **pseudobulbar affect (PBA).** Pseudobulbar affect occurs secondary to a variety of otherwise unrelated neurological conditions, and is characterized by involuntary, sudden, and frequent episodes of laughing and/or crying PBA episodes typically occur out of proportion or incongruent to the patient's underlying emotional state.
88. **Diacerin:** IL-1 antagonist being used as a disease modifying agent in **osteoarthritis.**
89. **Dimethyl fumarate:** An oral, small molecule immune modulator indicated for the treatment of adults with **relapsing forms of multiple sclerosis.** The mechanism by which dimethyl fumarate exerts its therapeutic effect in multiple sclerosis is unknown. However, it has been postulated that dimethyl fumarate has the potential to reduce the activity and impact of inflammatory cells on the central nervous system (CNS) and induce direct cytoprotective responses in CNS cells.
90. **Docosanol:** Long chain saturated alcohol useful topically for **herpes labialis.**
91. **Doloxifene and Toremifene:** SERMs used for the treatment of breast carcinoma.
92. **Dolutegravir:** **It is an integrase inhibitor.** It blocks HIV replication by preventing viral DNA from integrating into the genetic material of human immune cells (T-cells). It is specifically indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type **1 (HIV-1) infection** in adults and children aged 12 years and older and weighing at least 40 kg.
93. **Donepezil, Rivastigmine and Galantamine:** Cholinesterase inhibitors useful in **Alzheimer's disease.**
94. **Dornase-alpha:** Recombinant DNAase that hydrolyses purulent pulmonary secretions in **cystic fibrosis.**
95. **Dronabinol:** Cannabinoid receptor (CB1) agonist useful as an **antiemetic agent.**
96. **Dronedarone:** An antiarrhythmic drug indicated to reduce the risk of cardiovascular hospitalization in patients with **atrial fibrillation or atrial flutter.** It is similar to amiodarone but does not cause thyroid dysfunction.
97. **Drospirenone:** Progesterone with anti-mineralocorticoid and anti-androgenic properties useful as a **component of OCPs.**
98. **Drotrecogin-alfa:** Recombinant protein C useful in **severe sepsis.**
99. **Droxidopa:** It is a synthetic amino acid precursor of norepinephrine specifically indicated for the oral treatment of **orthostatic dizziness** or lightheadedness in adult patients with symptomatic neurogenic orthostatic hypotension caused by primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy.

100. **Ecallantide**: A plasma kallikrein inhibitor indicated for treatment of acute attacks of **hereditary angioedema** in patients years of age and older.
101. **Eculizumab**: It is a monoclonal antibody that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. It has now been approved for **atypical hemolytic uremic syndrome (aHUS)** to inhibit complement-mediated thrombotic microangiopathy. It is already being used for **paroxysmal nocturnal hemoglobinuria**.
102. **Efalizumab**: Monoclonal antibody against CD 11 for **psoriasis**.
103. **Elosulfase alfa**: It is a purified human enzyme 'N-acetylgalactosamine-6-sulfatase' produced by recombinant DNA technology in a Chinese hamster ovary cell line. It is indicated for **Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome)**.
104. **Eltrombopag**: A thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in patients with **chronic immune (idiopathic) thrombocytopenic purpura**.
105. **Enfuvirtide**: Fusion inhibitor useful for the treatment of **HIV** infection.
106. **Entecavir**: New viral DNA polymerase inhibitor for **HBV**.
107. **Enzalutamide**: An androgen receptor inhibitor like flutamide. It is specifically indicated for the oral treatment of patients with metastatic castration-resistant **prostate cancer** who have previously received docetaxel. It is an androgen receptor inhibitor that acts on different steps in the androgen receptor signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors and inhibit androgen receptor nuclear translocation and interaction with DNA.
108. **Epoprostenol and Treprostinil**: PGI₂ analogues useful for the treatment of **pulmonary hypertension**.
109. **Eribulin mesylate**: A microtubule inhibitor indicated for the treatment of patients with **metastatic breast cancer**.
110. **Eslicarbazepine acetate**: It is a voltage-gated sodium channel blocker indicated as adjunctive treatment for **partial-onset seizures**.
111. **Estramustine**: Combination of estrogen and mechlorethamine used for the treatment of **prostatic carcinoma**.
112. **Etravirine**: Non-nucleoside reverse transcriptase inhibitor (**NNRTI**) which in combination with other antiretroviral agents is indicated for the treatment of human immunodeficiency virus type 1 (**HIV-1**) infection in antiretroviral treatment-experienced adult patients.
113. **Everolimus**: It is a mTOR inhibitor approved for treatment of patients with **subependymal giant cell astrocytoma (SEGA)** and **renal angiomyolipoma** associated with tuberous sclerosis (TS), a rare genetic disorder. This approval was for treatments of SEGA that cannot be treated with surgery. It is also approved for the treatment of **progressive neuroendocrine tumors of pancreatic origin** in patients with unresectable, locally advanced or metastatic disease. Everolimus is supplied as a tablet for oral administration.
114. **Exenatide**: Recombinant GLP analog useful in **diabetes mellitus**.
115. **Ezogabine**: It enhances transmembrane potassium currents mediated by the KCNQ family of ion channels. By this mechanism, it is thought to stabilize the resting membrane potential and reduce brain excitability. It is specifically indicated as adjunctive treatment of **partial-onset seizures** in adults.
116. **Febuxostat**: It is a xanthine oxidase inhibitor indicated for the chronic management of **hyperuricemia** in patients with gout.
117. **Fedotozine**: New κ opioid receptor antagonist for **diarrhea dominant IBS**.
118. **Felbamate**: NMDA blocker useful in **epilepsy**. It can cause aplastic anemia.
119. **Ferric carboxymaltose**: It is an iron carbohydrate complex used as an intravenous injection for iron replacement. It is indicated for the treatment of **iron deficiency anemia** in adults who have intolerance to oral iron or have had unsatisfactory response to oral iron or adults who have non-dialysis dependent chronic kidney disease.
120. **Fesoterodine**: A competitive muscarinic receptor antagonist indicated for the treatment of **overactive bladder** with symptoms of urge urinary incontinence, urgency, and frequency.
121. **Fidaxomicin**: It is a narrow-spectrum macrocyclic antibiotic and is bactericidal against *C. difficile* in vitro. It acts by inhibiting RNA synthesis by RNA polymerases. It is specifically indicated in adults for oral treatment of **Clostridium difficile-associated diarrhea**. It can cause gastrointestinal hemorrhage, anemia and neutropenia.
122. **Filgrastim and Lenograstim**: Recombinant G-CSF used for **cancer chemotherapy induced leukopenia**.
123. **Fingolimod**: A sphingosine 1-phosphate receptor modulator indicated for the treatment of patients with **relapsing forms of multiple sclerosis**.
124. **Fomivirsen**: Antisense oligonucleotide useful against **CMV retinitis**.
125. **Fospropofol disodium**: An intravenous sedative-hypnotic agent for **monitored anesthesia care (MAC) sedation** in adult patients undergoing diagnostic or therapeutic procedures.
126. **Frovatriptan, Rizatriptan, Zolmitriptan, Eletriptan and Almotriptan**: 5HT_{1B/1D} agonists useful for the treatment of **acute migraine attacks** (similar to sumatriptan).

127. **Fulvestrant:** Estrogen antagonist useful in **tamoxifen resistant breast cancer**.
128. **Gabapentin enacarbil** is a gabapentin prodrug indicated for the once-daily treatment of moderate-to-severe primary **Restless Legs Syndrome**.
129. **Ganaxolone:** Neurosteroid useful for the treatment of **absence seizures, infantile spasms** and **catamenial epilepsy**.
130. **Geftinib and Erlotinib:** Tyrosine kinase inhibitors useful in **non small cell carcinoma of lung**.
131. **Gemtuzumab:** Monoclonal antibody against CD 33 for **AML**.
132. **Glatiramer:** Resembles myelin basic protein and is useful in **relapsing remitting multiple sclerosis**.
133. **Glucarpidase:** It contains a recombinant enzyme which rapidly lowers blood levels of **methotrexate**, reducing its concentration to below the threshold for **serious toxicity**. It converts methotrexate to its inactive metabolites DAMPA and glutamate. DAMPA and glutamate are metabolized by the liver, providing an alternative route of methotrexate elimination to renal clearance during high-dose methotrexate treatment. It is specifically indicated for the treatment of toxic plasma methotrexate concentrations (> 1 micromole per liter) in patients with delayed methotrexate clearance due to impaired renal function. It is administered by iv route.
134. **Golimumab:** A human anti-tumor necrosis factor (TNF)-alpha monoclonal antibody administered once-monthly for the treatment of **rheumatoid arthritis, psoriatic arthritis** and **ankylosing spondylitis**.
135. **Granisetron and Tropisetron:** 5HT₃ antagonists useful for **chemotherapy induced vomiting** (similar to ondansetron).
136. **Guanfacine:** A nonstimulant selective α_2A -receptor agonist for the treatment of children and adolescents with Attention-Deficit/Hyperactivity Disorder (**ADHD**).
137. **Isoprenaline:** Peripheral dopamine agonist useful for **CHF** and as a **mydriatic**.
138. **Ibritumomab:** Monoclonal antibody against CD 20 useful for **B-cell NHL**.
139. **Ibrutinib:** An orally available, selective inhibitor of Bruton's tyrosine kinase (Btk), a gene that is disrupted in the human disease X-linked agammaglobulinemia (XLA). BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. It is specifically approved for **chronic lymphocytic leukemia** in patients who have received at least one prior therapy. It is also approved for **mantle cell lymphoma** in patients who have received at least one prior therapy.
140. **Icatibant:** It is a competitive antagonist selective for the bradykinin B₂ receptor. Hereditary angioedema (HAE) is caused by an absence or dysfunction of C1-esterase-inhibitor, a key regulator of the Factor XII/kallikrein proteolytic cascade that leads to bradykinin production. Bradykinin is a vasodilator which is thought to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain. Icatibant (given subcutaneously) inhibits bradykinin from binding the B₂ receptor and thereby treats the clinical symptoms of an acute, episodic attack of hereditary angioedema. Icatibant is specifically approved for the treatment of **acute attacks of hereditary angioedema** in adults.
141. **Iloperidone:** A 5HT₂/D₂ antagonist (atypical) antipsychotic for the treatment of **schizophrenia**.
142. **Indacaterol:** It is a long-acting β_2 -adrenergic agonist like salmeterol and formoterol. It is specifically approved for the treatment of airflow obstruction in patients with **chronic obstructive pulmonary disease**, including chronic bronchitis and/or emphysema.
143. **Indoramin and urapidil:** Alpha blockers useful for **hypertensive emergencies**.
144. **Infliximab:** Monoclonal antibody against TNF- α useful as a disease modifying anti-rheumatoid arthritis drug (**DMARD**). It can also be used for **Crohn's disease, psoriatic arthritis, Wegener's granulomatosis** and **sarcoidosis**.
145. **Ingenol mebutate:** It is an inducer of apoptosis and is specifically indicated (topical gel formulation) for the topical treatment of **actinic keratosis** of the face, scalp, trunk and extremities. The mechanism of action by which it induces cell death in treating actinic keratosis lesions is unknown.
146. **Inosiplex:** Immunostimulant increasing NK cell activity, effective in **common cold, influenza, herpes and viral encephalitis**.
147. **Ipilimumab:** A human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody indicated for the treatment of unresectable or **metastatic melanoma**.
148. **Ivabradine:** Useful in **chronic stable angina** by slowing heart rate due to inhibition of I_f (K^+ channel carrying funny current) in SA node.
149. **Ivacaftor:** It is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator. Cystic fibrosis is caused by mutations in a gene that encodes for the CFTR protein that regulates ion (such as chloride) and water transport in the body. The defect in chloride and water transport results in the formation of thick mucus that builds up in the lungs, digestive tract and other parts of the body leading to severe respiratory and digestive problems. It is specifically approved for the treatment of **cystic fibrosis** in patients age 6 years and older who have a G551D mutation in the CFTR gene.
150. **Ixabepilone:** Used in combination with capecitabine for resistant **breast cancer**.
151. **Lacosamide:** Anti-convulsant drug for the treatment of **partial onset seizures** in adults with epilepsy.
152. **Lapatinib:** Approved as a first line therapy in combination with letrozole for the treatment of postmenopausal women with hormone receptor positive **metastatic breast cancer** that overexpresses the HER2 receptor for whom hormonal therapy is indicated. Lapatinib is an oral small-molecule inhibitor of the HER2/ErbB2 tyrosine kinase receptor.

153. **Laronidase:** Recombinant α -L-iduronidase for **Hurler disease**.
154. **Lenalidomide:** This thalidomide analogue is an immunomodulatory agent with antiangiogenic and antineoplastic properties. It is specifically indicated for the treatment of patients with **mantle cell lymphoma** (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.
155. **Letrozole, Anastrozole, Fadrozole and Exemestane:** Aromatase inhibitors useful for the treatment of tamoxifen resistant **breast cancer**.
156. **Levetiracetam:** Antiepileptic drug useful for **partial seizures**.
157. **Levoleucovorin:** A folate analog and the pharmacologically active isomer of calcium leucovorin. Levoleucovorin rescue is used after the administration of high-dose methotrexate in osteosarcoma. Levoleucovorin is also used to treat inadvertent **overdosage of folic acid antagonists**.
158. **Levomilnacipran:** An extended release selective norepinephrine and serotonin reuptake inhibitor is indicated for the treatment of **Major Depressive Disorder**.
159. **Levosimendan:** Calcium sensitizing agent and PDE-III inhibitor useful for CHF.
160. **Linacotide:** It is specifically indicated for the oral treatment of adults with **irritable bowel syndrome with constipation** and for adults with chronic idiopathic constipation. It is a guanylate cyclase-C (GC-C) agonist. Activation of GC-C results in an increase in both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevation in intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, resulting in increased intestinal fluid and accelerated transit.
161. **Linagliptin:** It is a newer orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme similar to sitagliptin and is approved for **type 2 diabetes mellitus**. Major adverse effect of this drug include nasopharyngitis, hypoglycemia and pancreatitis.
162. **Liraglutide:** A glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with **type 2 diabetes mellitus**.
163. **Lisdexamfetamine dimesylate:** First and only once-daily prodrug stimulant to treat **ADHD** in adults.
164. **Lomitapide:** It is indicated for the treatment of patients with **homozygous familial hypercholesterolemia**. It acts by inhibiting the microsomal triglyceride transfer protein (MTP or MTTP) which is necessary for very low-density lipoprotein (VLDL) assembly and secretion in the liver.
165. **Lorcaserin hydrochloride:** It is a serotonin 2C receptor agonist. It has been shown to decrease food consumption and promote satiety by selectively activating serotonin 2C receptors in the brain. It is specifically indicated as an adjunct to a reduced-calorie diet and increased physical activity **for chronic weight management** in clinically obese adults (BMI of 30 kg/m² or greater) and overweight adults (BMI of 27 kg/m² or greater) with at least one weight-related comorbid condition.
166. **Loxiglumide:** CCK1 receptor antagonist useful for **constipation dominant IBS**.
167. **Lucinactant:** A synthetic formulation of pulmonary surfactant. Endogenous pulmonary surfactant lowers surface tension at the air-liquid interface of the alveolar surfaces during respiration and stabilizes the alveoli against collapse at resting transpulmonary pressures. A deficiency of pulmonary surfactant in premature infants results in respiratory distress syndrome (RDS). Lucinactant is specifically indicated by intratracheal route **for the prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS**.
168. **Luliconazole:** Azole antifungal similar to miconazole class indicated for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum* and *Epidermophyton floccosum*, in adults 18 years of age and older.
169. **Lurasidone:** An atypical antipsychotic agent for the treatment of **schizophrenia**.
170. **Macitentan:** It is a tissue-targeting oral endothelin receptor antagonist (like bosentan) indicated for the treatment of **pulmonary arterial hypertension** (WHO Group I) to delay disease progression.
171. **Maraviroc:** CCR 5 antagonist for **HIV-1**.
172. **Mebeverine:** Reserpine analog for diarrhea dominant IBS.
173. **Mechlorethamine:** It is an alkylating agent whose gel formulation is recently approved for the topical treatment of Stage IA and IB **mycosis fungoides-type cutaneous T-cell lymphoma** in patients who have received prior skin-directed therapy.
174. **Memantine:** NMDA antagonist having the potential to slow the progression of **Alzheimer's disease**.
175. **Methylnaltrexone bromide:** Peripherally acting μ -opioid receptor antagonist indicated to treat opioid-induced constipation.
176. **Metreleptin:** A recombinant human leptin analog for once daily subcutaneous injection that binds to and activates the leptin receptor. It is specifically indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with **congenital or acquired generalized lipodystrophy**.

177. **Mifepristone:** A small-molecule progesterone and glucocorticoid antagonist has now been approved to **control hyperglycemia secondary to hypercortisolism in adults with endogenous Cushing's syndrome** who have type II diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.
178. **Milnacipran:** Serotonin and norepinephrine reuptake inhibitor indicated for the management of **fibromyalgia**.
179. **Miltefosine and Sitamaquine:** New drugs for the treatment of **kala azar**.
180. **Miltefosine:** It possess in vitro activity against the promastigote and amastigote stages of Leishmania species. It is specifically indicated for adults and adolescents >12 years of age for oral treatment of: **visceral leishmaniasis** due to Leishmania donovani, cutaneous leishmaniasis due to Leishmania braziliensis, Leishmania guyanensis, and Leishmania panamensis and mucosal leishmaniasis due to Leishmania braziliensis
181. **Mipomersen:** An anti-sense oligonucleotide inhibitor of mRNA of apolipoprotein B-100 synthesis indicated for the treatment of patients with **homozygous familial hypercholesterolemia**. It is administered as a weekly injection.
182. **Mirabegron:** It is a selective beta-3 adrenoceptor (Beta3-AR) agonist. The drug activates Beta3-ARs on the detrusor muscle of the bladder to facilitate filling of the bladder and storage of urine. It is specifically indicated for the oral treatment of **overactive bladder (OAB)** with symptoms of urge urinary incontinence, urgency, and urinary frequency.
183. **Mirtazapine:** Newer **antidepressant** drug also known as nor-adrenergic and specific serotonergic antidepressant (NSSA) It acts by inhibiting presynaptic auto- and hetero- α_2 receptors.
184. **Mizolastine, Ebastine and Acrivastine:** Newer **second generation antihistaminics**.
185. **Moxonidine and Rilmenidine:** Longer acting imidazoline receptor agonists (that modulate α_2 activity) useful in the treatment of **hypertension** (similar to clonidine).
186. **Natalizumab:** Monoclonal antibody used for the management of **multiple sclerosis**.
187. **Nesiritide:** Recombinant BNP useful in **CHF**.
188. **Nikkomycin:** **Antifungal** drug acting via the inhibition of chitin synthesis.
189. **Obinutuzumab:** It is a humanized anti-CD20 monoclonal antibody of the IgG1 subclass. It is specifically indicated for use in combination with chlorambucil for the treatment of patients with previously untreated **chronic lymphocytic leukemia**.
190. **Ocriplasmin:** It is an alpha-2 antiplasmin reducer. It is a truncated form of the natural human protein plasmin. Ocriplasmin has proteolytic activity against protein components of the vitreous body and the vitreoretinal interface, thereby dissolving the protein matrix responsible for the vitreomacular adhesion. It is specifically indicated for the treatment of **symptomatic vitreomacular adhesion by intravitreal injection**.
191. **Octreotide, Vapreotide, Seglitide and Lanreotide:** Long acting somatostatin analogs useful for **acromegaly, secretory diarrhoea and esophageal varices**.
192. **Ofatumumab:** A CD-directed cytolytic monoclonal antibody indicated for the treatment of patients with **chronic lymphocytic leukemia**.
193. **Olopatadine:** An antihistamine nasal spray for the treatment of symptoms of seasonal **allergic rhinitis** in adults and adolescents twelve years of age and older.
194. **Omacetaxine:** It is a first-in-class small molecule drug for the treatment of adult patients with **chronic or accelerated phase CML**. It inhibits protein translation by preventing the initial elongation step of protein synthesis. It interacts with the ribosomal A-site and prevents the correct positioning of amino acid side chains of incoming aminoacyl-tRNAs.
195. **Omapatrilat and Sompatriat:** Vasopeptidase inhibitors (inhibit two enzymes; ACE and NEP) useful in **CHF**.
196. **OnabotulinumtoxinA:** Botulinum toxin indicated to prevent headaches in adult patients with chronic migraine To treat chronic migraines, it is given approximately every 12 weeks as multiple injections around the head and neck to try to dull future headache symptoms It has not been shown to work for the treatment of migraine headaches that occur 14 days or less per month, or for other forms of headache.
197. **Oprelvekin:** Recombinant IL-11 useful for the treatment and prevention of **chemotherapy induced thrombocytopenia**.
198. **Ospemifene:** It is a SERM indicated for the treatment of **moderate to severe dyspareunia** (pain during sexual intercourse), a symptom of vulvar and vaginal atrophy due to menopause. It acts similar to estrogen the vaginal epithelium building vaginal wall thickness which in turn reduces the pain associated with dyspareunia. The boxed warning of the medication indicates that the drug may thicken the endometrium which could lead to unusual bleeding and endometrial cancer.
199. **Palifermin:** Keratinocyte growth factor for **oral mucositis**.
200. **Paliperidone:** Metabolite of risperidone developed as a separate drug for **schizophrenia**.
201. **Palivizumab:** Monoclonal antibody used for **RSV infections**.
202. **Pasireotide:** An orphan drug approved for the treatment of **Cushing's disease** in patients who fail or are ineligible for surgical therapy. It is a somatostatin analog (like octreotide) which has a 40-fold increased affinity to somatostatin receptor 5 than other somatostatin analogs.
203. **Pazopanib:** A multitargeted tyrosine kinase inhibitor against VEGF receptor -1, -2, and -3, PDGF receptor- α , β , and c-kit indicated for the treatment of patients with **advanced renal cell carcinoma and advanced soft tissue sarcoma**.

204. **Peginesatide:** A peptide-based erythropoiesis stimulating agent (ESA). Peginesatide binds to and activates the human erythropoietin receptor and stimulates erythropoiesis in human red cell precursors. It is specifically indicated for the treatment of **anemia due to chronic kidney disease** in adult patients on dialysis. It is administered i.v. or s.c.
205. **Pegloticase:** It is a PEGylated uric acid oxidase enzyme indicated for the treatment of **chronic gout** in adult patients refractory to conventional therapy.
206. **Pegvisomant:** GH receptor antagonist indicated for the treatment of **acromegaly**.
207. **Pemetrexed:** Approved by the FDA in combination with cisplatin for the initial treatment of advanced nonsquamous **non-small cell lung cancer** (NSCLC), a specific type of NSCLC.
208. **Perampanel:** A selective AMPA-type glutamate receptor antagonist. The AMPA receptor is widely present on most excitatory neuronal synapses and plays a role in a large number of central nervous system diseases. Perampanel is specifically indicated as oral adjunctive therapy for the treatment of **partial-onset seizures** with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.
209. **Pertuzumab:** It is a HER2/neu receptor antagonist compound. It is specifically indicated for the first-line treatment of **HER2+ metastatic breast cancer** in combination with trastuzumab and docetaxel. It has been shown to augment anti-tumor activity as a complement to trastuzumab, as the two medicines target different regions on the HER2 receptor. It is administered as intravenous infusion.
210. **Phosphoramidone:** Non-specific inhibitor of endothelin converting enzyme useful for **pulmonary hypertension**.
211. **Pitavastatin:** An HMG CoA reductase inhibitor indicated for the primary treatment of **hypercholesterolemia** and combined dyslipidemia.
212. **Plerixafor:** A small molecule CXCR4 chemokine receptor antagonist used in combination with granulocyte-colony stimulating factor **to mobilize hematopoietic stem cells** to the bloodstream for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma.
213. **Polidocanol:** Its injectable foam is a sclerosant and causes fibrosis inside varicose veins, occluding the lumen of the vessel, and reducing the appearance of the varicosity. It is indicated for the treatment of **incompetent great saphenous veins**, accessory saphenous veins and visible varicosities of the great saphenous vein system above and below the knee. It should be used under ultrasound guidance only.
214. **Pomalidomide:** A thalidomide analogue indicated for the treatment of patients with relapsed and refractory **multiple myeloma**. It has anti-angiogenic and immunomodulatory properties. It directly inhibit both the tumor cell and vascular compartments of myeloma cancers. This dual activity of pomalidomide makes it more efficacious than thalidomide in vitro and in vivo.
215. **Pomalidomide:** It is an immunomodulatory antineoplastic agent. It inhibits proliferation and induces apoptosis of hematopoietic tumor cells, enhances T cell- and natural killer cell-mediated immunity and inhibits production of pro-inflammatory cytokines by monocytes. It is specifically indicated for patients with **multiple myeloma** who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.
216. **Ponatinib:** Inhibitor of tyrosine kinase activated by abl-bcr fusion. It is indicated for **CML and Philadelphia positive ALL**.
217. **Pralatrexate:** A folate analogue metabolic inhibitor indicated for the treatment of patients with relapsed or refractory **peripheral T-cell lymphoma** (PTCL).
218. **Pramlintide:** Useful for **diabetes mellitus** by suppressing glucagon release and delaying gastric emptying.
219. **Prasugrel:** An oral antiplatelet agent acting by inhibition of P2Y₁₂ receptors of ADP (similar to clopidogrel) for the treatment of patients with **acute coronary syndrome (ACS)** who are managed with percutaneous coronary intervention including coronary stenting.
220. **Pyronaridine:** Antimalarial agent related to amodiaquine effective against **chloroquine resistant Plasmodium falciparum**.
221. **Quinagolide:** Non-ergot dopamine agonist useful in **Parkinsonism**.
222. **Radium Ra 223 dichloride:** It, an alpha particle-emitting pharmaceutical, a radiotherapeutic drug. It is specifically indicated for the treatment of patients with **castration-resistant prostate cancer**, symptomatic bone metastases and no known visceral metastatic disease.
223. **Raltegravir:** Integrase inhibitor for **HIV**.
224. **Ranibizumab:** It is a vascular endothelial growth factor (VEGF) inhibitor which was first approved for the treatment of **neovascular (wet) age-related macular degeneration (AMD)**. Now It has been approved for the treatment of **macular edema following retinal vein occlusion (RVO)**.
225. **Rasburicase:** Recombinant urate oxidase enzyme useful for **gout**.
226. **Raxibacumab:** A human monoclonal antibody indicated for the prophylaxis and treatment of **inhalational anthrax**. It targets the protective antigen (PA) component of the lethal toxin of Bacillus anthracis.

227. **Regorafenib:** A small molecule inhibitor of multiple membrane-bound and intracellular kinases indicated for patients with locally advanced, unresectable or metastatic **gastrointestinal stromal tumor** who have been previously treated with imatinib mesylate and sunitinib malate.
228. **Regorafenib:** It is specifically approved for the treatment of patients with **metastatic colorectal cancer** who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. It is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. This distinct anti-angiogenic profile includes inhibition of both VEGFR2 and TIE2 TK.
229. **Rilonacept:** Interleukin-1 inhibitor for the long-term treatment of **Cryopyrin-Associated Periodic Syndromes (CAPS)**.
230. **Rilpivirine:** A newer non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (**HIV-1**) similar to etravirine.
231. **Riluzole:** NMDA antagonist useful in **amyotrophic lateral sclerosis**.
232. **Riociguat:** It is a stimulator of soluble guanylate cyclase (sGC), an enzyme in the cardiopulmonary system and the receptor for nitric oxide (NO). These stimulators help arteries relax to increase blood flow and decrease blood pressure. It is specifically indicated for **persistent/recurrent chronic thromboembolic pulmonary hypertension**.
233. **Rivaroxaban:** It selective oral blocker of the active site of factor Xa and does not require a cofactor (such as Anti-thrombin III) for activity. It is indicated for the **prophylaxis of deep vein thrombosis**, which may lead to pulmonary embolism in patients undergoing knee or hip replacement surgery.
234. **Roflumilast:** An orally administered phosphodiesterase 4 (PDE4) enzyme inhibitor indicated as a treatment to reduce the risk of COPD exacerbations in patients with **severe COPD** associated with chronic bronchitis and a history of exacerbations.
235. **Romidepsin:** A histone deacetylase (HDAC) inhibitor indicated the treatment of **cutaneous T-cell lymphoma**.
236. **Romiplostim:** A thrombopoietin mimetic peptibody for the treatment of thrombocytopenia in adult patients with **chronic immune (idiopathic) thrombocytopenic purpura (ITP)**.
237. **Rotigotine transdermal formula:** A non-ergot dopamine agonist specifically approved for the treatment of moderate-to-severe primary **restless legs syndrome**. The precise mechanism of action of rotigotine as a treatment for Restless Legs Syndrome is unknown but is thought to be related to its ability to stimulate dopamine receptors. The application site for rotigotine should be moved on a daily basis. It should not be applied to the same application site more than once every 14 days.
238. **Rufinamide:** A triazole derivative antiepileptic drug for the adjunctive treatment of **seizures associated with Lennox-Gastaut syndrome**.
239. **Ruxolitinib:** It inhibits Janus associated kinases; JAK 1 and JAK 2, which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation and subsequent localization of STATs to the nucleus leading to modulation of gene expression. Myelofibrosis is a myeloproliferative neoplasm known to be associated with dysregulated JAK 1 and JAK 2 signaling. Ruxolitinib is approved for oral treatment of intermediate or high-risk **myelofibrosis**, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis. Anemia and thrombocytopenia are adverse effects.
240. **Sargramostim and Molgramostim:** Recombinant GM-CSF used for the treatment of **leukopenia**.
241. **Saxagliptin, Sitagliptin and Vildagliptin:** A dipeptidyl peptidase-4 (DPP4) inhibitor indicated for the treatment of **type 2 diabetes mellitus** in adults.
242. **Sermorelin and Hexarelin:** Recombinant GHRH analogs useful for **pituitary dwarfism**.
243. **Sevelamer:** To treat **hyperphosphatemia in CRF**.
244. **Silodosin:** An α adrenoreceptor antagonist for the treatment of the signs and symptoms associated with benign prostatic hyperplasia (**BPH**), or enlarged prostate.
245. **Simeprevir:** It is a small molecule orally active inhibitor of the NS3/4A protease of hepatitis C virus. It is specifically indicated for the oral treatment of **chronic hepatitis C** infection as a component of a combination antiviral treatment regimen. It should be administered with both peginterferon alfa and ribavirin for 12 weeks.
246. **Sofosbuvir:** A nucleotide analog inhibitor of HCV NS5B polymerase indicated for the treatment of **chronic hepatitis C** infection as a component of a combination antiviral treatment regimen.
247. **Somatrem and Somatropin:** Recombinant growth hormones approved for **pituitary dwarfism and AIDS related wasting**.
248. **Sorafenib and Sunitinib:** Tyrosine kinase inhibitors for **renal cell carcinoma**.
249. **Spinosad:** It is a pediculicide indicated for the topical treatment of **head lice infestations**.
250. **Sunitinib:** It is an oral multi-kinase inhibitor and works by blocking multiple molecular targets like vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), KIT, FLT 3 and RET etc. It has now

been approved for the treatment of progressive, well-differentiated **pancreatic neuroendocrine tumors** in patients with unresectable locally advanced or metastatic disease. It is being used already for renal cell carcinoma.

251. **Tadalafil:** Longest acting phosphodiesterase type 5 (PDE5) inhibitor for the treatment of **pulmonary arterial hypertension** (PAH) as single daily dose.
252. **Tafuprost:** A fluorinated analog of PGF₂ α like Latanoprost approved for reducing elevated intraocular pressure in patients with **open-angle glaucoma** or ocular hypertension by increasing uveoscleral outflow. It is supplied as ophthalmic solution for local use.
253. **Tapentadol:** A centrally acting **oral analgesic** indicated for the relief of moderate to severe acute pain.
254. **Tasimelteon:** An agonist of melatonin MT1 and MT2 receptors (like ramelteon). These receptors are thought to be involved in the control of circadian rhythms. It is specifically indicated for the treatment of **non-24-hour sleep-wake disorder in the totally blind**. It is given orally before bedtime, at the same time every night. Because of individual differences in circadian rhythms, drug effect may not occur for weeks or months.
255. **Teduglutide:** It is a recombinant analog of human glucagon like peptide 2 and is used for the treatment of adults with **short bowel syndrome**. It works by promoting mucosal growth and possibly restoring gastric emptying and secretion.
256. **Telaprevir and Boceprevir:** These inhibit the hepatitis C protease NS3-4 A, an enzyme that is essential for HCV viral replication. Combination of peginterferon alfa and ribavirin with telaprevir or boceprevir is indicated for the treatment of **genotype 1 chronic HCV** in adults with compensated liver disease, including cirrhosis. These are supplied as tablets for oral administration.
257. **Telavancin:** A bactericidal cell wall synthesis inhibitor (similar to vancomycin), once-daily injectable antibiotic for the treatment of **complicated skin and skin structure infections** (cSSSI) caused by susceptible Gram-positive bacteria, including *Staphylococcus aureus*, both methicillin-resistant (MRSA) and methicillin-susceptible (MSSA) strains.
258. **Telavancin:** It is a semisynthetic, lipoglycopeptide antibiotic. It inhibits cell wall biosynthesis and disrupts membrane barrier function. It is specifically indicated for the treatment of adult patients with **hospital-acquired and ventilator-associated bacterial pneumonia** (HABP/VABP), caused by susceptible isolates of *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates). It should be reserved for use when alternative treatments are not suitable.
259. **Telbivudine:** NRTI for **chronic hepatitis B**.
260. **Teriflunomide:** An immunomodulatory agent with anti-inflammatory properties like leflunomide. It is specifically indicated for the oral treatment of **relapsing forms of multiple sclerosis**. It inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de novo pyrimidine synthesis. The exact mechanism by which teriflunomide exerts its therapeutic effect in multiple sclerosis is unknown but may involve a reduction in the number of activated lymphocytes in CNS.
261. **Teriparatide:** Recombinant PTH1-34 useful in **osteoporosis**.
262. **Terlipressin:** A prodrug of vasopressin useful for **variceal bleeding due to selective V1 action**.
263. **Tesamorelin:** First and only treatment indicated to reduce excess abdominal fat in **HIV-infected patients with lipodystrophy** (abdominal lipohypertrophy). It is a synthetic analogue of growth hormone releasing factor (GRF), shown to reduce visceral fat in HIV-infected patients with excess abdominal fat associated with lipodystrophy. GRF is a hypothalamic peptide that acts on the pituitary cells in the brain to stimulate the synthesis and release of endogenous growth hormone.
264. **Tetrabenazine:** A selective and reversible centrally-acting dopamine depleting drug indicated for the treatment of chorea associated with **Huntington's disease**.
265. **Ticagrelor:** It is a reversible oral ADP receptor (P2Y₁₂) antagonist (unlike clopidogrel and ticlopidine which are irreversible antagonists at this receptor). It is indicated to reduce the rate of thrombotic cardiovascular events in patients with **acute coronary syndrome**.
266. **Tipranavir and Darunavir:** New protease inhibitors for **HIV**.
267. **Tocilizumab:** A humanized anti IL-6 receptor monoclonal antibody approved for patients 2 years of age and older with active **polyarticular juvenile idiopathic arthritis**.
268. **Tofacitinib:** It is an inhibitor of Janus kinase 3 indicated for the treatment of adult patients with moderate to severe **rheumatoid arthritis**. It interferes with the JAK-STAT signaling pathway, which transmits extracellular information into the cell nucleus, influencing DNA transcription.
269. **Tolvaptan:** An oral selective vasopressin antagonist for the treatment of patients with clinically significant **hypervolemic and euvolemic hyponatremia**.
270. **Trametinib:** It is an orally bioavailable inhibitor of mitogen-activated protein kinase kinase (MEK) with potential antineoplastic activity. It is specifically indicated for the treatment of patients with unresectable or **metastatic melanoma** with BRAF V600E or V600K mutations as detected by an FDA-approved test. It is not indicated for patients who have received prior BRAF-inhibitor therapy.

271. **Trastuzumab:** It is a monoclonal antibody against her-/neu gene product and is now approved in combination with chemotherapy (cisplatin plus either capecitabine or 5-fluorouracil [5-FU]) for HER2-positive metastatic (cancer that has spread) **cancer of the stomach or gastroesophageal junction**, in men and women who have not received prior medicines for their metastatic disease. Its already approved uses are: first line treatment of HER2+ **metastatic breast cancer** (in combination with paclitaxel) and alone for the treatment of HER2+ breast cancer in patients who have received one or more chemotherapy courses for metastatic disease.
272. **Trimetazidine and Ranolazine:** Partial fatty acid oxidation inhibitors useful in the treatment of **angina**.
273. **Ulipristal acetate:** It is a progesterone agonist/antagonist **emergency contraceptive** indicated for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure.
274. **Umeclidinium plus vilanterol:** This combination is specifically indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with **chronic obstructive pulmonary disease**, including chronic bronchitis and/or emphysema. Umeclidinium is an anticholinergic and vilanterol is a long-acting beta2-adrenergic agonist (LABA).
275. **Ustekinumab:** A human monoclonal antibody against IL-12 and IL-23 for the treatment of moderate to **severe plaque psoriasis**.
276. **Vandetanib:** It is a kinase inhibitor indicated for the treatment of symptomatic or progressive **medullary thyroid cancer** in patients with unresectable (non-operable) locally advanced or metastatic disease.
277. **Vemurafenib:** It is a low molecular weight, orally available, inhibitor of mutated BRAF serine-threonine kinase. It is a selective inhibitor of the activated BRAFV600E gene, a gene found in 70% of malignant melanomas and a significant percentage of other cancers. It is indicated for the treatment of unresectable or **metastatic melanoma** with BRAFV600E mutation.
278. **Vesnarinone:** Phosphodiesterase-3 inhibitor useful as an ino-dilator in **CHF** (similar to amrinone and milrinone).
279. **Vilazodone:** It is a dual-acting potent and selective serotonin reuptake inhibitor and a 5-HT_{1A} receptor partial agonist indicated for the treatment of major depressive disorder (MDD).
280. **Vismodegib:** It is an inhibitor of the hedgehog (Hh) signaling pathway. This pathway is typically over-activated in basal cell carcinoma. It is approved for the treatment of adults with metastatic **basal cell carcinoma**, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.
281. **Vortioxetine:** It is a serotonin modulator and stimulator indicated for **Major Depressive Disorder**. The mechanism of the antidepressant effect of vortioxetine is not fully understood, but is thought to be related to its enhancement of serotonergic activity in the CNS through inhibition of the reuptake of serotonin (5-HT). It also has several other activities including 5-HT₃ receptor antagonism and 5-HT_{1A} receptor agonism.
282. **Ziv-aflibercept:** A fusion protein specifically designed to bind all forms of Vascular Endothelial Growth Factor-A (VEGF-A) and Placental Growth Factor (PlGF). Both VEGF-A and PlGF are proteins that are involved in the abnormal growth of new blood vessels. It is specifically approved in combination with 5-fluorouracil, leucovorin, irinotecan (FOLFIRI) for patients with **metastatic colorectal cancer** that is resistant to or has progressed following an oxaliplatin-containing regimen. It is used i.v. Ziv-aflibercept is a recombinant fusion protein consisting of Vascular Endothelial Growth Factor (VEGF)-binding portions from the extracellular domains of human VEGF Receptors 1 and 2 fused to the Fc portion of the human IgG1. By binding to these endogenous ligands, ziv-aflibercept can inhibit the binding and activation of their cognate receptors. This inhibition can result in decreased neovascularization and decreased vascular permeability.
283. **Zoledronic acid:** **Only Once-yearly osteoporosis treatment** approved for prevention of fractures after a hip fracture.

NEW DRUGS APPROVED BY US-FDA IN 2014-2015

1. **Afrezza:** It is the commercial name of a **rapid acting inhaled insulin powder**. When the insulin is inhaled through the device, the powder is aerosolized and delivered to the lung. It is specifically indicated to improve glycemic control in adult patients with **diabetes mellitus**. It is not a substitute for long-acting insulin. It must be used in combination with long-acting insulin in patients with type 1 diabetes mellitus. It is not recommended for the treatment of diabetic ketoacidosis.
2. **Albiglutide and Dulaglutide:** These are agonists of glucagon-like peptide (GLP)-1 protein similar to exenatide. These augment glucose-dependent insulin secretion and slow gastric emptying. These are specifically indicated as an adjunct to diet and exercise to improve glycemic control in adults with **type II diabetes mellitus**. These should be administered subcutaneously once a week on the same day each week.
3. **Alemtuzumab:** It is a monoclonal antibody that targets CD52, a protein abundant on T and B cells. Circulating T and B cells are thought to be responsible for the damaging inflammatory process in MS. Alemtuzumab depletes circulating T

and B lymphocytes after each treatment course. Lymphocyte counts then increase over time with a reconstitution of the lymphocyte population that varies for the different lymphocyte subtypes. It is specifically indicated for the treatment of patients with **relapsing forms of multiple sclerosis**. Because of its safety profile, its use should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

4. **Apremilast:** It is an inhibitor of phosphodiesterase 4 (PDE4), a proinflammatory mediator. It is specifically indicated for the treatment of patients with moderate to **severe plaque psoriasis** who are candidates for phototherapy or systemic therapy. It is also approved for **psoriatic arthritis**. It is supplied as a tablet for oral administration.
5. **Atazanavir plus cobicistat:** It is a combination of atazanavir (protease inhibitor) with cobicistat (CYP 3A inhibitor) that is specifically indicated for use in combination with other antiretroviral agents for the treatment of **human immunodeficiency virus (HIV-1)** infection in adults.
6. **Belinostat:** It is a histone deacetylase inhibitor. It is specifically indicated for the treatment of **relapsed or refractory peripheral T-cell lymphoma**.
7. **Blinatumomab:** It is an immunotherapy that engages the body's T-cells to destroy leukemia cells. The drug acts as a connector between a protein called CD19, which is found on the surface of most B-cell lymphoblasts, and CD3, a protein on T-cell lymphocytes. It is specifically indicated for the treatment of **Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia**. It is administered intravenously.
8. **Ceftazidime-avibactam:** It is a combination of a cephalosporin and a beta-lactamase inhibitor. It is indicated for the treatment of **complicated urinary tract infections including pyelonephritis** and in combination with metronidazole, for the treatment of complicated intra-abdominal infections caused by the susceptible microorganisms. Its spectrum of activity includes *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Providencia stuartii*, *Enterobacter cloacae*, *Klebsiella oxytoca*, *Pseudomonas aeruginosa*, *Citrobacter koseri* and *Enterobacter aerogenes*. It is administered i.v.
9. **Ceftolozane plus tazobactam:** Ceftolozane is a new cephalosporin having activity similar to third generation cephalosporins but having very high activity against *Pseudomonas* (even higher than carbapenems). This combination is specifically indicated for the treatment of patients 18 years or older with **complicated intra-abdominal infections (with metronidazole) and complicated urinary tract infections**. It is supplied as a solution for intravenous infusion.
10. **Ceritinib:** It is a highly selective inhibitor of anaplastic lymphoma kinase (ALK). ALK is a key gene implicated in the development of some lung cancers. It is specifically indicated for the oral treatment of patients with anaplastic lymphoma kinase (ALK)-positive **metastatic non-small cell lung cancer** who have progressed on or are intolerant to crizotinib.
11. **Dalbavancin and Oritavancin:** These are lipoglycopeptide antibacterial drugs. Both of these are approved for the treatment of adult patients with **acute bacterial skin and skin structure infections (ABSSSI)** caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius*, *S. constellatus*). It is administered by i.v. route.
12. **Darunavir plus cobicistat:** It is a once-daily, fixed-dose combination containing darunavir, a protease inhibitor, and the pharmacokinetic enhancing or boosting agent cobicistat. This combination is specifically indicated for use in combination with other antiretroviral agents for the treatment of **human immunodeficiency virus (HIV-1)** infection in treatment-naïve and treatment-experienced adults with no darunavir resistance-associated substitutions (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V).
13. **Dinutuximab:** It is a chimeric monoclonal antibody. It is specifically indicated for use in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2) and 13-cis-retinoic acid (RA), for the treatment of pediatric patients with **high-risk neuroblastoma** who achieve at least a partial response to prior first-line multiagent, multimodality therapy. It irritates nerve cells, causing severe pain that requires treatment with intravenous narcotics and can also cause nerve damage and life-threatening infusion reactions, including upper airway swelling, difficulty breathing, and low blood pressure, during or shortly following completion of the infusion. It may also cause electrolyte abnormalities and bone marrow suppression.
14. **Edoxaban:** It is an inhibitor of coagulation factor Xa (like rivaroxaban) and works as an **oral anticoagulant**. It is specifically indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF). It is also indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5 to 10 days of initial therapy with a parenteral anticoagulant.
15. **Efinaconazole:** It is an azole antifungal. It is specifically indicated for the topical treatment of **onychomycosis** of the toenails due to *Trichophyton rubrum* and *Trichophyton mentagrophytes*.
16. **Eliglustat:** It is a small molecule inhibitor of glucosylceramide synthase. Glucosylceramide synthase is an enzyme that results in reduced production of glucocerebroside, a fatty substance that abnormally accumulates in the cells and tissues of those with Gaucher's disease. It is specifically indicated for the long-term treatment of adult patients with **Gaucher disease type 1**. It is administered by oral route.

17. **Empagliflozin:** It is a sodium-glucose co-transporter 2 (SGLT2) inhibitor similar to canagliflozin and dapagliflozin. It is specifically indicated as an adjunct to diet and exercise to improve glycemic control in adults with **type II diabetes mellitus**. It is administered by oral route.
18. **Ferric citrate:** It is an iron-based compound that has the capacity to bind to phosphate and form non-absorbable complexes. It lowers phosphate levels without raising calcium or aluminum levels. It is specifically indicated **for the control of serum phosphorus levels in patients with chronic kidney disease on dialysis**. It is administered orally.
19. **Finaxofloxacin:** It is a fluoroquinolone that has been approved as otic suspension (0.3%) for the treatment of **acute otitis externa** caused by susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus*.
20. **Idelalisib:** It is a small molecule inhibitor of phosphoinositide-3 kinase (PI3K) delta, an intracellular signaling component. PI3K-delta is expressed primarily in blood-cell lineages, including cells that cause or mediate hematologic malignancies. It is specifically indicated for the oral treatment of **Relapsed chronic lymphocytic leukemia** (in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities), **Relapsed follicular B-cell non-Hodgkin lymphoma** (in patients who have received at least two prior systemic therapies) and **Relapsed small lymphocytic lymphoma** (in patients who have received at least two prior systemic therapies).
21. **Isavuconazonium:** It is an azole antifungal. It is specifically indicated for patients 18 years of age and older for the treatment of **invasive aspergillosis and invasive mucormycosis**. It can be given i.v. as well as orally.
22. **Ivermectin:** It has been recently approved for topical treatment of **inflammatory lesions of rosacea**.
23. **Ledipasvir plus sofosbuvir:** It is a fixed-dose combination of ledipasvir, a hepatitis C virus (HCV) NS5A inhibitor, and sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor. It is specifically indicated for the oral treatment of **chronic hepatitis C genotype 1** infection in adults.
24. **Lenvatinib:** It is a receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1, as well as other RTKs that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions. It is specifically indicated for the treatment of locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer.
25. **Liraglutide [rDNA origin] injection:** It is a glucagon-like peptide-1 (GLP-1) receptor agonist. GLP-1 is a physiological regulator of appetite and calorie intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation. It is specifically indicated as an adjunct to a reduced-calorie diet and increased physical activity for **chronic weight management** in adult patients with an initial body mass index (BMI) of 30 kg/m² or greater (obese), or 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia). It is supplied as a solution for subcutaneous administration.
25. **Memantine plus Donepezil:** It is a fixed-dose combination of memantine hydrochloride extended-release, a NMDA receptor antagonist, and donepezil hydrochloride, an acetylcholinesterase inhibitor. This combination is specifically indicated for the treatment of moderate to severe **dementia of the Alzheimer's type** in patients stabilized on memantine hydrochloride and donepezil hydrochloride. It is given orally.
26. **Miltefosine:** It is an alkyllysophospholipid analogue drug with in vitro activity against the promastigote and amastigote stages of *Leishmania* species. It is specifically indicated for adults and adolescents >12 years of age weighing >30 kg (66 lbs) for the oral treatment of visceral leishmaniasis (due to *L. donovani*), cutaneous leishmaniasis (due to *L. braziliensis*, *L. guyanensis* and *L. panamensis*) and mucosal leishmaniasis (due to *L. braziliensis*).
27. **Naloxegol:** It is an antagonist of opioid binding at the mu-opioid receptor. When administered at the recommended dose levels, naloxegol functions as a peripherally-acting mu-opioid receptor antagonist in tissues such as the gastrointestinal tract, thereby decreasing the constipating effects of opioids. It is specifically indicated for the oral treatment of **opioid-induced constipation** in adults with chronic non-cancer pain.
28. **Naltrexone plus Bupropion:** It is a fixed dose combination of naltrexone, an opioid antagonist, and bupropion, an inhibitor of the neuronal reuptake of dopamine and norepinephrine. This combination is specifically indicated as an adjunct to a reduced-calorie diet and increased physical activity **for chronic weight management** in adults with an initial body mass index (BMI) of: 30 kg/m² or greater (obese) or 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbidity. It is supplied as an extended release tablet for oral administration. Patients using this combination at the maintenance dose should be evaluated after 12 weeks to determine if the treatment is working. If a patient has not lost at least 5 percent of baseline body weight, it should be discontinued. It has the potential to cause suicidal thoughts and behaviors and neuropsychiatric reactions.
29. **Natpara:** It is the commercial name of a parathyroid hormone that is approved as an adjunct to calcium and vitamin D to control hypocalcemia in patients with **hypoparathyroidism**. Because of the potential risk of osteosarcoma, Natpara is recommended only for patients who cannot be well-controlled on calcium supplements and active forms of vitamin D alone. It is supplied as a solution for subcutaneous injection.
30. **Netupitant plus palonosetron:** Netupitant is a NK1 antagonist similar to aprepitant whereas palonosetron is a serotonin-3 (5-HT₃) receptor antagonist. Oral palonosetron prevents nausea and vomiting during the acute phase and netupitant

prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy. This combination is specifically indicated for the **prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy**, including, but not limited to, highly emetogenic chemotherapy.

31. **Nintedanib:** It is a small molecule kinase inhibitor that blocks multiple pathways that may be involved in the scarring of lung tissue. It is specifically indicated for the oral treatment of **idiopathic pulmonary fibrosis**.
32. **Nivolumab:** It is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. It is specifically indicated for the treatment of patients with **metastatic squamous nonsmall cell lung cancer (NSCLC)** with progression on or after platinum-based chemotherapy. It is also approved for the treatment of patients with **unresectable or metastatic melanoma** and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.
33. **Olaparib:** It is a poly (ADP-ribose) polymerase (PARP) inhibitor. It selectively binds to and inhibits PARP, inhibiting PARP-mediated repair of single strand DNA breaks; PARP inhibition enhances the cytotoxicity of DNA-damaging agents and reverses tumor cell chemoresistance and radioresistance. It is specifically indicated as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced **ovarian cancer** who have been treated with three or more prior lines of chemotherapy. It is administered orally.
34. **Olodaterol:** It is a long-acting beta 2-adrenergic agonist and is specifically indicated as a long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with **chronic obstructive pulmonary disease (COPD)**, including chronic bronchitis and/or emphysema by inhalational route.
35. **Ombitasvir + Paritaprevir + Ritonavir + Dasabuvir:** It is a fixed dose combination of ombitasvir, a hepatitis C virus NS5A inhibitor, paritaprevir, a hepatitis C virus NS3/4A protease inhibitor, ritonavir, a CYP3A inhibitor and dasabuvir, a hepatitis C virus non-nucleoside NS5B palm polymerase inhibitor. This combination is specifically indicated for the treatment of patients with **genotype 1 chronic hepatitis C virus (HCV)** infection including those with compensated cirrhosis by oral route.
36. **Palbociclib:** It is an orally available pyridopyrimidine-derived cyclin-dependent kinase (CDK) inhibitor with antineoplastic activity. It is specifically indicated for use in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative **advanced breast cancer** as initial endocrine-based therapy for their metastatic disease.
37. **Panobinostat:** It is a histone deacetylase inhibitor. It is specifically indicated for use in combination with bortezomib and dexamethasone for the treatment of patients with **multiple myeloma** who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent. It is administered orally.
38. **Pasireotide:** It is a somatostatin analog similar to octreotide. It is specifically indicated for the treatment of patients with **acromegaly** who have had an inadequate response to surgery and/or for whom surgery is not an option. It is supplied as an injectable suspension for intramuscular injection.
39. **Pembrolizumab:** It is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. It is specifically indicated for the treatment of patients with unresectable or **metastatic melanoma** and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.
40. **Peramivir:** It is an influenza virus neuraminidase inhibitor. Neuraminidase is an enzyme that releases viral particles from the plasma membrane of infected cells. It is specifically indicated for the single dose treatment of acute **uncomplicated influenza** in patients 18 years and older who have been symptomatic for no more than 2 days. It is supplied as a solution for intravenous administration within 2 days of onset of symptoms of influenza.
41. **Pirfenidone:** It is an oral antifibrotic p38 MAP kinase inhibitor that reduces growth factor signaling. It acts on multiple pathways that may be involved in the scarring of lung tissue. It is specifically indicated for the treatment of **idiopathic pulmonary fibrosis (IPF)**. Its mechanism of action in the treatment of IPF has not been established.
42. **Ramucirumab:** It is a recombinant human IgG1 monoclonal antibody that specifically binds to vascular endothelial growth factor receptor 2. Thus, it is an angiogenesis inhibitor that blocks the blood supply to tumors. It is specifically indicated for **advanced gastric cancer or gastro-esophageal junction adenocarcinoma**, as a single-agent after prior fluoropyrimidine- or platinum-containing chemotherapy. It is supplied as a solution for intravenous infusion.
43. **Ruconest:** It is the commercial name of a recombinant C1 esterase inhibitor. **Hereditary angioneurotic edema** attacks stem from a deficiency of the C1 inhibitor protein in the blood. It is specifically indicated for the treatment of acute angioedema attacks in adult and adolescent patients with hereditary angioedema. It is given by intravenous route.
44. **Secukinumab:** It is a human IgG1 monoclonal antibody that selectively binds to the interleukin-17A and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Secukinumab inhibits the release of proinflammatory cytokines and chemokines. It is

specifically indicated for the treatment of moderate to severe **plaque psoriasis** in adult patients who are candidates for systemic therapy or phototherapy. It is administered as subcutaneous injection.

45. **Siltuximab:** It is an anti-interleukin-6 (IL-6) chimeric monoclonal antibody that binds to human IL-6. IL-6 is a multifunctional cytokine produced by various cells such as T cells, B cells, monocytes, fibroblasts and endothelial cells. It is specifically indicated for the treatment of patients with multicentric **Castleman's disease** who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative. Dysregulated overproduction of IL-6 from activated B cells in affected lymph nodes has been implicated in the pathogenesis of Castleman's disease.
46. **Suvorexant:** It is an orexin receptor antagonist. The orexin neuropeptide signaling system is a central promoter of wakefulness. Blocking the orexin receptor suppresses wakefulness. It is specifically indicated for the treatment of **insomnia** (by oral route) characterized by difficulties with sleep onset and/or sleep maintenance.
47. **Tavaborole:** It is an oxaborole antifungal. It is specifically indicated for the topical treatment of **onychomycosis of the toenails** due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*.
48. **Tedizolid:** It is an antibacterial agent of the oxazolidinone class similar to linezolid. It is specifically indicated for the treatment of adults with **acute bacterial skin and skin structure infections (ABSSSI)** caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* Group (including *Streptococcus inosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*), and *Enterococcus faecalis*. It can be given orally or intravenously.
49. **Testosterone undecanoate:** It is an ester of the testosterone that is specifically indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: **primary hypogonadism** (congenital or acquired) or **hypogonadotropic hypogonadism** (congenital or acquired). It is administered by intramuscular route. Recently intranasal gel of testosterone has also been approved for same indications.
50. **Topiramate:** The extended release formulation of topiramate has been approved as initial monotherapy in patients 10 years of age and older with **partial onset or primary generalized tonic-clonic seizures** and adjunctive therapy in patients 2 years of age and older with partial onset or primary generalized tonic-clonic seizures and as adjunctive therapy in patients 2 years of age and older with **seizures associated with Lennox-Gastaut syndrome**.
51. **Umeclidinium:** It is a long-acting muscarinic antagonist (LAMA). It is specifically indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with **chronic obstructive pulmonary disease (COPD)**, including chronic bronchitis and/or emphysema via inhalational route.
52. **Vedolizumab:** It is a humanized monoclonal antibody. Vedolizumab targets a protein called alpha-4-beta-7, an integrin on inflammatory cells that causes these cells to adhere to the gastrointestinal tract. It is specifically indicated for adults with moderately to severely active **ulcerative colitis (UC) or Crohn's disease (CD)** who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroid. It is indicated to induce and maintain clinical response/clinical remission, achieve corticosteroid-free remission and improve the endoscopic appearance of the mucosa (UC). It is administered intravenously.
53. **Vorapaxar:** It is a protease-activated receptor-1 (PAR-1) antagonist. It is specifically indicated for the **reduction of thrombotic cardiovascular events** in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD). It is administered by oral route.

TRICYCLIC ANTIDEPRESSANT POISONING:**Clinical Presentation**

The presenting signs of a TCA overdose include cardiac arrhythmias, hypotension, and anticholinergic signs (hyperthermia, flushing, dilated pupils, intestinal ileus, urinary retention, and sinus tachycardia). Central nervous system involvement is also common. Early signs, such as confusion, delirium, and hallucinations, typically occur before the onset of seizures or coma. The physical examination may reveal clonus, choreoathetosis, hyperactive reflexes, myoclonic jerks, and a positive Babinski sign. Cardiotoxic effects are responsible for the mortality in TCA overdose. The most important electrophysiologic action of TCAs is inhibition of the fast sodium channel, leading to slowing of phase 0 depolarization in His-Purkinje tissue and the myocardium. This toxic effect, which is inhibited by sodium bicarbonate, slows conduction with resultant QRS prolongation and the potential emergence of reentry arrhythmias (such as ventricular tachycardia, ventricular fibrillation, and torsade de pointes).

Treatment

- Treatment of TCA overdose must be aggressive from the outset. Initial therapy consists of establishing airway and breathing, continuous electrocardiographic monitoring, **gastric lavage**, and the administration of activated charcoal. Gastric decontamination can be considered for up to 12 hours after ingestion because the anticholinergic properties of these drugs delay gastric emptying.
- **Intravenous sodium bicarbonate** is the single most effective intervention for the management of TCA cardiovascular toxicity. This agent can reverse QRS prolongation, ventricular arrhythmias, and hypotension. Because acidosis aggravates TCA toxicity, the beneficial action of sodium bicarbonate may be partly due to correction of acidosis. It is clear, however, that sodium bicarbonate administration is effective even when the arterial pH is normal. Alkalinization to an arterial pH of 7.5, for example, appears to reduce the incidence of cardiac arrhythmias and intravenous sodium bicarbonate is the treatment of choice for sudden-onset ventricular tachycardia, ventricular fibrillation, or cardiac arrest.
- **Lignocaine is the drug of choice for TCA-induced ventricular dysrhythmias.** However, care must be taken to avoid precipitation of seizures. In comparison, many antiarrhythmic drugs should not be used with TCA overdoses. Propranolol, for example, depresses myocardial contractility and conduction while procainamide, disopyramide, and quinidine, via membrane stabilizing effects, may enhance tricyclic toxicity.
- **Intravenous fluids** are the preferred therapy in hypotensive patients. Dopamine can be used if needed because it has both inotropic and vasoconstrictor activity. On the other hand, sympathomimetic vasopressor agents carry the risk of precipitating tachyarrhythmias.
- **Diazepam** is the drug of choice in the management of acute-onset seizures. Phenytoin or phenobarbital may be used as second-line drugs.
- **Physostigmine**, a short-acting cholinesterase inhibitor, has been referred to as the antidote for TCAs because of its ability to increase cholinergic tone and reverse anticholinergic effects. It can, however, causes severe bradycardia, seizures, and asystole by overcompensating for cholinergic tone and suppressing supraventricular and ventricular pacemakers. As a result, physostigmine should only be used in patients with coma or those with convulsion or arrhythmias resistant to standard therapy.

 Drug treatment of obesity started if:

- BMI > 30 kg/m²
or
- BMI > 27 with obesity related risk-factors.

 Bariatric surgery for obesity recommended if:

- BMI > 40 kg/m²
or
- BMI > 35 with obesity related co-morbidities

 FDA-approved antiobesity drugs are:

- Lorcaserin
- Phentermine + Topiramate
- Orlistat

ANTI OBESITY DRUGS

Obesity is a complex metabolic disorder resulting from the abnormality between energy intake and energy expenditure. Generally this imbalance is because of life style and behavioral origin. It is also associated with insulin resistance, dyslipidemia and cardiovascular disease.

Pathogenesis

Glucose forms a dependable source of energy for short term basis whereas lipids are utilized on the long term basis. The **arcuate nucleus** in the mediobasal hypothalamus forms the main integrating centre for feeding and regulation of body weight. The following compounds/peptides play an important role in the regulation of food intake:

OREXINS AND GHRELIN

- *Orexin* is a 33 amino acid peptide, which acts on the orexin receptor (oxR) to *stimulate food intake* in a dose dependent manner.
- *Ghrelin* is an acetylated peptide secreted by gastric mucosal cells that causes release of growth hormone from the pituitary. It also acts directly on the arcuate nucleus to *stimulate food intake*. The plasma level of ghrelin increases before meals and falls following intake of food.

NEUROPEPTIDE Y (NPY) AND AGOUTI RELATED PEPTIDE (AGRP)

These **two peptides**; NPY and AgRP, **stimulate food intake**, reduce energy expenditure and promote weight gain.

MELANOCYTE STIMULATING HORMONE (MSH) AND CART (COCAINE AND AMPHETAMINE RELATED TRANSCRIPT)

Both MSH and CART **reduce food intake** by eventually causing *activation of 5-HT_{2C} (serotonin) receptors*.

INSULIN AND LEPTIN

These signals are increased in obesity. These are *inhibitory to NPY and AgRP neurons and facilitatory to MSH and CART neurons*.

CANNABINOIDS

The endocannabinoids act on their receptor *CB₁ and CB₂* to stimulate the anabolic pathway (NPY and AgRP). They also *inhibit* the catabolic pathways (CART and MSH) eventually *resulting in excessive food intake and obesity*.

Therapies for the Management of Obesity**1. DIET**

Which diet plan is best at promoting sustained weight loss remains a controversial issue. Four types of diets are recommended for weight loss. These are

- **Atkins** (*very low carbohydrate*)
- **Traditional** (*lifestyle, exercise, attitudes, relationships, nutrition* [LEARN])
- **Ornish** (*very high carbohydrate*)
- **Zone** (*low carbohydrate*)

Note: These can be remembered as **A TO Z**

2. DRUGS

5-HT₂ receptor activation leads to weight loss. Therefore, drugs increasing the level of serotonin (reuptake inhibitors) can be used to treat obesity.

- Lorcaserin:** It is a **selective 5HT_{2C} agonist**. It decreases appetite. Most common adverse effect is headache. Studies focus *concerns of breast tumors in animals, increased valvular heart disease and psychiatric adverse effects*.
- Phentermine + Topiramate:** This combination has been approved for obesity. Common side effects include mood changes, fatigue, insomnia and tachycardia. The combination is teratogenic and is contra-indicated in pregnancy.
- Orlistat:** It is an *inhibitor of gastrointestinal lipases*, which are necessary for absorption of fat from the diet. This drug decreases fat absorption by up to 30%, resulting in weight loss. Adverse effects include loose stools, increased defecation and oily discharge. Most of these can be managed by the simultaneous use of natural fibre.
- Amphetamines, fenfluramine and dexfenfluramine:** These were used previously for the treatment of obesity but are not used now. *Fenfluramine and dexfenfluramine are banned due to the risk of cardiotoxicity*.
- Sibutramine:** It blocks the presynaptic uptake of *both nor-epinephrine and serotonin* resulting in the potentiation of anorexic effects of both of these neurotransmitters in the CNS. Side effects include mild elevation in BP, headache, insomnia, dry mouth and constipation.
- Rimonabant:** It is a *cannabinoid receptor antagonist* which acts on CB₁ receptor resulting in the increased levels of serotonin and dopamine. It blocks the orexigenic action of ghrelin and causes reduction in appetite. It also causes lipolysis and increases basal metabolic rate. Adverse effects include nausea, vomiting, depression (leading to suicidal tendencies) and anxiety. **It can decrease blood pressure.**
- Naltrexone plus bupropion:** This combination has been recently approved for chronic weight management. It has the potential to cause suicidal thoughts and neuropsychiatric reactions.

Rimonabant is an anti-obesity drug that can lower blood pressure.

Though all of the above drugs may result in weight loss but tolerance develops to the anorexic effect, when these are used for a long duration of time.

NEW TARGETS

- NPY and AgRP antagonists
- MSH and CART agonists

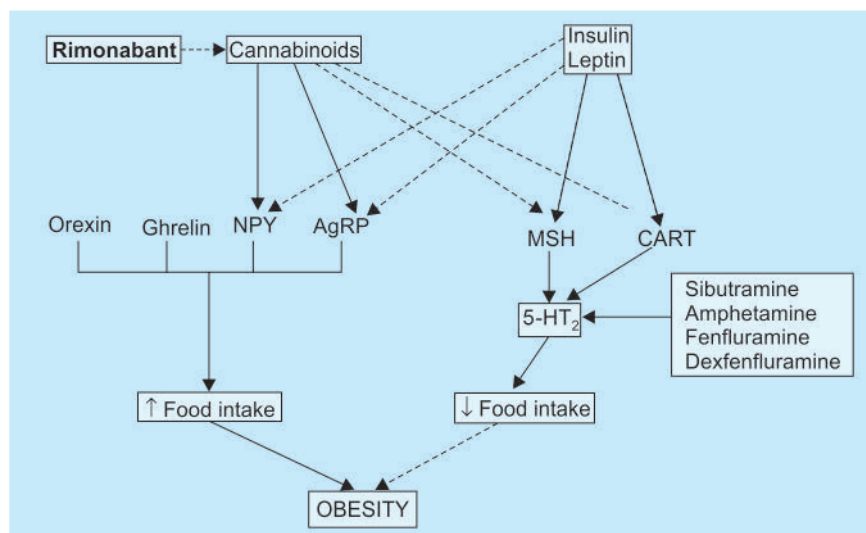


Fig. 20.1: Physiological and pharmacological regulation of food intake (Bold arrow indicates stimulation whereas dotted arrow indicates inhibition)

ERECTILE DYSFUNCTION

Inability of the male to attain and maintain penile erection for a duration sufficient to permit satisfactory intercourse is called as erectile dysfunction (ED).

Physiology of Penile Erection

Both the parasympathetic system (S2-4) and NO synthesis and release process should be intact for the normal erection of penis. NO increases the level of cGMP leading to relaxation of smooth muscles of corpora cavernosa. This leads to penile erection.

Etiology

The causes of erectile dysfunction can be psychological (most common), vascular, neurological and hormonal. Arteriosclerosis, hypertension, diabetes, smoking, alcohol consumption and drugs (like beta blockers) are the secondary causes of erectile dysfunction.

Drugs useful in the Management of Erectile Dysfunction

Tadalafil is the longest acting phosphodiesterase inhibitor.

Phosphodiesterase inhibitors should not be prescribed to a patient on nitrates due to the risk of severe hypotension.

Avanafil is a new PDE-5 inhibitor similar to sildenafil

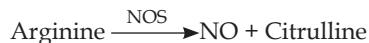
- *Phosphodiesterase inhibitors*: Normally cGMP formed by the action of NO is metabolized by phosphodiesterase. Sildenafil selectively inhibits PDE-V leading to increased cGMP levels and so is useful in erectile dysfunction. It can be administered orally. Adverse effects include headache, nasal congestion, flushing, visual disturbances (blue vision) etc. Colour vision defect is due to inhibition of PDE-VI present in the retina. Apart from their use in ED, sildenafil can also be used in the management of pulmonary hypertension. Other drugs of this group are *varденаfil*, *уденаfil*, *аванаfil* and *тадалаfil*.
- **Tadalafil** is the **longest acting** phosphodiesterase inhibitor.
- These drugs should not be prescribed to a patient on nitrates due to the risk of severe hypotension.
- *Other orally effective drugs*: Apomorphine, a dopamine agonist can also be used. Its main adverse effect is nausea. Trazodone (an antidepressant) and phentolamine (non-selective α blocker) have also shown promise for the management of ED.
- *Alprostadil*: It is a PGE_1 analogue administered directly in the cavernosal tissue (more useful in patients not responding to oral sildenafil therapy). Phentolamine is another drug which can be used intracavernosally.
- *Aviptadil*: It is the analogue of vasoactive intestinal peptide that causes smooth muscle relaxation. It can be used along with phentolamine for ED.
- *Ketanserin*: It is a 5-HT_2 and α receptor antagonist used in combination with alprostadil for ED.
- *Thymoxamine*: It is an α blocker used as intracavernosal injection for ED.
- Recently, *naltrexone* has been tried for the restoration of erectile function.
- *Herbal drugs* (like Ginseng, kava, ginkgo etc.) have been claimed to be useful for erectile dysfunction but efficacy has not been established clinically.

NITRIC OXIDE

Nitric oxide (NO) is a signaling molecule having important role in various pathophysiological conditions. It is also known as endothelium derived relaxing factor (EDRF).

Synthesis

NO is formed by the action of the enzyme NO synthase on the amino acid arginine. The enzyme NO synthase (NOS) has three isoforms: endothelial NOS (eNOS), inducible NOS (iNOS) and neuronal NOS (nNOS). Both eNOS and nNOS are expressed constitutively whereas iNOS is inducible in many inflammatory conditions.



Mechanism of action

NO formed from the action of NOS binds to iron in heme and causes an increase in the concentration of cGMP by stimulating guanylyl cyclase. This cGMP is responsible for its vasodilatory actions.

Nitric Oxide Donors

NO donors are primarily used for smooth muscle relaxation. The important NO donors are:

- **Organic nitrates:** Nitroglycerin and isosorbide dinitrate are metabolized to NO releasing compounds. Rapid tolerance is seen with the vasodilatory properties of nitrates because of inhibition of the mitochondrial aldehyde reductase.
- **Organic nitrites:** Amylnitrite also causes relaxation of vessels (especially arteries) but it does not exhibit tolerance.
- **Sodium nitroprusside:** It is an antihypertensive drug that acts by releasing NO.
- **Hydralazine:** It is an antihypertensive drug that acts partly by releasing NO and partly by opening the K⁺ channels.
- **Nebivolol:** It is a third generation beta-blocker that contains additional vasodilatory activities due to the release of NO.
- **Alternative drugs:** Drugs like sildenafil act by increasing the duration of NO induced cGMP elevation in the tissues.

Nitric Oxide in Health and Disease

- **Vascular effects:** Effect of NO on blood vessels are:
 - Vasodilatation
 - Inhibition of vascular smooth muscle proliferation
 - Inhibition of platelet aggregation
 - Increase in fibrinolysis
- **Septic shock:** NO plays an important role in the pathogenesis of septic shock. This is confirmed by the increased urinary excretion of oxidative products of NO (nitrates) and the reversal of hypotension by NO synthase inhibitors (L-NMMA, 7-nitroimidazole) in this condition.
- **Inflammation:** Inhibitors of iNOS have a dose dependent protective effect on arthritis, psoriasis, inflammatory bowel disease and asthma.
- **CNS:** NO is involved in the regulation of synaptic plasticity (the process underlying memory and behaviour).
- **Peripheral nervous system:** NO is an important mediator of non-adrenergic, non-cholinergic (NANC) transmission in neurons of GIT and other areas of the body.
- **Respiratory diseases:** NO can be used for the treatment of several diseases of respiratory system.
 - Inhalational NO is used for the management of pulmonary artery hypertension.
 - NO inhalation is also beneficial in ARDS (Adult Respiratory Distress Syndrome).

ANTI SMOKING DRUGS

The following agents can be used as anti-smoking drugs:

- **Vareniciline:** It is a **direct acting nicotinic agonist** having selectivity for $\alpha_4\beta_2$ isoform of N_A receptors. It can be used orally and has a half life of 14-20 hours. Its adverse effects include headache, nausea and sleep disturbances.
- **Nicotine patch:** A transdermal patch containing nicotine is applied to the patient's body. The dose of nicotine is then slowly decreased and finally withdrawn. It is effective in only 18-20% of the patients.
- **Bupropion:** It is an anti-depressant drug that can be used for cessation of smoking. It acts by **inhibition of neuronal reuptake of 5-HT, NE and DA**. The duration of treatment is for 8-10 weeks. It can result in CNS stimulation leading to seizures.

- **Amfebutamone:** This drug selectively inhibits neuronal uptake of NE and DA resulting in the decreased craving for nicotine. Its efficacy is increased in combination with nicotine patch but it should not be used in epileptic patients.
- **Clonidine:** It is a very effective drug for reducing the **withdrawal effects of nicotine**. It is better than nicotine chewing gum as it can be used in patients with cardiac diseases also. It decreases the craving as well as is useful for insomnia.
- **Rimonabant:** It is a cannabinoid receptor antagonist that results in the increased 5-HT and dopamine levels. The adverse effects include nausea, vomiting, suicidal tendencies (depression) and anxiety.
- **Topiramate:** It is an antagonist at AMPA/kainate receptors of glutamate. It can also cause weight loss.
- **Nortriptyline:** It is the main active metabolite of amitriptyline with longer $t_{1/2}$ than the parent compound. It produces prolonged abstinence rates as compared to the placebo. The adverse effects include dry mouth and sedation.
- **Glucose:** Single dose of nicotine relieve hunger in smokers and hunger pains which are associated with craving for cigarettes. Therefore, glucose tablets can also be used to decrease craving.
- **Mecamylamine:** It is a nicotine antagonist and may block the rewarding effects of nicotine. The adverse effect of this drug is constipation.
- **Tryptophan and high carbohydrate diet:** Serotonin enhancing substances such as tryptophan and high carbohydrate diets have been shown to reduce the withdrawal symptoms of nicotine.

IMPORTANT HUMAN TERATOGENIC DRUGS

Drug	Congenital Adomalies
ACE inhibitors	IUGR, oligohydramnios, bony malformations, PDA, hypoplasia of organs, renal anomalies
Alcohol	Fetal alcohol syndrome: IUGR, microcephaly, developmental delay, dysmorphic facies (low nasal bridge, midface hypoplasia long featureless philtrum, small palpebral fissure, thin upper lip)
Antithyroid drugs (Carbimazole, methimazole, propylthiouracil)	Fetal hypothyroidism, congenital goiter, scalp defects (<i>aplasia cutis congenita</i>)
Androgens	Virilization; limb, esophageal and cardiac defects
Carbamazepine	Neural tube defects, defects similar to fetal hydantoin syndrome
Diethylstilbesterol	Clear cell adenocarcinoma of vagina, hypospadias
Isotretinoin	Craniofacial, heart and CNS defects
Lithium	Fetal goiter, Ebstein's anomaly
Misoprostol	Moebius syndrome
Methotrexate	Hydrocephalus, meningomyelocele, cleft palate, external ear anomalies
Phenytoin	Fetal hydantoin syndrome: Microcephaly, cleft lip, cleft palate, hypoplastic phalanges, nail hypoplasia
Progesterone	Virilization of female fetus

Contd...

Contd...

Drug	Congenital Adomalies
Tetracyclines	Discoloration of teeth, retardation of bone growth
Thalidomide	<i>Phocomelia</i> , polydactyly, syndactyly, external ear defects (from agenesis to pre-auricular tags), moebius syndrome, abnormalities in gut musculature
Valproate	Neural tube defects
Warfarin	Fetal warfarin syndrome (contradi syndrome): Nasal hypoplasia, calcific stippling of epiphyses, IUGR, eyes defects, hearing loss

HYPERKALEMIA

Emergency treatment of hyperkalemia is indicated when cardiac toxicity or muscular paralysis or severe hyperkalemia (> 6.5 mEq/L) is present, even in the absence of ECG changes.

TREATMENT OF HYPERKALEMIA

Modality	Indication	Mechanism
1. Glucose + Insulin	Emergency	Distribution of K^+ into cells
2. β -agonists like salbutamol	Emergency	Distribution of K^+ into cells
3. Bicarbonate	Emergency	Distribution of K^+ into cells
4. Calcium gluconate	Emergency	Antagonize cardiac conduction abnormalities due to K^+
5. Loop Diuretics	Non-Emergency	Renal K^+ excretion
6. Resins [Sodium polystyrene sulfate]	Non-Emergency	Binds K^+
7. Hemodialysis	Both Emergency as well as non-emergency	Extracorporeal K^+ removal
8. Peritoneal dialysis	Non-Emergency	Peritoneal K^+

THALIDOMIDE

It was used as a sedative drug but was withdrawn from the market in 1960s due to its teratogenic effects (Phocomelia).

Recently, it has been re-introduced due to its immunomodulatory properties. **Its major actions are:**

- Inhibition of angiogenesis
- Inhibition of $TNF-\alpha$
- Increased production of IL-10
- Reduces phagocytosis
- Alteration of adhesion molecule expression
- Enhances cell-mediated immunity via interactions with T- cells.
- **Currently, it is indicated for**
 - Multiple myeloma at initial diagnosis
 - Relapsed- refractory cases of multiple myeloma
 - Erythema nodosum leprosum
 - Skin manifestations of SLE
- **Its major adverse effects are:**
 - Teratogenicity
 - Peripheral neuropathy
 - Constipation
 - Rash



Immunomodulatory derivatives of thalidomide are called IMiDs. One of these is Lenalidomide, which is approved as a first line therapy for multiple myeloma with dexamethasone and bortezomib.



Another group of thalidomide analogs are called SelCIDs (Selective Cytokine Inhibitory Drugs).

- Hypothyroidism
- Increased risk of DVT
- Immunomodulatory derivatives of thalidomide are called IMiDs. One of these is Lenalidomide, which is approved as a first line therapy for multiple myeloma with dexamethasone and bortezomib.
- Another group of thalidomide analogs are called SelCIDs (Selective Cytokine Inhibitory Drugs).

HEPARIN INDUCED THROMBOCYTOPENIA

Heparin Induced Thrombocytopenia (HIT) results from formation of IgG antibodies to heparin- platelet factor 4 complexes. The antibodies then bind platelets and activate them. It results in pro-thrombotic state even in the presence of thrombocytopenia.

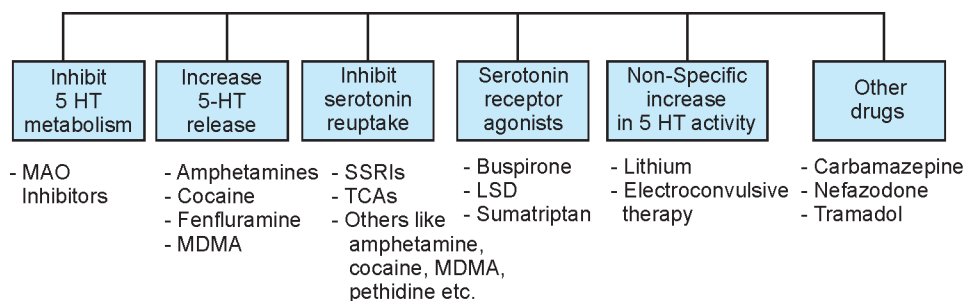
- HIT usually occurs 5-10 days after exposure to heparins

MANAGEMENT OF HIT

- Stop all forms of heparins and LMW Heparins.
- Direct thrombin inhibitors (Lepirudin and Argatroban) are anticoagulants of choice.
- Lepirudin is safe in liver failure whereas argatroban can be safely administered in anuria (renal failure).
- Initially, warfarin causes hypercoagulability, therefore should be avoided.
- Lepirudin is continued till platelet count reaches 1,00,000/ μ L.
- Now, warfarin should be started and direct thrombin inhibitors discontinued. Warfarin should be given for at least 30 days.
- Fondaparinux can also be used for HIT.

SEROTONIN SYNDROME

Serotonin syndrome is a condition associated with skeletal muscle contractions, hyperthermia, hyperreflexia, diarrhea, mydriasis, agitation, myoclonus and coma. It results from excessive serotonin in the synapse. It can be caused by:



Myoclonus is present in serotonin syndrome but absent in neurolept malignant syndrome (NMS) whereas rigidity is present in NMS but absent in serotonin syndrome.

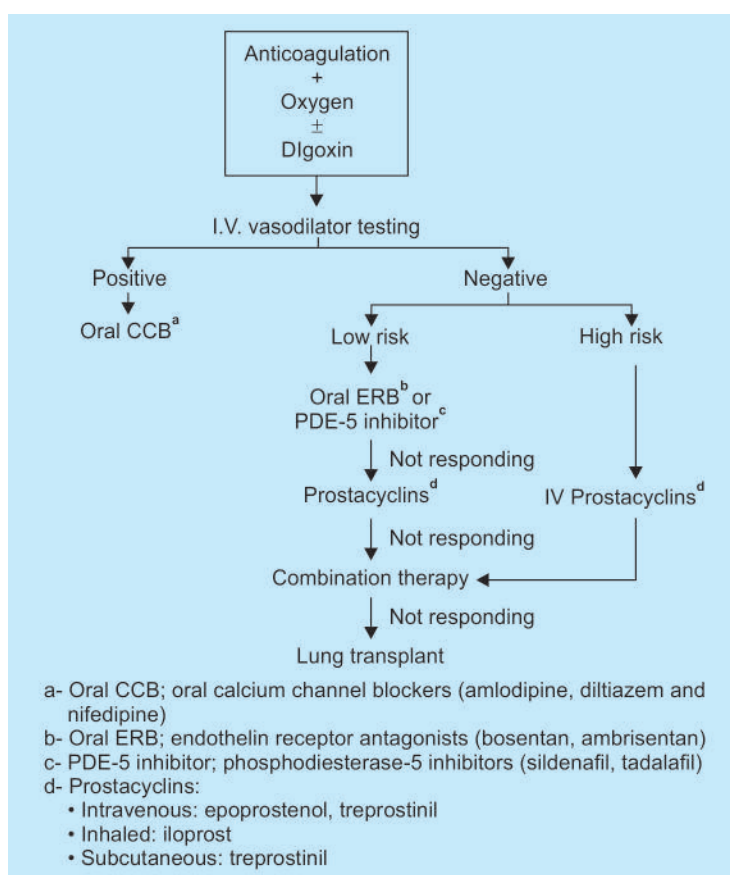
Myoclonus is present in serotonin syndrome but absent in neurolept malignant syndrome (NMS) whereas rigidity is present in NMS but absent in serotonin syndrome.

TREATMENT OF IDIOPATHIC PULMONARY HYPERTENSION

- If the patient responds to intravenous vasodilators, then oral calcium channel blockers (including amlodipine, diltiazem, and nifedipine) are the first-line therapy.
- If these are ineffective or the patient does not respond to vasodilators, then therapy depends on function.
 - If the patient has WHO Class 2 symptoms, then either phosphodiesterase inhibitors (sildenafil or tadalafil) or endothelin receptor blockers (bosentan or ambrisentan) are recommended.

- If the patient has WHO Class 3 symptoms, then prostacyclin analogs (epoprostenol intravenously, iloprost by inhalation, or beraprost or treprostinil subcutaneously) should be added to the regimen.
- For patients with WHO Class 4 symptoms, either epoprostenol or iloprost should be used as the sole agent, though some experts still advocate combination therapies.
- Most authorities advocate long-term oral anticoagulation.
- Supplemental oxygen, particularly at night, appears to improve symptoms and helps reduce pulmonary pressures.
- Diuretics help with right heart edema.
- Pulmonary transplantation is a viable option in selected centers, though the operative mortality is high (around 20–25%).
- Women with significant pulmonary hypertension should not get pregnant, and permanent birth control measures should be considered.
- Future advances in therapy include the possible use of angiogenesis inhibitors, growth factor inhibitors, and endothelial stem cells or progenitor cells.

Calcium channel blockers (including amlodipine, diltiazem, and nifedipine) are the first-line therapy for idiopathic pulmonary hypertension.



NOTES

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AIIMS NOVEMBER 2014

1. **Dexmedetomidine is a:**
 - a. Centrally acting α_2 agonist
 - b. Peripherally acting α_2 agonist
 - c. Centrally acting α_2 antagonist
 - d. Peripherally acting α_2 antagonist
2. **Cholinomimetics are useful in all of the following conditions EXCEPT:**
 - a. Glaucoma
 - b. Myasthenia gravis
 - c. Post operative atony of bladder
 - d. Partial heart block
3. **Which of the following is NOT a tertiary amine?**
 - a. Atropine
 - b. Hyoscine
 - c. Glycopyrrolate
 - d. Physostigmine
4. **Which of the following statement about NSAIDs is FALSE?**
 - a. They interfere with the antihypertensive effect of diuretics
 - b. NSAIDs are useful in neuropathic pain
 - c. NSAIDs should be avoided in renal disease as they can cause nephrotoxicity
 - d. Many NSAIDs can be used topically
5. **A person consumes large quantities of alcohol daily since 20 years. He is physically dependent on alcohol. Drug that should not be given to this person is:**
 - a. Disulfiram
 - b. Acamprosate
 - c. Naltrexone
 - d. Chlordiazepoxide
6. **Which of the following serum concentration of lithium indicates lithium toxicity?**
 - a. 2 mEq/L
 - b. 4 mEq/L
 - c. 6 mEq/L
 - d. 8 mEq/L
7. **A patient of schizophrenia was started on haloperidol 5 mg. Next day, he presented with uprolling of eyes. Complete neurological examination revealed no spasticity or any other abnormality. Visual acuity and ophthalmoscopic findings are normal. Most likely diagnosis is:**
 - a. Akathisia
 - b. Acute dystonia
 - c. Seizure
 - d. Tardive dyskinesia
8. **Which of the following agents is used for day care surgery?**
 - a. Propofol
 - b. Thiopentone
 - c. Diazepam
 - d. Ketamine
9. **A substance has molecular weight 30,000. It exerts oncotic pressure similar to albumin and is non-antigenic. It does not interfere with blood grouping and cross-matching. It is:**
 - a. Dextran 40
 - b. Dextran 70
 - c. Polygeline
 - d. Hetastarch
10. **All of the following adverse effects are associated with the use of proton pump inhibitors EXCEPT:**
 - a. Community acquired pneumonia
 - b. *Clostridium difficile* infection
 - c. Osteoporosis leading to hip fracture
 - d. Hypothyroidism
11. **Time dependent killing with prolonged post antibiotic effect is seen with:**
 - a. Fluoroquinolones
 - b. Beta lactams
 - c. Clindamycin
 - d. Erythromycin
12. **Which of the following cephalosporin has activity against methicillin resistant *Staphylococcus aureus*?**
 - a. Ceftriaxone
 - b. Ceftazidime
 - c. Cefuroxime
 - d. Ceftobiprole

13. Drug of choice for antibiotic associated pseudomembranous colitis is?
- Oral vancomycin
 - Metronidazole
 - Clindamycin
 - Penicillin G
14. TRUE statement about penicillin G is?
- It is administered orally
 - It has a wide spectrum
 - It can be used for rat bite fever
 - Co-administration of probenecid decreases its duration of action
15. Which of the following drugs is active against *Pseudomonas*?
- Ceftriaxone
 - Piperacillin-tazobactam
 - Ampicillin
 - Cefalexin
16. All of the following drugs have activity against hepatitis B virus EXCEPT:
- Lamivudine
 - Zidovudine
 - Emtricitabine
 - Telbivudine
17. Most effective treatment for severe malaria is:
- Artesunate
 - Chloroquine
 - Quinine
 - Primaquine
18. Which of the following statement about rituximab is FALSE:
- It is a chimeric monoclonal antibody against CD-20
 - It has dose-dependent kinetics
 - It is used for treatment of non-Hodgkin lymphoma
 - Its most common adverse effect is infusion related reactions
19. All of the following statements about paclitaxel are true EXCEPT:
- It is obtained from *E. coli*
 - It acts by enhancing the polymerization of β -tubulin
 - It can cause bone marrow suppression
 - It is used in ovarian and breast cancer
20. Which of the following drugs has been recently approved for treatment of prostate cancer?
- Leuprolide
 - Goserelin
 - Abarelix
 - Degarelix
21. Abatacept is a new drug approved for:
- SLE
 - Rheumatoid arthritis
 - Sjogren syndrome
 - Scleroderma

EXPLANATIONS

1. Ans. (a) Centrally acting α_2 agonist (Ref: KDT 7th/384, Katzung 12th/445)

Dexmedetomidine is a highly selective central α_2 - adrenergic agonist (like clonidine). It is the active S-enantiomer of medetomidine (used in veterinary medicine).

Effects:

- It produces sedation and hypnosis by activating central α_2 receptors at locus caeruleus. The sedative effect of this drug resembles a physiological sleep (unlike other anesthetic agents).
- Analgesic effects are produced by activation of α_2 receptors in spinal cord.
- By inhibiting central sympathetic outflow, it can produce bradycardia and hypotension. Intravenous bolus dose can produce transient hypertension with reflex bradycardia. It occurs due to stimulation of post synaptic α_2 receptors.

Clinical uses:

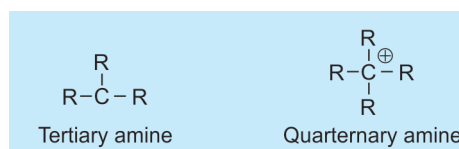
- Dexmedetomidine is primarily used for short-term sedation of intubated and ventilated patients in an ICU setting.
- In operation theatres, it is used as an adjunct to general anaesthesia or to provide sedation e.g. during awake fiberoptic tracheal intubation or regional anesthesia.
- It decreases the dose requirements for inhaled and injected anaesthetics. It produces analgesia and sedation without causing respiratory depression

2. Ans. (d) Partial heart block (Ref: KDT 7/e p108-110)

- Cholinergic drugs decrease the conduction from atrium to ventricle, thus should be avoided in partial heart block
- Cholinergic drugs like pilocarpine and physostigmine are used in angle closure glaucoma
- Neostigmine (acetylcholinesterase inhibitor, a cholinergic drug) is used for treatment of myasthenia gravis
- Neostigmine is also used for post operative paralytic ileus and post operative urinary retention.

3. Ans (c) Glycopyrrolate (Ref: KDT 7th/113,108)

The structure of tertiary and quarternary amines can be depicted as



- As seen in the diagram, quarternary amines are ionized and thus water soluble. These drugs are not able to cross the blood brain barrier.
- Atropine, hyoscine and physostigmine are tertiary amines (thus lipid soluble) and can cross the blood brain barrier whereas glycopyrrolate is quarternary amine and cannot cross blood brain barrier.

4. Ans. (b) NSAIDs are useful in neuropathic pain (Ref: KDT 7th/197-200, Katzung 12th/637-638)

- All NSAIDs may cause nephrotoxicity and hepatotoxicity.
- NSAIDs are ineffective in neuropathic pain.
- NSAIDs blunt the antihypertensive effects of diuretics and ACE inhibitors.
- Diclofenac, ibuprofen, piroxicam etc. are available as topical NSAID preparations.

5. Ans. (a) Disulfiram (Ref: KDT 7th/393-394)

The aim of treatment in alcohol dependence is to prevent withdrawal symptoms first and to avoid relapse thereafter.

- Drugs to reduce craving are:
 - N- Naltrexone
 - O- Ondansetron
 - T- Topiramate
 - A- Acamprosate
- Disulfiram is used in psychological dependent persons who are motivated to quit alcohol. It is contraindicated in physically dependent persons.

6. Ans. (a) 2 mEq/L (Ref: KDT 7th/449, Katzung 12th/517)

Important serum levels of lithium

For bipolar disorder	0.5–0.8 mEq/L
For acute mania	0.8–1.2 mEq/L
Lithium toxicity	> 2 mEq /L
Dialysis done if level	> 4 mEq/L

7. Ans. (b) Acute dystonia (Ref: Harrison 18th/3544)

Acute muscular dystonia is the earliest appearing extrapyramidal symptom caused by antipsychotic drugs like haloperidol.

8. Ans. (a) Propofol (Ref: Katzung 12th/440)

Propofol is drug of choice for day care surgery.

9. Ans. (c) Polygeline (Ref: KDT 7th/645)

Dextran-40	Dextra-70	Polygeline	Hetastarch
• Mol. wt.-40,000	• Mol. wt.-70,000	• Mol. wt.-30,000	• Mol. wt. 4.5 Lac
• Expands plasma for < 24 hours	• Expands plasma for 24 hours	• Expands plasma for 12 hours	• Expands plasma for > 24 hours
• Stable for 10 years	• Stable for 10 years	• Stable for 3 years	
• Interfere with blood grouping and cross matching (BGCM)	• Interfere with BGCM	• Do not interfere with BGCM	• Interfere with BGCM
• Interfere with coagulation and platelet function	• Most commonly used		

10. Ans. (d) Hypothyroidism (Ref: CMDT 2015/609-610)

- Long-term use of proton pump inhibitors may lead to
 - Mild to moderate decrease in vitamin B₁₂, iron and calcium absorption.
 - Increased risk of enteric infections including *C. difficile* and bacterial gastroenteritis.
 - Modest increase in risk of hip fractures.
 - Modest increase in risk of pneumonia.

11. Ans. (b) Beta lactams (Ref: Katzung 12th/907-908)

Friends, this question has been unnecessarily made controversial by giving different answers in different books for competitive exams. Please try to search for the references provided in those books. Now coming to explanation:

- The terms time dependent killing (TDK) and concentration dependent killing (CDK) are applicable only for cidal drugs. Beta lactams and vancomycin follow TDK whereas aminoglycosides and fluoroquinolones follow CDK.
- Long post-antibiotic effect is shown by most of the drugs against gram positive bacteria (including aminoglycosides, beta lactams, clindamycin and macrolides) but few drugs have long PAE against gram negative bacteria. The table given in Katzung is modified as:

Long PAE against	
Gram +ve cocci	Gram -ve bacilli
- Aminoglycosides - Beta lactams - Chloramphenicol - Clindamycin - Daptomycin - Vancomycin - Macrolides - Linezolid - Fluoroquinolones - Rifampicin - Sulfonamides - Tetracyclines - Streptogramins	- Aminoglycosides - Carbapenems - Fluoroquinolones - Chloramphenicol - Rifampicin - Tetracyclines

- Clindamycin and erythromycin are static drugs, so can be easily excluded
- Fluoroquinolones follow CDK.
- So, answer is beta lactams as these follows TDK and have long PAE against gram positive cocci.

12. **Ans. (d) Ceftobiprole** (Ref: Harrison 18th/1247-1248)

Fifth generation cephalosporins (ceftobiprole and ceftaroline) are the only beta-lactams active against MRSA.

13. **Ans. (b) Metronidazole** (Ref: KDT 7th/757, CMDT 2015/633)

- For mild cases of pseudomembranous colitis; metronidazole, vancomycin and fidaxomicin (poorly absorbed macrolide) are equally effective. However, due to cost issues, **metronidazole is drug of choice**.
- For severe cases or metronidazole unresponsive cases, oral vancomycin is drug of choice.

14. **Ans. (c) It can be used for rat bite fever** (Ref: KDT 7th/718-720)

Penicillin G

- It is acid labile thus not effective orally.
- Penicillin G has short duration of action. Probenecid inhibits tubular secretion and prolongs its duration of action.
- It has narrow antibacterial spectrum, mainly for gram positive bacteria.
- Penicillin G is drug of choice for infections caused by Treponema like syphilis (*T. pallidum*) and Rat bite fever (*Spirillum minus*).

15. **Ans. (b) Piperacillin-tazobactam** (Ref: KDT 7th/724)

Drugs active against Pseudomonas are

Penicillins	Cephalosporins	Aminoglycosides
Carbenicillin	Cefoperazone	Fluoroquinolones
Ticarcillin	Ceftazidime	Polypeptides
Mezlocillin	Cefepime	
Azlocillin	Cefpirome	
Piperacillin		

16. **Ans. (b) Zidovudine** (Ref: KDT 7th/803-805)

Anti-HIV drugs effective against HBV are

- **L:** Lamivudine
- **E:** Emtricitabine
- **T:** Tenofovir

Apart from these, other drugs for HBV are

- Interferons
- Telbivudine
- Entecavir
- Adefovir

17. **Ans. (a) Artesunate** (Ref: Harrison 18th/1699-1701)

Drug of choice for severe or complicated malaria is artesunate. For more details, see text.

18. **Ans. (b) It has dose-dependent kinetics** (Ref: Goodman Gilman 12th/1746-1747)

- Rituximab is a chimeric **monoclonal antibody against CD-20 B-cell antigen**. It acts by depleting B-cells.
- Rituximab **follows first order kinetics**. Its clearance remains constant irrespective of plasma concentration. Dose-dependent kinetics means zero-order kinetics i.e. clearance and $t_{1/2}$ change with dose (plasma concentration). Drugs following zero-order kinetics are warfarin, alcohol, high dose aspirin, tolbutamide, theophylline and phenytoin.
- **Infusion-related reactions** are seen in approximately 50% of patients receiving first infusion. The incidence decreases with subsequent infusions. Starting with low doses and pre-treatment with steroids or antihistaminics are the methods to reduce infusion-related reactions.
- Rituximab **may cause reactivation of hepatitis B**. Patients should be screened for hepatitis B before initiation of therapy. It rarely causes reactivation of JC virus leading to progressive multifocal leukoencephalopathy.

- Rituximab can be used for treatment of

- Non Hodgkin lymphoma
- Mantle cell lymphoma
- Chronic lymphocytic leukemia
- Auto-immune hemolytic anemia
- Diffuse large B cell lymphoma
- Gastric lymphoma
- Rheumatoid arthritis
- Immune thrombocytopenic purpura (ITP)
- Pemphigus vulgaris
- Sjogren syndrome
- SLE
- Thrombotic thrombocytopenic purpura (TTP)

19. Ans. (a) It is obtained from *E. coli* (Ref: KDT 7th/865)

- Paclitaxel is obtained from bark of western yew tree (not from *E. coli*).
- Vinca alkaloids (like vincristine and vinblastine) inhibit polymerization whereas paclitaxel and docetaxel enhance polymerization of β -tubulin.
- Like most anticancer drugs, paclitaxel can also result in bone marrow suppression.
- Major indications of taxanes like paclitaxel are:

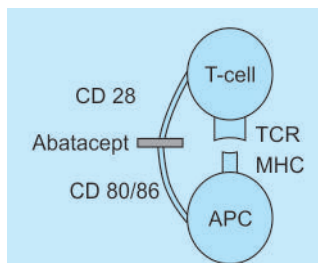
- Ovarian cancer
- Breast carcinoma
- Head and neck cancer
- Small cell carcinoma of lung
- Esophageal adenocarcinoma
- Prostate cancer

20. Ans. (d) Degarelix (Ref: CMDT 2015/1624)

- **Degarelix** is a GnRH antagonist, that has recently been approved for advanced prostate cancer.
- GnRH agonists like **leuprolide** and **goserelin** are being used in prostate cancer since many years.
- **Docetaxel** is first cytotoxic agent that **improve survival** in patients with hormone-refractory prostate cancer.
- **Sipulecel-T** is an immunotherapy recently approved for prostate cancer.
- Other drugs for prostate cancer are:
 - Cabazitaxel
 - Abiraterone
 - Enzalutamide
 - Radium-223 dichloride

21. Ans. (b) Rheumatoid arthritis (Ref: Harrison 18th/2748)

Abatacept is a co-stimulation inhibitor. Two signals are required for activation of T-cells:



1. **Main signal:** Interaction of T-cell receptor (TCR) with MHC of antigen presenting cells (APC)
2. **Co-stimulatory signal:** Interaction of CD 28 of T-cells with CD-80/86 of APC.

When both signals are present, T-cell gets activated. Abatacept acts by blocking the co-stimulatory signal and prevents activation of T-cells. It is approved for treatment of Rheumatoid arthritis.

AIIMS MAY 2014

1. Which of the following is not converted into an active metabolite?
 - a. Lisinopril
 - b. Fluoxetine
 - c. Cyclophosphamide
 - d. Diazepam
2. Alpha 2 agonists cause all of the following EXCEPT:
 - a. Analgesia
 - b. Hyperalgesia
 - c. Sedation
 - d. Anxiolysis
3. Which of the following is a mixed alpha and beta agonist?
 - a. Dobutamine
 - b. Fenoldopam
 - c. Epinephrine
 - d. Phenylephrine
4. Which of the following drugs acts on trabecular meshwork and affects the aqueous outflow?
 - a. Timolol
 - b. Pilocarpine
 - c. Brimonidine
 - d. Brinzolamide
5. Which of the following antihypertensives is not given in pregnancy?
 - a. Enalapril
 - b. α -methyldopa
 - c. Labetalol
 - d. Nifedipine
6. All of the following can be administered in acute hypertension during labour EXCEPT:
 - a. IV Labetalol
 - b. IV Nitroprusside
 - c. IV Hydralazine
 - d. IV Esmolol
7. The site of action of the furosemide is:
 - a. Thick ascending limb of loop of Henle
 - b. Descending limb of loop of Henle
 - c. Proximal convoluted tubule
 - d. Distal convoluted tubule
8. Which of the following pairs of drug and its indications is matched incorrectly?
 - a. Carbamazepine – Syndrome of inappropriate ADH secretion
 - b. Octreotide – Treatment of diarrhea associated with vasoactive intestinal peptide tumors
 - c. Desmopressin – Treatment of diabetes insipidus
 - d. hCG – Treatment of infertility in men and women
9. Peripheral vasospasm is observed with which of the following anti-Parkinsonian drugs?
 - a. Ropinirole
 - b. Levodopa
 - c. Bromocriptine
 - d. Entacapone
10. True statement regarding methadone are all EXCEPT:
 - a. It is a long acting μ -receptor agonist
 - b. It is rapidly absorbed from the gastrointestinal tract and is detected in plasma 30 minutes after oral administration
 - c. The primary use of methadone is relief of chronic pain
 - d. The onset of analgesia is 30–60 minutes after parenteral administration and 1–2 hours after oral administration
11. The plane of surgical anesthesia during ether anesthesia is defined as:
 - a. Loss of consciousness
 - b. Loss of consciousness to the onset of spontaneous respiration
 - c. From onset of regular respiration to cessation of spontaneous breathing
 - d. Absence of reflexes
12. Which of the following intravenous anesthetic agents is contraindicated in epileptic patients posted for general anesthesia?
 - a. Ketamine
 - b. Thiopentone
 - c. Propofol
 - d. Midazolam
13. Laxative abuse is associated with:
 - a. Hypokalemia
 - b. Hypomagnesemia
 - c. Hypoglycemia
 - d. Colonic spasticity
14. Which of the following drugs is used in the treatment of acute bacterial meningitis?
 - a. Erythromycin
 - b. Sulfamethoxazole
 - c. Ceftriaxone
 - d. Streptomycin
15. Time dependent killing and prolonged post-antibiotic effect is seen with:
 - a. Fluoroquinolones
 - b. Beta lactam antibiotics
 - c. Clindamycin
 - d. Erythromycin

16. **Non-nucleoside reverse transcriptase inhibitors (NNRTIs) include all of the following except:**
 - a. Nevirapine
 - b. Delavirdine
 - c. Etravirine
 - d. Lamivudine
17. **Which of the following antitubercular drugs is associated with hypothyroidism?**
 - a. Rifampicin
 - b. Pyrazinamide
 - c. Ethionamide
 - d. Streptomycin
18. **The most common side effect of cancer chemotherapy is nausea with or without vomiting. The anticancer drugs vary in their ability to cause nausea and vomiting. Which of the following anti-cancer drugs is least likely to cause nausea and vomiting?**
 - a. Chlorambucil
 - b. Cisplatin
 - c. Doxorubicin
 - d. Daunorubicin
19. **Which of the following medications is essential for ameliorating the toxicity of pemetrexed?**
 - a. Folinic acid and vitamin B₆
 - b. Folic acid and vitamin B₁₂
 - c. Vitamin B₆ and Vitamin B₁₂
 - d. Folic acid and dexamethasone
20. **Which of the following drugs is useful for the treatment of advanced prostate cancer?**
 - a. Ganirelix
 - b. Cetrorelix
 - c. Abarelix
 - d. Goserelin

EXPLANATIONS

1. **Ans. a. Lisinopril** (Ref: KDT 7th/22-23)

"All ACE inhibitors are prodrugs except captopril and lisinopril."

Drug	Active Metabolite
Fluoxetine	Nor-fluoxetine
Cyclophosphamide	Aldophosphamide
Diazepam	Oxazepam

2. **Ans. b. Hyperalgesia** (Ref: Goodman and Gilman 12th/296; Katzung 12th/176)

- Alpha 2 agonists cause analgesia, not the hyperalgesia.
- Clonidine is used for treatment of hypertension. It decreases blood pressure by acting on central alpha 2 adrenergic receptors.
- Dexmedetomidine is another alpha 2 receptor agonist that is used to produce sedation and anxiolytic state by action on alpha 2 receptors in the brain. It can also produce analgesia by acting on alpha 2 receptors in spinal cord.

3. **Ans. c. Epinephrine** (Ref: Goodman and Gilman 12th/277)

- Epinephrine is having both alpha (1 and 2) and beta (1 and 2) agonist property.
- Dobutamine stimulates only beta 1 whereas phenylephrine acts only on alpha 1 receptors.
- Fenoldopam does not act on alpha or beta receptors, rather it is D1 agonist.

4. **Ans. b. Pilocarpine** (Ref: Katzung 12/e p161; KDT 6/e p145)

Miotics like pilocarpine act by increasing the trabecular outflow.

Drugs for Glaucoma	Mechanism of Action
Brimonidine	Reducing aqueous production and Increasing uveoscleral flow
Latanoprost	Increase the uveoscleral outflow
Pilocarpine	Increases trabecular outflow
Betaxolol	Reduces aqueous secretion by ciliary body

5. **Ans. a. Enalapril** (Ref: Goodman and Gilman 12th/736)

ACE inhibitors like enalapril are contraindicated in pregnancy. These are teratogenic drugs. Other drugs given in the options are safe in pregnancy.

6. **Ans. b. IV Nitroprusside** (Ref: KDT 7th/572)

Sodium nitroprusside is contra-indicated in eclampsia.

7. **Ans. a. Thick ascending limb of loop of Henle** (Ref: Goodman and Gilman 12th/678)

Furosemide is a loop diuretic and this group of drugs act on thick ascending limb of loop of Henle.

8. **Ans. a. Carbamazepine- Syndrome of inappropriate ADH secretion** (Ref: Goodman and Gilman 12th/712, 1338)

- Carbamazepine releases ADH from hypothalamus and is used for treatment of diabetes insipidus as an alternative to desmopressin. It is not indicated in SIADH.
- Octreotide is a long acting somatostatin used for secretory diarrhea due to carcinoid syndrome and VIPoma.
- Desmopressin is drug of choice for diabetes insipidus.
- Human chorionic gonadotropin can be used for induction of ovulation in female infertility and treatment of oligospermia and thus male infertility.

9. **Ans. c. Bromocriptine** (Ref: KDT 7th/176; Goodman and Gilman 12th/1114)

Ergot derivatives like bromocriptine can lead to worsening of vasospasm especially in patients of peripheral vascular disease due to their strong vasoconstrictor activity.

10. Ans. d. The onset of analgesia is 30–60 minutes after parenteral administration and 1–2 hours after oral administration (Ref: Goodman and Gilman 12th/506-507)

Methadone

- The onset of analgesia occurs 10–20 minutes after parenteral administration of methadone and 30–60 minutes after oral administration.
- Methadone is a long-acting μ opioid receptor agonist with pharmacological properties qualitatively similar to those of morphine.
- It is well absorbed from the GI tract and can be detected in plasma within 30 minutes of oral ingestion.
- Primary uses are relief of chronic pain and in maintenance therapy of opioid addiction.

11. Ans. c. From onset of regular respiration to cessation of spontaneous breathing (Ref: KDT 7th/373-374)

The plane of surgical anesthesia during ether anesthesia is defined as from onset of regular respiration to cessation of spontaneous breathing.

Guedel's Stages of Anesthesia

- Guedel described four stages with ether anesthesia, dividing the stage III into four planes.

I: Stage of analgesia

- It starts from beginning of anesthetic inhalation and lasts up to the loss of consciousness.
- Pain is progressively abolished.
- Patient remains conscious, can hear and see, and feels a dream-like state; amnesia develops by the end of this stage.
- Reflexes and respiration remain normal.
- Though some minor operations can be carried out during this stage, it is rather difficult to maintain. The use is thus limited to short procedures.

II: Stage of delirium

- It lasts from loss of consciousness to the beginning of regular respiration.
- Apparent excitement is seen – patient may shout, struggle and hold his breath.
- Muscle tone increases.
- Jaws are tightly closed
- Breathing is jerky.
- Vomiting, involuntary micturition or defecation may occur.
- Heart rate and BP may rise and pupils dilate due to sympathetic stimulation.
- No stimulus should be applied or operative procedure carried out during this stage.
- This stage is inconspicuous in modern anesthesia.

III: Stage of surgical anesthesia

- It extends from onset of regular respiration to cessation of spontaneous breathing.
- This has been divided into four planes, which may be distinguished as:
 - Plane I: Roving eyeballs
 - Plane II: Loss of corneal and laryngeal reflexes
 - Plane III: Pupil starts dilating and light reflex is lost
 - Plane IV: Intercostal paralysis, shallow abdominal respiration, dilated pupil

IV: Stage of medullary paralysis

- It lasts from cessation of spontaneous breathing to failure of circulation and death.
- Pupil is widely dilated, muscles are totally flabby, pulse is thready or imperceptible and BP is very low.

12. Ans. a. Ketamine (Ref: Morgan 4/e p197-199)

Ketamine should be avoided in patients with history of seizures as it further increases ICP and also causes delirium and hallucinations.

Contraindications of Ketamine:

- Head injury, intracranial space occupying lesion, eye injury (increases ICT, IOT).
- Ischemic heart disease, vascular aneurysm and hypertension (increases myocardial oxygen demand and blood pressure).
- Psychiatric diseases and drug addicts (more incidence of hallucination and emergence reaction).

13. **Ans. a. Hypokalemia** (Ref: Harrison 18th/351)
Laxative abuse is associated with hypokalemia.

14. **Ans. c. Ceftriaxone** (Ref: Harrison 18th/3414)

Erythromycin and sulfamethoxazole are bacteriostatic drugs and cannot be relied upon in serious infections like bacterial meningitis. Streptomycin is an aminoglycoside effective mainly against gram negative bacteria but is not preferred for meningitis due to following reasons:

- It cannot kill gram positive organisms responsible for bacterial meningitis like *Streptococcus*, *Staphylococcus* and *Listeria*, etc.
- To prevent the emergence of drug resistance; as it is first line antitubercular drug.

Ceftriaxone is a third generation cephalosporin with broad spectrum antibacterial activity and good CSF penetration. It is commonly used for empirical treatment of acute bacterial meningitis.

15. **Ans. b. Beta lactam antibiotics** (Ref: Katzung 12th/907-908)

Friends, this question has been unnecessarily made controversial by giving different answers in different books for competitive exams. Please try to search for the references provided in those books. Now coming to explanation:

- The terms time dependent killing (TDK) and concentration dependent killing (CDK) are applicable only for cidal drugs. Beta lactams and vancomycin follow TDK whereas aminoglycosides and fluoroquinolones follow CDK.
- Long post-antibiotic effect is shown by most of the drugs against gram positive bacteria (including aminoglycosides, beta lactams, clindamycin and macrolides) but few drugs have long PAE against gram negative bacteria. The table given in katzung is modified as:

Long PAE against	
Gram +ve cocci	Gram -ve bacilli
• Aminoglycosides • Beta lactams • Chloramphenicol • Clindamycin • Daptomycin • Vancomycin • Macrolides • Linezolid • Fluoroquinolones • Rifampicin • Sulfonamides • Tetracyclines • Streptogramins	• Aminoglycosides • Carbapenems • Fluoroquinolones • Chloramphenicol • Rifampicin • Tetracyclines

Now coming to options:

- Clindamycin and erythromycin are static drugs, so can be easily excluded
- Fluoroquinolones follow CDK.
- So, answer is beta lactams as these follows TDK and have long PAE against gram positive cocci.

16. **Ans. d. Lamivudine** (Ref: Katzung 12th/870)

Lamivudine is nucleoside reverse transcriptase inhibitor (NRTI), not the non-nucleoside reverse transcriptase inhibitor (NNRTI).

NNRTIs include:

- Efavirenz
- Nevirapine
- Delavirdine
- Etravirine
- Rilpivirine

17. **Ans. c. Ethionamide** (Ref: KDT 7th/771)

Ethionamide and PAS are two antitubercular drugs associated with hypothyroidism and goiter.

18. Ans. a. Chlorambucil (Ref: KDT 7th/859; Harrison 18th/708)

Cisplatin and cyclophosphamide have very high emetogenic potential whereas chlorambucil and busulfan have the least.

19. Ans. b. Folic acid and vitamin B₁₂ (Ref: Goodman and Gilman 12th/1694; Harrison 18th/703)

Folic acid and vitamin B₁₂ are essential for ameliorating the toxicity of pemetrexed.

Pemetrexed Toxicity

- Pemetrexed toxicity mirrors that of methotrexate, with the additional feature of a prominent erythematous and pruritic rash in 40% of patients.
- Severe myelosuppression with pemetrexed, seen especially in patients with pre-existing homocystinemia and possibly reflecting folate deficiency, is largely eliminated by concurrent administration of low dosages of folic acid beginning 1–2 weeks prior to pemetrexed and continuing while the drug is administered.
- Patients should receive intramuscular vitamin B₁₂ with the first dose of pemetrexed to correct possible B₁₂ deficiency.
- These small doses of folate and B₁₂ do not compromise the therapeutic effect.

20. Ans. d. Goserelin (Ref: Katzung 12th/972; Goodman and Gilman 12th/1763-1764)

Gonadotropin releasing hormone agonists like leuprolide and goserelin are useful for the treatment of advanced prostate cancer. Among GnRH antagonists, only degarelix is approved for the treatment of advanced prostate cancer.

NOTES

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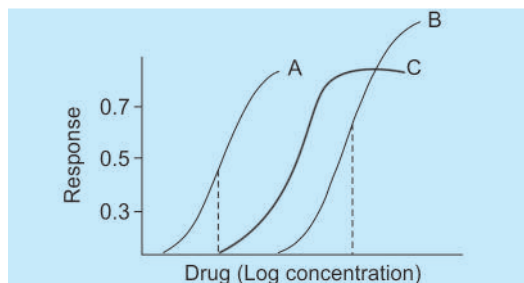
NOTES

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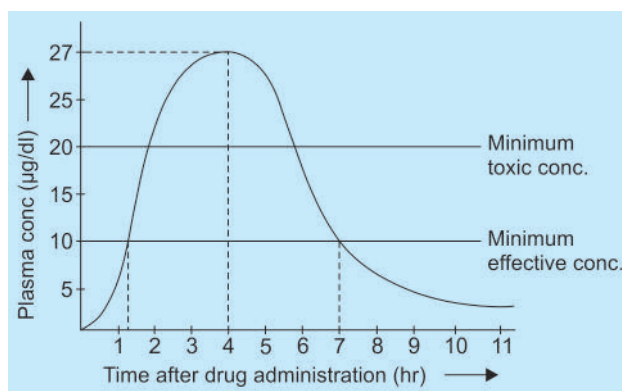
IMAGE BASED QUESTIONS

Image Based Questions

1. The results of a graph shown below were obtained in comparison of drugs that increased the force of cardiac contraction. Which of the following statements is most correct? *(AIIMS Nov 2001)*



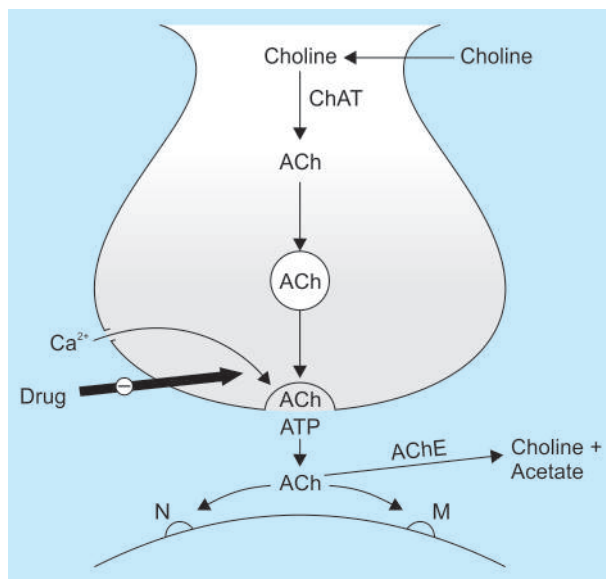
- (a) Drug A is most effective
 - (b) Drug C is most potent
 - (c) Drug B is less potent and more efficacious than drug C
 - (d) Drug A is more potent than drug B but less efficacious than drug C
2. A new drug X is given orally to a healthy volunteer in a dose of 100 mg. Plasma concentration of the drug is measured at hourly interval and a graph is plotted between plasma concentration and time as shown below.



Which of the following statements about drug X is TRUE?

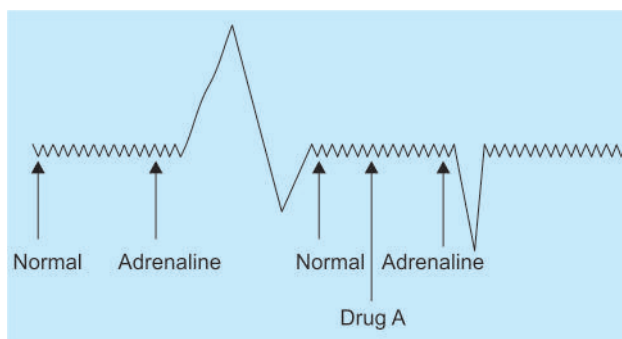
- (a) Its C_{max} is 20 $\mu\text{g/dl}$.
- (b) AUC from the above graph reflects rate of absorption
- (c) T_{max} for drug X is 7 hours.
- (d) Instead of 100 mg drug X should be given in divided doses.

3. A 30 year old theatre actress developed few wrinkles on the face. The treating physician advised her to have local injections of a drug. This drug is also indicated in cervical dystonia and other spastic disorders like cerebral palsy. Very recently, it has also been approved for prophylaxis of migraine. The physician warned of the drug to cause dry mouth and blurring of vision. The actress searched the compound on internet and found the site of action of the drug as shown in the diagram below.



Which of the following drug is being talked about?

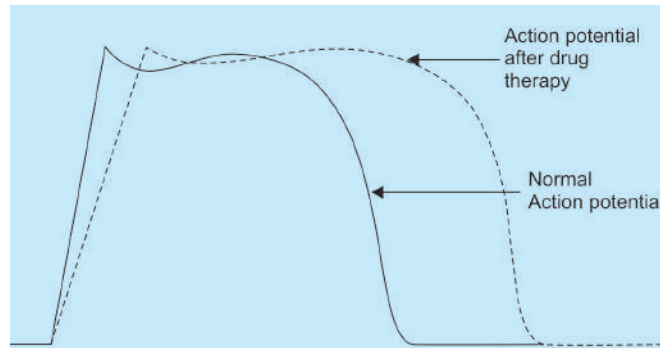
- (a) Hemicholinium
 - (b) Vesamicol
 - (c) Botulinum toxin
 - (d) Physostigmine
4. A 70 year old male developed difficulty in ability to form urinary stream and urgency. On per-rectal examination, prostate was found to be enlarged. Serum prostate specific antigen was within normal limits. The person is also a known hypertensive for which he is not taking any drug. The surgeon prescribed him a drug A which can quickly relieve his urinary problems as well as control his blood pressure. Effect of this drug on blood pressure of a dog in experimental set up is shown below. Drug A is likely to be.



- (a) Finasteride
- (b) Tamsulosin
- (c) Doxazosin
- (d) Propanolol

5. A new antiarrhythmic drug is found to be effective against both atrial and ventricular arrhythmias. Its effect on action potential is shown as below. The effect of this new drug is most similar to

- (a) Lignocaine
- (b) Propranolol
- (c) Encainide
- (d) Quinidine

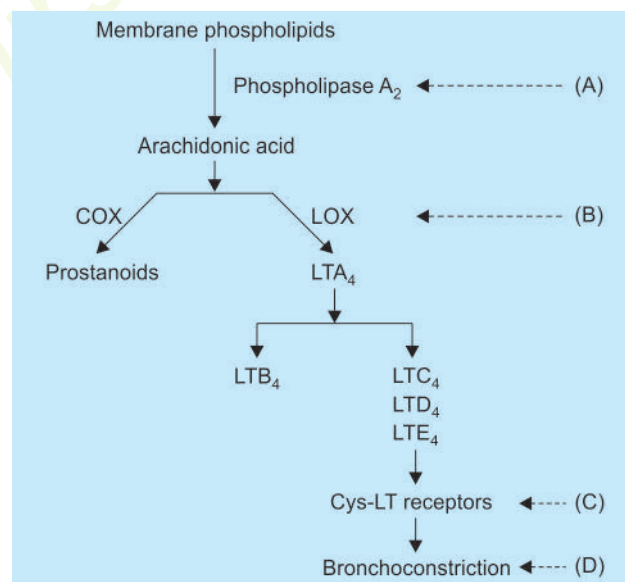


6. A 52-year-old male, Vivek was treated with enalapril for hypertension. It was able to control his blood pressure. Which of the following is the most likely combination of changes in response to this patient's treatment?

	Renin	Angio-tensin I	Angio-tensin II	Aldos-terone	Bradykinin
(a)	↑	↑	↓	↓	↑
(b)	↑	↑	↓	↓	↓
(c)	↑	↓	↓	↓	↓
(d)		↓	↓	↓	No change

7. A 20-year-old male, Chintu is being treated with zafirlukast for bronchial asthma. The most likely site of action of this drug from the diagram can be deciphered as:

- (a) A
- (b) B
- (c) C
- (d) D

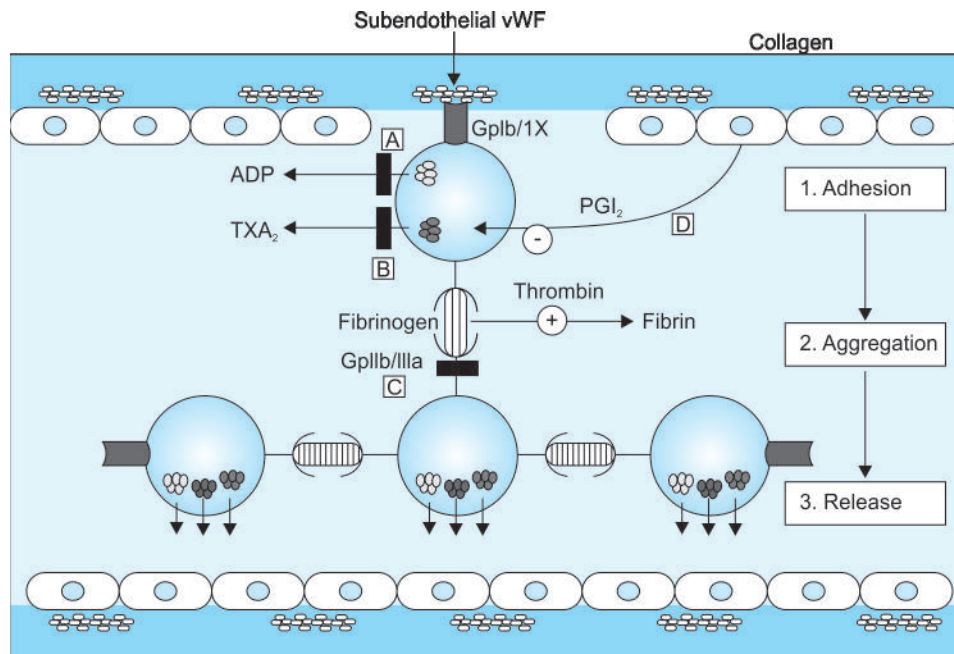


8. A 50-year-old male, Rajesh presented to OPD with fever and sore throat with mouth ulcers. He has a history of myocardial infarction and is taking several drugs. One month back he had an episode of transient ischemic attack. His complete blood count shows:

Hb	14.2 g/dL
WBC	900/mm ³
Platelet	220000/mm ³

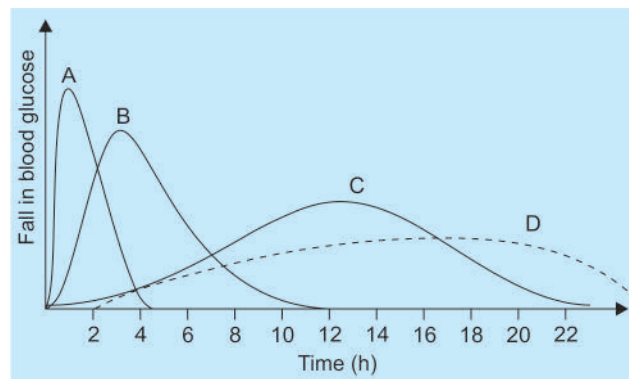
If an antiplatelet drug is responsible for the above symptoms of the patients, Which of the following drugs is most likely mechanism of the drug?

- (a) A
(b) B
(c) C
(d) D



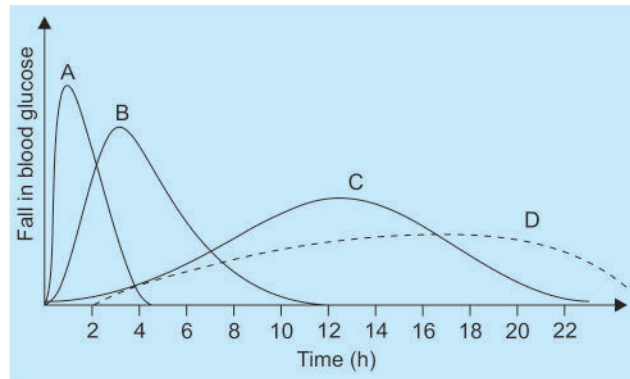
9. A 15-year-old female, Rashmi presents to the emergency in comatose state. She is a known case of type 1 diabetes mellitus. Immediate blood sugar is measured by glucometer and found to be 658 mg/dl. Urine is found to be positive for glucose as well as ketone bodies. Which of the following insulin types depicted in the graph below is most appropriate for the treatment of this patient's condition?

- (a) A
(b) B
(c) C
(d) D



10. Amarnath, a 58 year old businessman is a known case of type 2 diabetes and was well controlled on metformin. But since last 5 years the different combinations of oral antidiabetic drugs were tried and still the blood sugar was not controlled. So, the physician thought of giving him insulin. Which of the following insulin can be used to maintain the basal levels of insulin without producing significant risk of hypoglycemia in this patient.

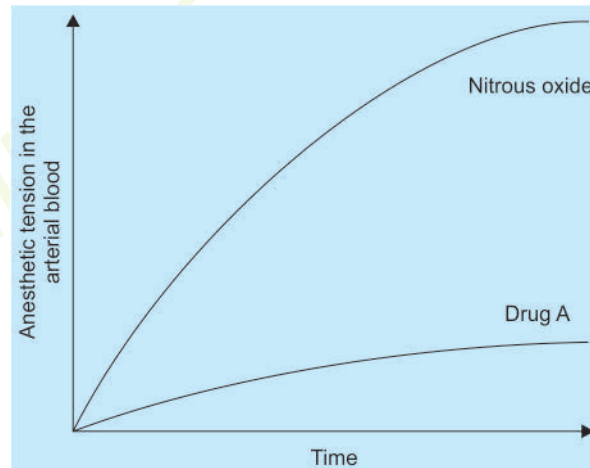
(a) A
(b) B
(c) C
(d) D



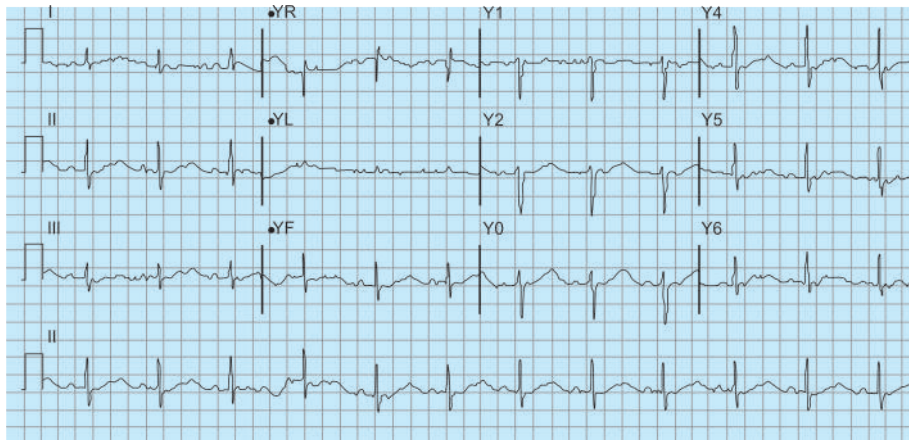
11. A new inhaled anesthetic has been developed and is tested in a series of experiments. Anesthetic tension in the arterial blood is shown on the graph below as a function of time after beginning inhalation (Drug A). A similar curve for nitrous oxide is also shown.

Which of the following best describes the properties of the new anesthetic compared to nitrous oxide?

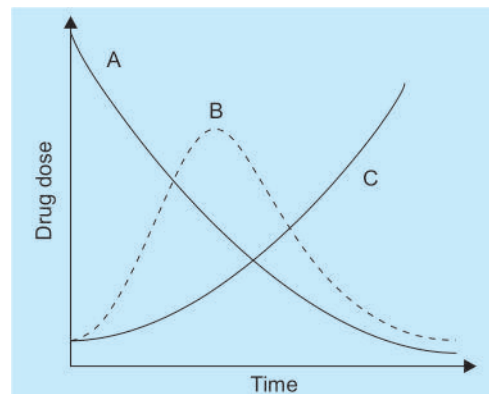
(a) High blood: gas partition coefficient
(b) Low solubility in the blood
(c) Rapid onset of action
(d) Low potency



12. A 53 year old male Arjun presented to emergency with blunt injury to abdomen and crushing of his left leg under the tyres of a bus in a road traffic accident. His blood pressure was 80/40 mmHg. Emergency laparotomy was planned to repair the ruptured viscera and to know the cause of internal bleeding. Succinylcholine was used for intubation and vecuronium for maintenance of muscle relaxation. Anaesthesia was induced by thiopentone and maintained by halothane. However, during intraoperative period, the patient developed arrhythmias as shown in ECG below. Which of the following is the likely cause of this ECG finding?
- Presence of atypical pseudocholinesterase in this patient
 - Succinylcholine induced hyperkalemia
 - Vecuronium overdose
 - Accident intra-arterial injection of thiopentone



13. You are studying pharmacokinetic properties of thiopentone. A dose-time relationship in various tissues after a single bolus of thiopentone is shown in the graph below. Curves A, B and C in the graph represent

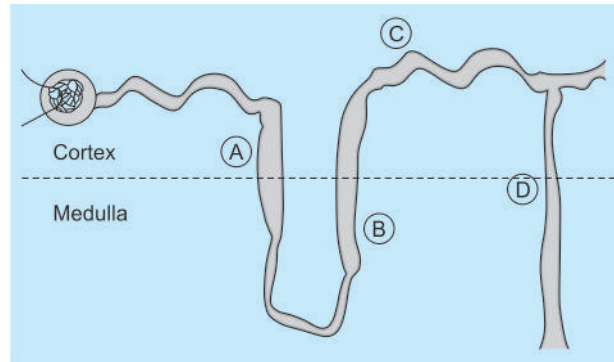


Curve A	Curve B	Curve C
(a) Brain	Blood	Adipose tissue
(b) Blood	Brain	Adipose tissue
(c) Brain	Adipose tissue	Blood
(d) Adipose tissue	Brain	Blood

14. A 72-year-old male, Hemraj was admitted to the hospital with severe dyspnoea and orthopnea. On investigations and clinical examination, he was found to be suffering from congestive heart failure. He was given some drug intravenously and the patient experienced brisk diuresis and significant relief of symptoms. This drug acts predominantly on which of the following segments of nephron?

(a) A
(c) C

(b) B
(d) D



EXPLANATIONS

1. **Ans. (c) Drug B is less potent and more efficacious than drug C** (Ref: KDT 7/e p54-55)
 Potency is the dose at which the response is half of the maximum. More the curve is towards left, greater is the potency. In this question, drug A is most potent followed by drug C and the drug B is least potent.
 Efficacy is determined by the height of dose response curve. In this question, drug A and B have high efficacy whereas drug C is the least efficacious.
2. **Ans. (d) Instead of 100 mg, drug X should be given in divided doses.** (Ref: Goodman Gilman 12/e p35)
 C_{max} is the maximum plasma concentration obtained. In this question, C_{max} is 27 $\mu\text{g/dl}$.
 T_{max} is the time to reach C_{max} . It tells about rate of absorption. From the given graph, T_{max} is 4 hours.
 AUC reflects extent of absorption and not the rate of absorption.
 This drug, when given as 100 mg, produce a C_{max} which is higher than the minimum toxic concentration (20 $\mu\text{g/dl}$). Thus to avoid the toxic effects, C_{max} must be lower and to produce a lower C_{max} , the dose has to be reduced.
3. **Ans. (c) Botulinum toxin** (Ref: KK Sharma 2/e p211)
 As shown in the diagram, the drug is inhibiting the exocytosis of ACh. Botulinum toxin act by this mechanism. Other features pointing towards botulinum toxin are :
 - Anticholinergic adverse effects (dry mouth, blurring of vision)
 - Use in wrinkles, spastic disorders, prophylaxis of migraine.
4. **Ans. (c) Doxazosin** (Ref: KK Sharma 2/e p182-183)
 The diagram is showing vasomotor reversal of Dale. Thus drug A should be α -blocker. Tamsulosin is selective α_{1A} blocker and has minimal effect on blood pressure whereas doxazosin blocks both α_{1A} and $\alpha_{1B/D}$ receptors.
5. **Ans. (d) Quinidine** (Ref: KK Sharma 2/e p301)
 This drug is decreasing the slope of phase 0 (Na^+ channel blocking property) as well as increasing the action potential duration (K^+ channel blocking property). Thus, it exhibits the properties of class Ia anti-arrhythmic agents like quinidine.
6. **Ans. (a)** (Ref: KK Sharma 2nd/265)
 ACE inhibitors decrease angiotensin II by inhibiting the conversion of Ang I to Ang II and thus aldosterone also decrease. Due to compensatory increase in plasma renin activity, renin and angiotensin I levels increase. By inhibiting the metabolism of bradykinin, the level of these vasoactive peptides also increase.
7. **Ans. (c)** (Ref: Katzung 11/e p349)
 The drug zafirlukast is a cys-LT receptor antagonist.
8. **Ans. (a) A** (Ref: Katzung 11/e p598)
 The patient is having neutropenia and the drug most likely being discussed about is ticlopidine. Clopidogrel and ticlopidine act as ADP antagonists. Ticlopidine is rarely used due to the occurrence of serious side effects like neutropenia that typically presents with fever and mouth ulcers. Though this is rare, it is a serious complication and complete blood count should be monitored biweekly for the first three months.
9. **Ans. (b) B** (Ref: KK Sharma 2/e p633)
 This is a case of diabetic coma due to diabetic ketoacidosis (DKA). The insulin of choice for DKA is regular insulin by intravenous route. Curve A shows rapidly acting insulins like aspart, glulisine and lispro (onset in 15-20 min.). However, these are given by subcutaneous route and not the first choice in diabetic ketoacidosis. Curve B represents regular insulin that can be given i.v. and is insulin of choice for DKA. Curve C represents ultralente and curve D represents insulin glargine.
10. **Ans. (d) D** (Ref: KK Sharma 2/e p635)
 Curve D represents the ultra-long acting insulin also known as peakless insulin as glargine and detemir.
11. **Ans. (a) High blood: gas partition coefficient** (Ref: Katzung 11/e p427)
 - The depth of anesthesia depends on the partial pressure of anesthetic in CNS. The transfer of anesthetic into the brain starts only after the blood is fully saturated (or, in other words partial pressure of the anesthetic in blood equals the partial pressure in the inspired air). The speed of transfer of anesthetic to the brain determines its onset of action

(rapid vs slow induction of anesthesia) and is dependent on the solubility of anesthetic in the blood. Solubility of an anesthetic is directly related to its blood/gas partition coefficient: highly soluble anesthetics have high blood/gas partition coefficient.

- If the agent is poorly soluble the amount of gas needed to saturate the blood is small and saturation occurs fairly quickly. Nitrous oxide is an example of poorly soluble gas with a blood/gas partition coefficient of 47. On the graph above the curve of partial pressure of NO in blood rises rapidly. In the highest point on the curve the partial pressure on NO in blood equals that in the inspired air, and the transfer to brain occurs.
- The second curve (drug A) portrays the process of blood saturation for a highly soluble gas. The higher the solubility the more gas can be taken up by blood before it is saturated. Note that the curve of the partial pressure of drug A in blood rises slower than that for NO. When the blood is fully saturated with NO the partial pressure of drug A in blood is approximately 25% of that in inspired air. For drug A, it takes a longer time to fully saturate the blood and to start transfer in tissues. Drug A, therefore is characterized with high blood/gas partition coefficient and slower onset of action.

Effect	Poorly soluble gas NO	Highly soluble gas (Halothane)
Amount needed to saturate the blood	small	Large
Rise in tension of gas in blood	rapid	slow
Equilibrium with the brain	rapid	slow
Onset of action	rapid	slow

12. Ans. (b) Succinylcholine induced hyperkalemia (Ref: *Katzung 11/e p460*)

Succinylcholine has high risk of causing hyperkalemia if used in patients with injury to muscles and nerves. The ECG shows changes characteristic of hyperkalemia and the patient also has crush injury, so this seems to be the most likely hyperkalemia caused by succinylcholine.

13. Ans. (b) Blood, Brain, Adipose tissue (Ref: *Katzung 11/e p434*)

Thiopentone is a short-acting barbiturate used for induction of anesthesia. After equilibration with the brain it rapidly redistributes into skeletal muscles and adipose tissue, which results in rapid recovery from.

14. Ans. (b) B (Ref: *KK Sharma 2/e p227*)

The drug administered to this patient is most likely a loop diuretic that act on ascending limb of the loop of Henle.

