GENERAL PHARMACOLOGY

Winners of "**Nobel"** prize for their contribution to pharmacology

Year	Name	Contribution
1923	**Frederick Banting**	**Discovery of insulin**
	John McLeod	
1939	Gerhard Domagk	Discovery of antibacterial effects of prontosil
1945	Sir Alexander Fleming	Discovery of penicillin & its purification
	Ernst Boris Chain	
	Sir Howard Walter Florey	
1952	Selman Abraham Waksman	Discovery of streptomycin
1982	Sir John R.Vane	Discovery of prostaglandins
1999	Alfred G.Gilman	Discovery of G proteins & their role in signal transduction in cells
	Martin Rodbell	
1999	Arvid Carlson	Discovery that dopamine is neurotransmitter in the brain whose depletion leads to symptoms of Parkinson's disease

Drug nomenclature:

i. Chemical name
ii. Non-proprietary name
iii. Proprietary (Brand) name

Source of drugs:

Natural – plant /animal derivatives

Synthetic/semisynthetic

Plant	Part	Drug obtained
Pilocarpus microphyllus	Leaflets	Pilocarpine
Atropa belladonna Datura stramonium		Atropine

Physostigma venenosum	dried, ripe seed	Physostigmine
Ephedra vulgaris		Ephedrine
Digitalis lanata		Digoxin
Strychnos toxifera Chondrodendron tomentosum		Curare group of drugs
Cannabis indica (Marijuana)	Various parts are used ***Bhang*** - the dried leaves ***Ganja*** - the dried female inflorescence ***Charas***- is the dried resinous extract from the flowering tops & leaves	Δ^9Tetrahydrocannabinol (THC)
Papaver somniferum, P album	Poppy seed pod/ Capsule	Natural opiates such as morphine, codeine, thebaine
Cinchona bark		Quinine
Vinca rosea	periwinkle plant	Vinca alkaloids
Podophyllum peltatum	the mayapple root	Etoposide
Camptotheca acuminata		Topotecan, Irinotecan

Expansions need to be known:

CPCSEA: Committee for the Purpose of Control and Supervision of Experiments on Animals

PETA: People for the ethical treatment of animals

CDSCO: Central Drugs Standard Control Organization

PSUR: Periodic safety updates report

CADD: Computer aided drug design

HTS: High throughput screening

Terminologies:

Pharmacogenetics: The study of interindividual variation in DNA sequences related to pharmacokinetics & pharmacodynamics is known as Pharmacogenetics **or** it is study of the genetic basis for variation in drug response

Pharmacogenomics: It refers to the entire spectrum of genes that interact to determine drug efficacy & safety

Pharmacoepidemiology: It is the study of the use and effects of drugs in large number of people

Pharmacoeconomics: the science that evaluates the costs & consequences of drug therapy & or other interventions

Chronopharmacology: It is the study of how the effects of drugs vary with biological timing & endogenous periodicities

Orphan drugs[Q]: These are drugs or biological products for diagnosis/treatment/intervention of a rare disease or condition or a more common disease (endemic only in resource poor countries) for which there is no reasonable expectation that the cost of developing and marketing willbe recovered from the sales of a drug
Examples: Fomepizole, liposomal amphotericin B, somatropin, digoxin immune Fab (digoxin antibody), liothyronine (T_3)…

Spurious drugs: Also known as counterfeit medicines. They may comprise low quality manufacture of correct ingredients; wrong ingredients; adulteration; insufficient quantity of ingredients; false labeling; or no active ingredient at all.

E.g: Glucocorticoids added to herbal medicines, & turmeric dispensed as tetracycline

Essential medicines: Essential medicines are those drugs (medications) that satisfy the health care needs of the majority of the population. They should, therefore be available at all times in adequate amounts & in appropriate dosage forms, at a price the individual & the community can afford.

Me-too drug: is a term used to describe a pharmaceutical that is usually structurally similar to one or more drugs that already are on the market.

E.g: esomeprazole

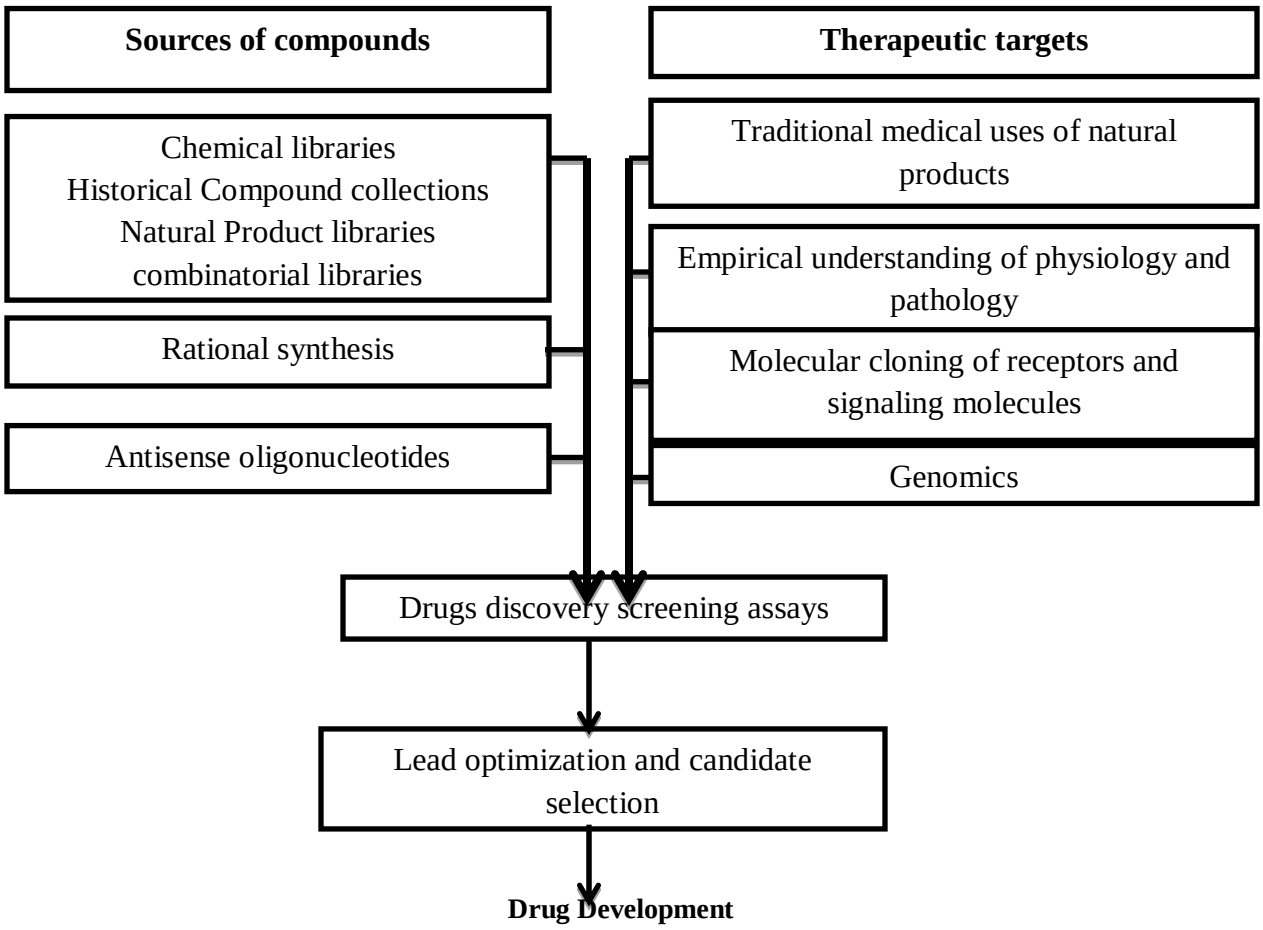
P-drug: These are the drugs you (Physician or personal) have chosen to prescribe regularly, & with which you have become familiar. They are your priority choice for given indications

P-treatment: Not every personal treatment includes a P-drug, **E.g:** Life style modifications in obesity

Biopharmaceuticalsis an umbrella term applied to the use of nucleic acids or 'engineered' proteins &antibodies in medicine.

Drug discovery & new drug development:

Drug discovery sources in context



A "**Hit"** is a molecule with confirmed structure, confirmed activity in primary throughput screening & a good profile in secondary assay.

A "**lead"** is a hit series with proven structure activity relationship both in vitro & in vivo

Lead optimization: aim is to increase the potency of the compound on its target and to optimize it with respect to other properties, such as selectivity and metabolic stability

The objective of the lead optimization phase is to identify one or more *drug candidates* suitable for further development.

TECHNIQUES OF DISCOVERY

Molecular modeling aided by three-dimensional computer graphics (including virtual reality) allows the design of structures based on new and known molecules to enhance their desired and to eliminate their undesired, properties to create highly selective targeted compounds.

CADD (Computer aided drug design)[Q]: CADD is a widely used term that represents computational tools & resources for the storage, management, analysis & modeling of compounds.

CADD now plays a critical role in the search for new molecular entities. Current focus includes,

i. Improved design & management of data sources
ii. Creation of computer programs to generate huge libraries of pharmacologically interesting compounds
iii. Development of new algorithms to assess the potency & selectivity of lead candidates
iv. Design of predictive tools to identify potential ADME/Tox liabilities

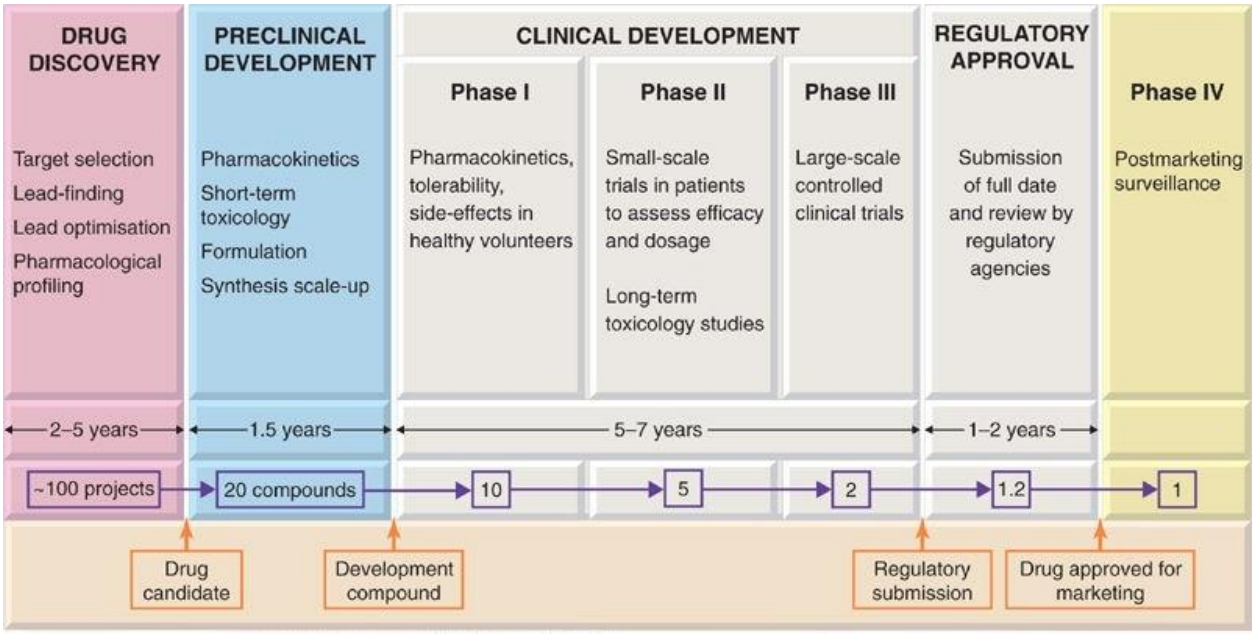
Commonly used CADD Technologies include,

a) Ligand based drug design (Pharmacophore based approach)
b) Structure based drug design (Molecular docking based approach)
c) Quantitative structure activity relationship (QSAR)
d) Quantitative structure property relationship

Combinatorial chemistry involves the random mixing and matching of large numbers of chemical building blocks (amino acids, nucleotides, simple chemicals) to produce 'libraries' of all possible combinations

Genetic medicines: Synthetic oligonucleotides are being developed to target sites on DNA sequences or genes or messenger RNA (**the antisense approach**), so that the production of disease-related proteins is blocked.E.g: **Fomivirsen** is an antisense oligonucleotide which has been approved for use in CMV retinitis

The stages of development of a 'typical' new drug:



Pre-clinical development: The work falls into four main categories

i. Pharmacological testing to check that the drug does not produce any obviously hazardous acute effects, such as bronchoconstriction, cardiac dysrhythmias etc. This is termed ***safety pharmacology***
ii. Preliminary toxicological testing to eliminate genotoxicity & to determine the **maximum non-toxic dose** of the drug (usually when given daily for 28 days, & tested in two species)
iii. Pharmacokinetic testing, including studies on the absorption, metabolism, distribution & elimination (**ADME studies**) in laboratory animals
iv. Chemical &pharmaceutical development to assess the feasibility of large-scale synthesis &purification, to assess the stability of the compound under various conditions & to develop a formulation suitable for clinical studies.

Much of the work of preclinical development, especially that relating to safety issues, is done under a formal operating code, known as ***Good Laboratory Practice*** **(GLP).**

Animal toxicity studies: Carried out in rodents such as rat, mice etc. & non-rodents such as dog, monkey. These tests include:

a) Systemic toxicity studies: i) with single dose; & ii) with repeated doses
b) Local toxicity studies
c) Specialized toxicity studies:
   i) Male Fertility Studies
   ii) Female Reproduction & Developmental Toxicity Studies
   iii) Allergenicity/ hypersensitivity tests
   iv) Genotoxicity tests
   v) Tests for carcinogenicity

Genotoxicity tests: are in *vitro & in vivo* tests conducted to detect compounds which induce genetic damage directly or indirectly.

- **In-vitro** studies should include Ames' Salmonella assay & chromosomal aberrations (CA) in cultured cells.
- **In-vivo** studies should include micronucleus assay (MNA) or CA in rodent bone marrow.

Ames' Test (Reverse mutation assay in Salmonella)Q: S. typhimurium tester strains such as TA98, TA100 etc or *Escherichia coli* WP2 *uvrA*should be used

Carcinogenicity tests: Carcinogenicity studies should be performed for all drugs that are expected to beclinically used for > 6 months.

Carcinogenicity studies should be done in a rodent species (preferably rat).At least three dose levels should be used. Observations should include macroscopic changes observed at autopsy &detailedhistopathology of organs & tissues.

Additional tests for carcinogenicity: i) Short-term bioassays

ii) Neonatal mouse assay

iii) Tests employing transgenic animals

Clinical development:

Clinical development proceeds through four distinct phases,

i. **Human Pharmacology (Phase I):** The objective of studies in this Phase is the estimation of **safety** &tolerability with the initial administration of an investigational new drug into human(s).

ii. **Therapeutic exploratory trials Q(Phase II):** The primary objective of Phase II trials is to evaluate **the efficacy** of a drug for a particular indication or indications in patients with the condition under study and to determine the common short-term side-effects and risks associated with the drug.

iii. **Therapeutic confirmatory trialsQ (Phase III):** Phase III studies have primary objective of demonstration or confirmation of therapeutic benefit(s)

iv. **Post Marketing Trials (Phase IV):** Post marketing trials are studies (other than routine surveillance) performed after drug approval arid related to the approved indication(s).

Typical Characteristics of the Various Phases of the Clinical Trials Required for Marketing of New Drugs:

PHASE I First in Human	PHASE II First in Patient	PHASE III Multi-Site Trial	PHASE IV Post-Marketing Surveillance
10-100 participants	50-500 participants	A few hundred to a few thousand participants	Many thousands of participants
Usually healthy volunteers; occasionally patients with advanced or rare disease	Patient-subjects receiving experimental drug	Patient-subjects receiving experimental drug	Patients in treatment with approved drug
Open label	Randomized and controlled (can be placebo-controlled); may be blinded	Randomized and controlled (can be placebo-controlled) or uncontrolled; may be blinded	Open label
Safety and tolerability	Efficacy and dose ranging	Confirm efficacy in larger population	Adverse events, compliance, drug-drug interactions

- **Microdosing:** is one kind of early phase exploratory clinical trial, administering the compound at doses estimated to have no pharmacological or toxicological effects, aimed at screening candidates for further clinical development

Routes of drug administration: Routes can be broadly divided in to those for,

(a) Local action & (b) Systemic action

Factors governing choice of route:

i. Physical & chemical properties of the drug
ii. Site of desired action
iii. Rate & extent of absorption of the drug from different routes
iv. Effect of digestive juices& first pass metabolism on the drug
v. Rapidity with which the response is desired (Routine or emergency treatment)
vi. Accuracy of dosage required
vii. Condition of the patient (Unconsciousness, vomiting)

Drug delivery systems: Method of administration of a pharmaceutical compound to achieve a therapeutic concentration or goal in humans or animals. E.g of few drug delivery systems

a. **Controlled release technology (CRT):**
   i) Transdermal & transmucosal controlled release delivery systems
   ii) m[16]nasal & buccal aerosol sprays
   iii) Drug impregnated lozenges
   iv) Encapsulated cells, oral soft gels, iontophoretic devices
b. **Beaded delivery systems: E.g:** Tolterodine tartrate
c. **Liposomal & targeted drug delivery system**

- **Important to know regarding drugs given bytransdermal drug delivery systems**

  E.g: Drugs given as transdermal patch

  Nicotine patch – for tobacco smoking withdrawl

  Scopolamine – for motion sickness

  Nitroglycerine – for angina pectoris

  Testosterone & estrogen- for replacement therapy

  Fentanyl patch – for pain relief

  Rotigotinepatch – for **Parkinson's disease** (The product was recalled in the United States in 2008 because of **crystal formation** on the patches, affecting the availability&efficacy of the agonist

  Clonidine patch- in reducing the incidence of menopausal hot flushes

Note: First pass effect is not seen with following routes

i. Sublingual/buccal
ii. Intravenous
iii. Intra-arterial
iv. Inhalation
v. Transdermal

Pharmacokinetics:

Definition: It deals with the relationship between drug administration, time-course of distribution, &concentration achieved in the body (i.e. the manner in which the body handles a drug)

Physicochemical factors in transfer of drugs across the membranes:

The absorption, distribution, metabolism, excretion, and action of a drug all involve its passage across cell membranes.

Drug molecules move around the body in 2 ways,

i. **Bulk flow** (that in the blood stream, lymphatics or CSF): Chemical nature of a drug makes no difference to its transfer by bulk flow
ii. **Passive transport:** Occurs by
    a). Paracellular transport
    b). Diffusion

- Paracellular passage is limited by-
  1) Blood flow **E.g:** Filtration across the glomerulus in the kidney
  2) Tight intercellular junctions **E.g:** BBB, Placental barrier
- The characteristics of a drug that predict its movement & availability at sites of action are, its **molecular size** & structural features, **degree of ionization**, relative **lipid solubility** of its ionized & non-ionized forms, & its binding to serum & tissue proteins
- **There are 4 main ways by which small molecules cross cell membranes:**
  - **i.** by diffusing directly through the lipid
  - ii. by diffusing through aqueous pores formed by special proteins (***aquaporins*)** that traverse the lipid
  - **iii.** by combination with a ***solute carrier*** **(SLC)** or other membrane transporter
  - **iv.** by ***pinocytosis*** **(**e.g. **insulin**, which crosses the BBB by this process)

1. **Diffusion through lipid:** Non-polar molecules dissolve freely in membrane lipids & consequently diffuse readily across cell membranes. The number of molecules crossing the membrane per unit area in unit time is determined by,
   i) The *permeability coefficient*, ***P***

ii) The concentration difference across the membrane

- Two physicochemical factors contribute to *P*,
  a. **Solubility in the membrane**: which can be expressed as a partition coefficient for the substance distributed between the membrane phase &the aqueous environment&there is a close correlation between **lipid solubility**& the permeability of the cell membrane to different substances.
  b. Diffusivity: which is a measure of the mobility of molecules within the lipid & is expressed as a diffusion coefficient

  Diffusion coefficient for small molecules $\alpha \quad \frac{1}{\sqrt{\bar{Mol}.wt}}$

2. Diffusion by the use proteins such as aquaporins in few tissues/organs:

Collecting duct of nephrons, eye etc.

3. **Carrier mediated transport:**Mediated by carrier proteins or transporters

They are broadly divided into *solute carrier (SLC) transporters*&ATP-*binding cassette (ABC) transporters*

SLC transporters	**ABC transporters**
Mediate passive movement of solutes down their electrochemical gradient SLC carriers: i) Organic cation transporters (OCTs) ii) Organic anion transporters (OATs)	These are active pumps fuelled by ATP ABC transporters can be divided into 7 groups based on their sequence homology: A-G **E.g:**P-glycoprotein/MDR1/ABCB1
OCT's	**OAT's**
These translocate dopamine, choline & various drugs including **vecuronium**, **quinine**&**procainamide** They are uniporters & cause facilitated diffusion down the electrochemical gradient **OCT2** (transporter in proximal tubular cells in the kidney) concentrates drugs such as **cisplatin** in these cells, an explanation of its selective nephrotoxicity Competition with **cimetidine** for OCT2 offers possible protection against cisplatin nephrotoxicity	These are responsible for the renal secretion of urate, prostaglandins, several vitamins&*p*-amino hippurate It may involve exchange of 1 molecule for another ('antiport') or transport of 2 molecules together in the same direction ('symport'). i.e. secondary active transport Drugs such as probenecid, penicillin, uric acid, salicylates, indomethacin, methotrexate utilize this type of transport Uptake is driven by exchange with intracellular dicarboxylic acids

P-glycoprotein (ABCB1):P-glycoproteins (P-gp; P for 'permeability'), are present in renal tubular brush border membranes, in bile canaliculi, in astrocyte foot processes in brain micro vessels, & in the gastrointestinal tract

They play an important part in absorption, distribution & elimination of many drugs& are often co-located with SLC drug carriers

They are responsible for multidrug resistance in cancer cells, hence ABCB1 is also known as "Multiple drug resistance-1 (**MDR-1)".**

Substrates for P-gp:

Anticancer drugs: Actinomycin D, cisplatin, daunorubicin, docetaxel, irinotecan, mitomycin C, vinca alkaloids

Cardiac drugs: Atorvastatin, celiprolol, diltiazem, digoxin, losartan, quinidine, verapamil

Antiviral drugs: Protease inhibitors such as ritonavir

Antibacterial agents: Erythromycin, rifampicin, levofloxacin

GITdrugs: Cimetidine, domperidone, ondensetron

Others: Chloroquine, morphine, phenytoin, tacrolimus

Inhibitors of P-gp: Itraconazole, verapamil, cyclosporine A, cimetidine, digoxin, vandate

- **pH and ionisation:**Many drugs are weak acids or weak bases; their state of ionization varies with pH according to the **"Henderson Hasselbalch equation**".

  The Henderson Hasselbalch equation describes the relation between the pKa of an acidic or basic drug & the pH of the biological medium containing the drug;

  For acids:

  $pH = pKa + \log_{10}\frac{\text{Ionized concentration}}{\text{Unionized concentration}}$

  For bases:

  $pH = pKa + \log_{10}\frac{\text{Unionized concentration}}{\text{Ionized concentration}}$

  - As $\log_{10}(1) = 0$, the pKa of a compound is the pH at which the unionized & ionized concentrations are equal
- **When is pH important in pharmacokinetics?**
  - Drug absorption from the stomach
  - Drug elimination via the kidneys
  - Drug distribution into milk, the placenta & third spaces

- **Ion trapping:** Milk, the fetus & most third spaces have pH values that are acidic (~7.0) in relation to plasma (~7.4). Therefore bases tend to concentrate in these compartments because they are relatively ionized on the acidic side, & effectively trapped .This is called **"ion trapping".**
- **pH partition**: it means that weak acids tend to accumulate in compartments of relatively high pH, vice versa with weak bases.
  - **Important consequences of pH partition:**
    i. Free base trapping of chloroquine in the acidic environment in the food vacuole of the malaria parasite contributes to the disruption of the hemoglobin digestion pathway → toxic effect on the parasite
    ii. Urine acidification accelerates excretion of weak bases & urinary alkalinization has the opposite effects
    iii. Increase in the plasma pH causes weakly acidic drugs to be extracted from the CNS in to the plasma, conversely reducing the plasma pH with acetazolamide causes weakly acidic drugs to become concentrated in the CNS → neurotoxicity

- **Drugs with pH –dependent renal elimination:**

  Acids (Elimination enhanced by alkaline diuresis): Phenobarbitone, salicylates

  Bases: Amphetamine, methadone, mexiletine, ephedrine, quinidine

Important concepts with respect to absorption:

Bioavailability is a term used to indicate the fractional extent to which a dose of drug reaches its site of action**or** the relative amount of a drug administered in a pharmaceutical product that enters the systemic circulation in an unchanged form, & the rate at which this occurs.

i. Absolute bioavailability (F)
ii. Relative bioavailability

- Absolute bioavailability= $\frac{AUC_{oral}}{AUC_{IV}}$

The area under the blood concentration curve is proportional to the extent of bioavailability for a drug if its elimination is first order.

- If the comparison is made between two different oral formulations, then the *relative bioavailability* of these formulations is determined.

- **Factors affecting bioavailability:**
  i. Extent of absorption
  ii. First pass elimination/effect
  iii. Rate of absorption

- **Factors determining extent of absorption**: Tablet disintegration time, dissolution time, presence of other materials such as diluents, binders, stabilizing agents & other excipients. Others include lipid solubility & drug transporters involved in –influx or efflux of the drug
- **Factors affecting rate of absorption**: Route of administration, type of formulation - IR or SR tablet/capsule, gastric emptying time, intestinal transit time, surface area of GIT, pH, solubility of drug , mesenteric blood flow & interaction with other drugs, ions or food
- **Bioequivalence** (BE): BE of a drug product is achieved if its extent & rate of absorption are not statistically significantly different from those of the reference product when administered at the same molar dose.

❖ **First pass effect (Presystemic metabolism):**

This refers to metabolism of a drug during its passage from the site of absorption in to the systemic circulation **or** biotransformation that occurs before the drug reaches its site of action.Following absorption across the gut wall, the portal blood delivers the drug to the liver prior to entry into the systemic circulation

A drug can be metabolized in the gut wall (e.g., by the CYP3A4) or even in the portal blood, but most commonly it is the liver that is responsible for metabolism before the drug reaches the systemic circulation. In addition, the liver can excrete the drug into the bile.

The effect of first-pass hepatic elimination on bioavailability is expressed as the **extraction ratio (ER):**

$$\mathbf{ER} = \frac{CL_{liver}}{Q}$$

CL- Clearance by the liver

Q – Hepatic blood flow

The systemic bioavailability of the drug (F) can be predicted from the extent of absorption (f)& the extraction ratio (ER):

$$F = f \times (1-ER)$$

A drug such as morphine is almost completely absorbed (f = 1), so that loss in the gut is negligible. However, the hepatic ER for morphine is 0.67, so (1 – ER) is 0.33. The bioavailability of morphine is therefore expected to be about 33%.

- **Rapidly metabolized drugs whose hepatic clearance is blood flow-limited:**

Alprenolol	Lidocaine
Amitriptyline	Meperidine
Clomethiazole	Morphine
Desipramine	Pentazocine
Imipramine	Propoxyphene
Isoniazid	Propranolol
Labetalol	Verapamil

- **Effect of food :** Food intake may influence absorption of drugs in different ways

i. **Rate of absorption:** Absorption of digoxin is delayed by the presence of food. Concurrent administration of food may enhance the rate of absorption of some drugs. E.g.Phenytoin

ii. **Extent of absorption:** is known to be affected by the food in the stomach for most drugs, the effect if any is clinically insignificant

E.g.: Food enhances the absorption of hydrochlorothiazide, phenytoin, nitrofurantoin, & the antihelminthic drugs such as mebendazole & albendazole

In contrast, some antibiotics such as penicillin, rifampicin & isoniazid are comparatively poorly absorbed if taken with food.

iii. Effect on presystemic clearance: Concurrent food intake may reduce this presystemic clearance & thus increase the bioavailability of lipophilic bases such as propranolol, metoprolol & hydralazine

Volume of distribution:

It relates the amount of drug in the body to the concentration of drug in the blood or plasma depending on the fluid measured.

Apparent volume of distribution (Vd): It is the volume of fluid required to contain the total amount, Q, of drug in the body at the same concentration as that present in the plasma, Cp.

In the simple one compartment model,

$Vd = \frac{Dose}{C_0}$ C_0- is the initial or the fictitious plasma concentration at time zero

- Drugs confined to plasma compartment – Heparin, Evans blue
- Drugs distributed in the **extracellular compartment** – Vecuronium, gentamicin, carbenicillin
- Drugs distributed **throughout body water**- Phenytoin, ethanol
- **Fat compartment**- DDT, thiopentone sodium
- Bony compartment- lead, fluoride

- **In more complicated models,**

$Vd = \frac{CL}{K_e}$

CL- Clearance K_e – Elimination rate constant

- **Factors governing volume of distribution**:

i. Lipid: water partition coefficient of the drug
ii. pKa value of the drug
iii. Degree of plasma protein binding
iv. Affinity for different tissues
v. Fat: lean body mass ratio, which can vary with age, sex, obesity, etc.
vi. Diseases like CHF, uraemia, cirrhosis

- **Area under the curve: AUC** is a measure of the total systemic exposure of a drug. It is not a primary PK parameter, it is derived from clearance & dose

- **Plasma protein binding of drugs:**Acidic drugs bind largely to albumin. Basic drugs bind mainly to α1-acid glycoprotein as well as to albumin &β-lipoproteins.

  The fraction of total drug in plasma that is bound is determined by the drug concentration, the affinity of binding sites for the drug, & the number of binding sites.

  The extent of this binding will influence the drug's distribution & rate of elimination because *only the unbound drug can diffuse through the capillary wall, produce its systemic effects, be metabolized,* & *be excreted.*

  Increasing concentrations of the drug can progressively saturate the binding sites. Drugs with saturable protein binding include ceftriaxone, hydrocortisone, prednisone, thioridazine & sodium valproate.

  Free drug concentration is dependent on free drug CL, &does not vary in relation to changes in plasma proteins. Therefore, except for rare exceptions, no alteration in dosage is required in states of altered protein binding.

  One drug can bind to many sites on the albumin molecule. Conversely, more than one drug binds to the same site. This can give rise to **displacement interactions** among drugs bound to the same site (s). The overall impact of many displacement interactions is minimal; **clinical significance** being attained only in case of highly bound drugs with limited Vd & where interaction is more complex.

  Some clinically important displacement interactions:

  a. Salicylates displace sulfonylurea's
  b. Indomethacin, phenytoin displace warfarin
  c. Sulfonamides &vitamin K displace bilirubin - kernicterus in neonates

  Drug metabolism (Biotransformation)

  Biotransformation →chemical alteration of the drug in the body

  Primary site: Liver, others are kidney, intestine, lungs and plasma, brain, skin

Salient features:

- It is needed to render non-polar (lipid-soluble) compounds polar (lipid insoluble or water soluble), so that they are not reabsorbed in the renal tubules and are excreted
- Most hydrophilic drugs e.g. streptomycin, neostigmine, pancuronium etc., are little bio transformed and are largely excreted unchanged in the urine.
- Bio activation/biotransformation of the drugs may lead to,

I. **Inactivation :** Most drugs and their active metabolites are rendered inactive or less active

   E.g. Ibuprofen, paracetamol, lidocaine etc.

II. Active metabolite from an active drug:

E.g: Morphine → Morphine – 6- glucuronide

Diazepam → Oxazepam

Spironolactone → Canrenone.

The effects observed are the sum total of that due to the parent drug and its active metabolite(s)

III. Activation of inactive drug : - prodrugs

E.g. Levodopa → Dopamine

Enalapril → Enalaprilat

α- Methyldopa → α methyl NE

Biotransformation reactions can be classified as.

a) **Non synthetic / phase I / Functionalization reactions**

i. Oxidation- **E.g**: Barbiturates, Phenothiazines, imipramine, theophylline, etc...
ii. Reduction- **E.g:** Chloramphenicol, halothane, warfarin
iii. Hydrolysis- **E.g:**Choline esters, procaine, carbamazepine-epoxide
iv. Cyclization- **E.g:** Proguanil
v. Decyclization- **E.g:**Barbiturates, phenytoin

b) Synthetic/phase II / conjugation reactions →

i. Glucuronide conjugation- **E.g:** Chloramphenicol, paracetamol, morphine, lorazepam
ii. Acetylation- **E.g:**Sulfonamides, hydralazine, isoniazid, procainamide, PAS (SHIP)
iii. Methylation- **E.g :** Adrenaline, histamine , captopril & mercaptopurine
iv. Sulfate conjugation- **E.g:** Chloramphenicol, methyldopa, adrenal & sex steroids
v. Glycine conjugation- **E.g:**Salicylates & other drugs having carboxylic acid group
vi. Ribonucleoside / nucleotide synthesis- **E.g:** Antimetabolites

- Drug metabolizing enzymes can be divided in to

1. **Microsomal enzymes** :-

These are – located on smooth endoplasmic reticulum, primarily in liver, also in kidney, intestinal mucosa, brain and lungs

E.g.: The mono-oxygenases (Mixed- function oxidases) (MFO)

Cytochrome p450 enzymes (system)

UDP-glucuronosyl transferase

- Microsomal enzymes are inducible by drugs, diet and other agencies

THE CYTOCHROME P450 SYSTEM

The name Cytochrome P450 is derived from the spectral properties of this hemoprotein

- In its reduced (ferrous) form, it binds carbon monoxide to give a complex that absorbs light maximally at 450 nm
- Microsomal drug oxidations require P450, P450 reductase, NADPH & molecular oxygen.
- > 50 individual CYP's have been identified in humans
- **Functions**

1) Metabolism of dietary and xenobiotic chemicals
2) Synthesis of endogenous compounds (e.g. steroids)
   Fatty acid – derived signaling molecules such as epoxyeicosatrieonic acid
3) Production of bile acids from cholesterol

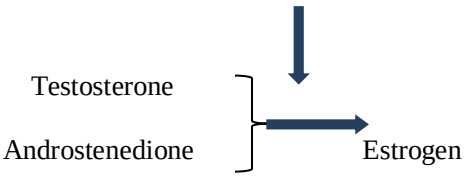
CYP's

Involved in catabolism /steroid and bile acid synthesis

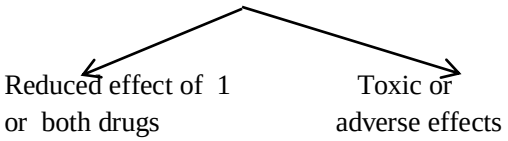
↓

Very specific substrate preferences

E.g.CYP19 or aromatase



- Involved in xenobiotic metabolism, have the capacity to metabolize diverse chemicals.
- Significant overlapping substrate specificity among CYP's
- Reason for drug -drug interaction



The CytochromeP450 super family is divided into families & subfamilies of enzymes that are defined on the basis of their amino acid sequence similarities

- With a few exceptions, enzymes that share > 40% of their amino acid sequence belong to the same family.
- P450's in a single subfamily share > 55% sequence homology

Factors affecting drug metabolism

1) Genetic influences:

Genetic polymorphisms of drug metabolism

Pathway	Marker drug	Enzyme	Substrates	Incidence of deficiency	
Acetylation	Isoniazid	NAT -2	Sulfonanides	Caucasians 50-30%	Asians
	Caffeine		Hydralazine		10-15%
			Dapsone		
			Procainamide		
O-oxidation	Debrisoquine	CYP2D6	Antidepressants	5 – 10%	1 %
	Dextromethorphan		Antipsychotics		
	Sparteine		β – Blockers		
	Desipramine		Antiarrhythmics		
S-oxidation	Mephenytoin	CYP2C19	Clomipramine	3%	15 -25%
	Omeprazole		Imipramine		
			Citalopram		
			Omeprazole		
			Proguanil		

2) Interethnic differences

3) **Age :** Age does affect the pharmacokinetics of drugs
Neonates: Decreased ability to metabolize drugs

In the elderly - Renal function decrease with age & this will cause the accumulation in plasma of drugs or their active metabolites that are cleared by the kidney

4) Gender and pregnancy
5) Foreign compounds & environmental factors

6) Diet and alcohol
   - Effect of alcohol on drug metabolism depends on
     i. The amount of alcohol consumed
     ii. Duration and regularity of alcohol in take
7) Presence of other drugs : **Enzyme inducers or inhibitors**

Inducers of cytochrome P450	**Inhibitors of cytochrome P450**
Barbiturates	Imidazoles (cimetidine, etomidate, ketoconazole, omeprazole)
Phenytoin	Macrolide antibiotics (erythromycin, clarithromycin)
Carbamazepine	Antidepressants
Rifampicin	HIV protease inhibitors
Griseofulvin	Cyclosporine
Alcohol (chronic consumption)	Amiodarone
Polycyclic hydrocarbons (tobacco smoke, grilled meat)	Gestodene
	Grapefruit juice

8) Time of day (chronopharmacology)

Drug excretion:

- The **molecular weight** of drugs & their metabolites plays an important part in determining their route of elimination
- Most low molecular weight compounds & their metabolites are excreted in urine. Drugs with a higher molecular weight (>400-500 Da in man) are preferentially eliminated in bile

Renal elimination: The kidney is responsible for excreting all water soluble substances

The amount of drug **or** its metabolites ultimately present in urine is the sum total of glomerular filtration, tubular reabsorption & tubular secretion. i.e,

Net renal excretion = (Glomerular filtration + TS) – tubular reabsorption

Glomerular filtration is partly responsible for the elimination of poorly lipid soluble drugs & drug metabolites in urine. Comparatively few drugs are excreted unchanged by the kidney because of **tubular reabsorption** of lipid soluble drug.

Glomerular filtration depends on: 1) Plasma protein binding

2) Renal blood flow & 3) Molecular size

Tubular secretion: Carriermediated transport; it can achieve maximum drug clearance even when most of the drug is bound to plasma protein. **E.g:** Penicillin

Tubular reabsorption: This occurs by passive diffusion & depends on the lipid solubility& ionization of the drug at the existing urinary pH.

Avoid toxicity from drug or metabolite accumulation by adjusting a drug'sdosage according to the elimination characteristics of the patient (**E.g.** inrenal impairment).

Estimation of GFR: The GFR provides a useful index of kidney function at the level of the glomerulus. Renal function is assessed clinically using serum creatinine (Cr) levels

$\mathbf{C_{cr}}$ can be estimated from the formula of **Cockcroft & Gault,** Modification of Diet & Renal Disease (MDRD) study.

- Other useful, well-validated estimators of GFR includethe CKD-EPI formula. Cystatin C is another endogenous marker of GFR

Drugs which need dose modification in renal failure:

Aminoglycosides	**Acyclovir**
Amphotericin B	Cephalexin
Cyclosporine	Co-trimoxazole/Sulfonamides
Ethambutol	Gentamicin
Metronidazole	Tetracycline except doxycycline
NSAID's	Vancomycin

Drugs which are excreted in the bile: Erythromycin, ampicillin, rifampin, doxycycline, ceftriaxone, cefoperazone, oral contraceptives

Drugs which undergo enterohepatic circulation: Digitoxin, estrogens, indomethacin etc..

Saliva & sweat: Lithium, potassium iodide, rifampin & heavy metals

Drug's contraindicated in lactating mother (Secretion in breast milk):

Amiloride, amiodarone, androgens, anticancer drugs, chloramphenicol, ciprofloxacin, cyclosporine, ethosuximide, fluconazole, lithium carbonate, vigabatrin

Drug clearance: The clearance of a drug is the theoretical volume of plasma from which the drug is completely removed in unit time. It can be calculated as,

CL (L/h) = Rate of elimination (mg/h)/C (mg/L)

Determination of CL: From the *A*rea *under* the *C*urve (AUC)

After IV dosing: $CL = \frac{Dose}{AUC}$

After oral dosing: $CL = \frac{F.Dose}{AUC}$

It is important to note the additive character of clearance. Elimination of drug from the body may involve processes occurring in the kidney, the lung, the liver, and other organs.

Kinetics of elimination

In the body drug molecules reach their sites of action after crossing cell membranes &cells, and many are metabolized in the process.The rate at which these movements or changes take place is subject to important influences called the **"order of reaction or process**"

First order (exponential) processes or elimination:

- In which a constant fraction of drug is transported / metabolized in unit time.
- In the majority of instances, the rates at which ADME of a drug occur are directly proportional to its concentration in the /body
- Increased elimination of a drug – if the drug concentration is high & falls in direct proportion to be low at low concentrations (**an exponential relationship**)
- This is because the processes follow the law of mass action, which states i.e., ' the rate of a reaction is directly proportional to the active filtration masses of reacting substances'.
- In doses used clinically, most drugs are subject to first order kinetics & this knowledge is useful to know the time to achieve steady-state plasma concentration, time to eliminate the drug & for construction of dosing schedules.
- **$t_{1/2}$ remains → constant**, because $t_{1/2}$ &CL do not change with dose

Zero-order kinetics

- As the amount of drug in the body rise, metabolic reactions or processes that have limited capacity becomes saturated (**Decrease in clearance)**
- Zero-order processes in which a constant amount of drug is transported, metabolized in unit time
- Drugs with zero order elimination have no fixed $t_{1/2}$ **($t_{1/2}$ is variable)**
- The rate of elimination is constant & does not depend on the drug concentration
  In other words, the rate of the process reaches a maximum amount at which it stays constant **E.g.** due to limited activity of an enzymes & any further increase in rate is impossible despite an increase in the dose of a drug
  80 mg 4hr → 70mg 4 hr → 60 mg 4 hr → 50 mg 4 hr → 40 mg

$t_{1/2}$ $t_{1/2}$ $t_{1/2}$ $t_{1/2}$

- In practice, enzyme mediated metabolic reactions are the most likely to show rate limitation because the amount of enzyme present is finite & can become saturated
- Passive diffusion does not become saturated
- Drugs which exhibit saturation kinetics

  Ethanol → except at low blood levels

  Phenytoin → at high therapeutic doses

  Salicylates → Toxic doses of aspirin

  Note: Clearance has no real meaning for drugs with capacity-limited elimination, &AUC should notbe used to describe the elimination of such drugs

  Kinetics of a drug does not depend on the route of entry[Q]

Flow-dependent elimination: The elimination of these drugs will thus depend primarily on the rate of drug delivery to the organ of elimination. Such drugs can be called "high-extraction" drugs.

- **Half-life** ($t_{1/2}$) is the time required to change the amount of drug in the body by one-half during elimination (or during a constant infusion).
- The t½ provides an index of:

a. The time-course of drug elimination
b. The time-course of drug accumulation
c. Choice of dose interval

Taking the simplest case of a drug which has rapid one compartment distribution & first order elimination, & is given i.v. a semilog plasma concentration -time plot is obtained. The plot has 2 slopes,

- Initial rapidly declining **(α) phase**- due to distribution
- Later less declining **(β) phase**- due to elimination

Relationship between t½, Vd& CL:

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

Note: Other clinical pharmacokinetic concepts useful in pharmacotherapy

- Concentration of drug in plasma at steady state (Cp_{ss})
- Dose rate
- Loading dose
- Maintenance dose

- Importance of TDM (Therapeutic drug monitoring)

Steady state: the concentration at which the same amount of drug entering the system eliminated from the system.It usually takes 5-7 $t_{1/2}$ to attain steady state plasma concentration.

Maintenance Dose:

In most clinical situations, drugs are administered in such a way as to maintain a steady state of drug in the body, i.e., just enough drug is given in each dose to replace the drug eliminated since the preceding dose.

Clearance is the most important pharmacokinetic term to be considered in defining a rational steady-state drug dosage regimen.

At steady state,

The dosing rate ("rate in") =the rate of elimination ("rate out")

= CL X TC (Target concentration)

If intermittent doses are given, the maintenance dose is calculated from:

Maintenance dose = Dosing rate X dosing interval

Loading Dose: When the time to reach steady state is appreciable, as it is for drugs with long half-lives, it may be desirable to administer a loading dose that promptly raises the concentration of drug in plasma to the target concentration

Loading dose = Vd X TC

Or

Loading dose = maintenance dose X accumulation factor

Other key pharmacokinetic relationships:

- Initial dose = Loading dose/Vd
- Steady state concentration = $\frac{\text{Fraction absorbed X maintenance dose}}{\text{Dosing interval X clearance}}$

Therapeutic drug monitoring (TDM) :

TDM is the clinical practice of measuring specific drugs at designated intervals to maintain a constant concentration in a patient's blood, serum or other biological fluid, there by optimizing individual dosage regimens

- **Indications for requesting plasma drug concentration**
  i. Monitoring compliance, when there is failure of therapeutic effect at a known effective dose
     E.g. Anti-epileptic drugs or psychopharmacological
  ii. Individualizing therapy – Increase effectiveness

During early treatment during dosage change

E.g. Plasma gentamicin – against sensitive bacteria

Plasma theophylline – For asthma

iii. Diagnosing under treatment (**E.g**. Lithium, phenytoin)

iv. Avoiding toxicity (Particularly for drugs with narrow TI)

E.g. Digoxin, lithium, Cyclosporine

v. Monitoring & detecting drug interactions

vi. Guiding withdrawal of therapy

vii. If individual variations are large - antidepressants, lithium

Criteria that a drug should satisfy for plasma concentration measurements to be useful

a) Difficulty in interpreting clinical evidence of therapeutic or toxic effects
b) A good relationship between the plasma drug concentration & the therapeutic or toxic effect or both
c) A low toxic : therapeutic ratio
d) Does not metabolize to important active metabolites

Plasma concentration may not be worth measuring:

- Where dose can be titrated against a quickly &**easily measured effect** such as BP (antihypertensives), body – weight (diuretics), INR (oral anticoagulants) or blood sugar (OHA'S or Insulin)

- **Plasma concentration has no correlation with effect:**

  With drugs that act irreversibly (**hit &run drugs**) such drugs inactivate targets (enzymes, receptors& restoration of effect occurs only after days or weeks when resynthesis takes place)

  E.g. MAOI's, Aspirin Some anticholinesterases & anticancer drugs

- **When plasma concentration may correlate poorly with effect**

  i. When a drug is metabolized to several products

  ii. Binding of basic drugs

  E.g. Lidocaine to acute phase reactants (proteins) **e.g**.α_1- acid glycoprotein, spuriously increase the total concentration in plasma.

Pharmacodynamics: It is the study of drug effects. It attempts to elucidate the **complete action-effect**& the **dose effect relationship**. Modification of the action of one drug by another drug is also an aspect of pharmacodynamics

Majority of drugs produce their effects by interacting with a discrete target biomolecule, which usually is a protein. Functional proteins that are targets of drug action can be grouped into 4 major categories, *viz*

a. Enzymes
b. Ion channels
c. Transporters
d. Receptors

However, a few drug do act on other proteins (e.g. colchicine, vinca alkaloids, taxanes bind to the structural protein tubulin) or on nucleic acids

RECEPTOR

Receptor is a cellular macromolecule or an assembly of macromolecules, mainly protein in nature, present on the surface of the cell membrane or inside a cell, concerned directly and specifically in chemically signaling between and within the cells.

- Based on molecular structure & the nature of the transduction mechanism – 4 types

Type 1: **Ligand-gated ion channels** also known as **ionotropic** receptors

E.g: nAChR, $GABA_A$ & glutamate receptors of the NMDA, AMPA & kainate types

Type 2: **G-protein-coupled receptors** (GPCRs)

E.g: mAChR, adrenoceptors & chemokine receptors

Type 3: **kinase-linked and related receptors**

E.g: include those for insulin, & various cytokines & growth factors

Type 4: **nuclear receptors**

Classification of nuclear receptors

Class I - Receptors for steroid hormones

E.g. Glucocorticoid receptors, Mineralocorticoid receptors, Estrogen receptors, Progesterone receptors, Androgen receptors.

Class II – PPAR (Peroxisome proliferator activated receptor)

Liver oxysterol receptor (**LXR)** – Acts as a cholesterol sensor

Farnesoid X-receptor **(FXR)** – Xenobiotic receptor that recognizes a great many foreign substances, including therapeutic drugs

Constitutive androstane receptor (**CAR)** : Recognizes androstane & also drugs such as phenobarbital

Class III - Nuclear receptors similar to subgroup II receptors bind with RXR to form hetero dimers, but rather than sensing the lipids, they play a part in an endocrine signaling

E.g. Thyroxine receptors (TR), Vitamin D receptors & RAR

Physiological Receptors: A major group of drug receptors consists of proteins that normally serve as receptors for endogenous regulatory ligands. These drug targets are termed *physiological receptors*

Drugs that bind to physiological receptors & mimic the regulatory effects of the endogenous signaling compounds are termed ***agonists.*** If the drug binds to the same *recognition site* as the endogenous agonist the drug is said to be a ***primary agonist.***

Allosteric (allotopic)* agonists** bind to a different region on the receptor referred to as an allosteric site.Drugs that block or reduce the action of an agonist are termed ***antagonist. Antagonism most commonly results from competition with an agonist for the same or overlapping site on the receptor **(a *syntopic* interaction).**

Theories of drug receptor interaction (Receptor concept for drug action)

i. Occupational theory- by **Clark.A.J**
ii. Rate theory – by **Patson**
iii. The operational model- by **Black**
iv. The ternary complex model – by **De lean & colleagues**
v. Probabilistic theory for GPCR's-

All these theories explain some of the important concepts like, Efficacy, effectiveness, potency & affinity

The chemistry of drug receptor binding: Mediated through the interaction among the drug & receptor interfaces

Bond type	Bond strength
Vander Waals	+
Hydrogen	++
Ionic	+++
Covalent	++++

Drug receptors & biological responses:
Biological response is brought about by second messengers like cAMP, IP_3-DAG-Ca++

Adenylyl cyclase: cAMP		**PLC; IP_3-DAG**	**Channel regulation**		
↑	↓		↑ Ca^{2+}	↓ Ca^{2+}	↑ K^+
β- Adrenergic	**α_2-Adrenergic**	**α_1 Adrenergic**	**β_1-Adrenergic**	**D_2**	α_2
H_2	**M_2**	**H_1**		**$GABA_B$**	M_2
D_1	**D_2**	**M_1, M_3**		**Opioid-κ**	D_2
Glucagon	**5-HT_1**	5-HT_2		**Adenosine-A_1**	5-HT_{1A}
ACTH	**Somatostatin**	**Vasopressin**		**Somatostatin**	$GABA_B$
FSH & LH	**AT_1**	**Thromboxane**			**Opioid- μ, δ**
TSH	**Opioid- μ, δ**	**Angiotension**			**Adenosine-A_1**
EP_2 & IP	**Adenosine-A_1**				

Dose response relationship:

Efficacy & potency are the two important pharmacodynamic characteristics of a drug thatcan be quantified using dose-response curve

Potency: Potency refers to the concentration (EC 50) or dose (ED 50) of a drug required to produce 50% of that drug's maximal effect.

Efficacy: is the maximal response produced by the drug

Therapeutic index:

It aims to provide a measure of the margin of safety of a drug

In experimental animals,

TI= Median lethal dose

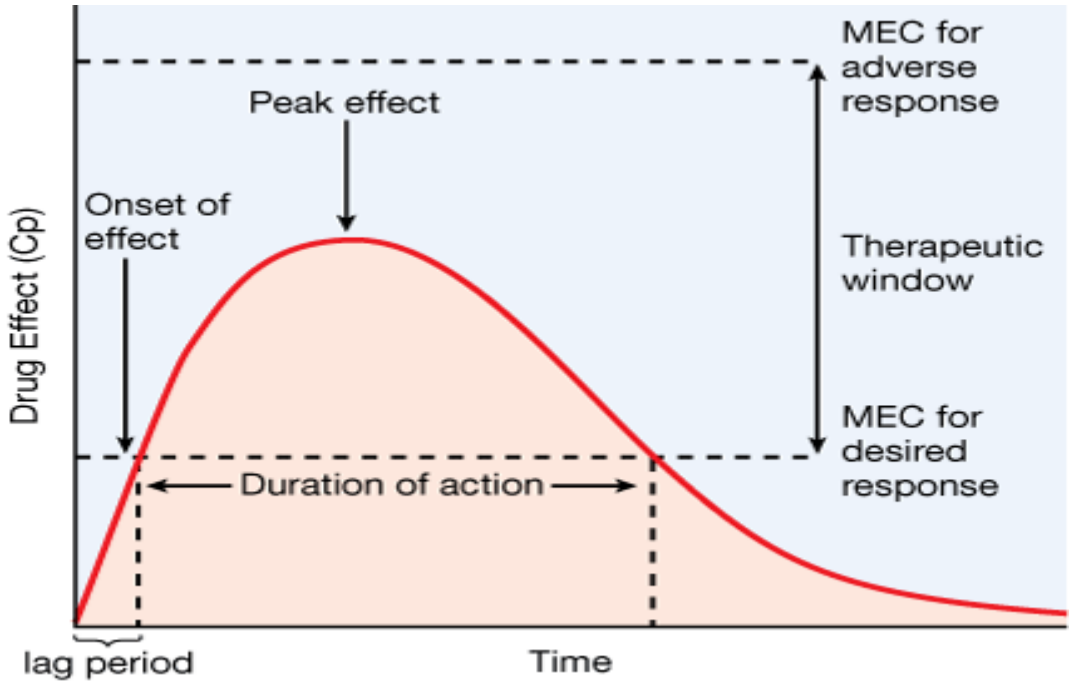
Median effective dose

As a general rule, a drug should have a high therapeutic index. That means TI should be > 1

Drug's with low therapeutic index:

Digoxin	Anticonvulsants	Theophylline	Aminoglycosides
Antiarrhythmics	Lithium	Lidocaine	TCA's

Therapeutic window: It is the range of plasma concentration between that required for the efficacy & that at which toxicity occurs



Drugs showing therapeutic window phenomenon:

TCA's –imipramine, clonidine, glipizide

Combined effect of drugs:

Synergism: When the action of one drug is facilitated or increased by the other

i. Additive – A+B= Effect of drug A+ Effect of drug B
ii. Potentiation- A+B> Effect of drug A+ Effect of drug B

Antagonism: When one drug decreases or abolishes the action of another –A+B < Effect of drug A+ Effect of drug B

Types: i) Functional antagonism- E.g: Histamine & adrenaline, Glucagon & insulin

ii) Chemical antagonism

iii) Dispositional antagonism

iv) Receptor antagonism:

a) **Competitive antagonism: i) Reversible**

ii) Irreversible

b) **Non-competitive antagonism**

Competitive antagonism: Antagonist resembles chemically with the agonist & binds with the same receptor as agonist. In the presence of the antagonist, the agonist log concentration-effect curve is shifted to the right without change in slope or maximum, the extent of the shift being a measure of the *dose ratio.* The dose ratio increases linearly with antagonist concentration; the slope of this line is a measure of the affinity of the antagonist for the receptor.
E.g: Acetylcholine – Atropine, morphine- naloxone
Irreversible antagonism: It occurs with drugs that possess reactive groups that form covalent bonds with the receptor
E.g: Phenoxybenzamine is a non-equilibrium or irreversible antagonist of adrenaline at the α adrenergic receptors
Non-competitve antagonism: Antagonist binds to another site (allosteric) of receptor. Flattening of agonist DRC E.g: Diazepam- Bicuculline

Factors modifying drug action:

- **Genetic factors:**
  E.g: Atypical pseudocholine esterase result in prolonged succinylcholine apnoea
  G-6PD deficiency is responsible for hemolysis with primaquine & other oxidizing drugs

Drugs that Carry Risk of Clinical Hemolysis in Persons with G6PD Deficiency

	Definite Risk	**Possible Risk**	**Doubtful Risk**
Antimalarials	Primaquine	Chloroquine	Quinine
	Dapsone/chlorproguanil*		
Sulphonamides/sulphones	Sulfamethoxazole	Sulfasalazine	Sulfisoxazole
	Others	Sulfadimidine	Sulfadiazine
	Dapsone		
Antibacterial/antibiotics	Cotrimoxazole	Ciprofloxacin	Chloramphenicol
	Nalidixic acid	Norfloxacin	*p*-Aminosalicylic acid
	Nitrofurantoin		
	Niridazole		
Antipyretic/analgesics	Acetanilide	Acetylsalicylic acid high dose (>3 g/d)	Acetylsalicylic acid (<3 g/d)
	Phenazopyridine		Acetaminophen
			Phenacetin
Other	Naphthalene	Vitamin K analogues	Doxorubicin
	Methylene blue	Ascorbic acid >1 g	Probenecid
		Rasburicase	

- Pathological states:

  Liver disease, kidney disease or cardiac disease

- Tolerance

Drugs induced renal disease (C/I or require dose reduction in patients with renal failure):

Mechanisms of renal toxicity of drugs:

Reduction in renal perfusion through alteration of intrarenal haemodynamics
NSAID, ACE inhibitors, cyclosporine, contrast media, norepinephrine, angiotensin receptor blockers, diuretics, interleukins, cocaine, mitomycin C, tacrolimus, oestrogen, quinine
Acute tubular necrosis
Antibiotics: aminoglycosides, cephaloridine, cephalothin, amphotericin B, rifampicin, vancomycin, foscarnet, pentamidine
NSAIDs, glafenin, contrast media, acetaminophen, cyclosporine, cisplatin, IV immune globulin, dextran, maltose, sucrose, mannitol, heavy metals
Acute interstitial nephritis with or without glomerulopathy
Antibiotics: ciprofloxacin, methicillin[Q], penicillin G, ampicillin, cephalothin, oxacillin, rifampicin
NSAIDs, glafenin, ASA, fenoprofen, naproxen, phenylbutazone, piroxicam, tolemetin, zomepirac, contrast media, sulfonamides, thiazides, phenytoin, furosemide, allopurinol, cimetidine, omeprazole, phenindione
Tubular obstruction
Sulfonamides, methotrexate, methoxyflurane, glafenin, triamterene, ticrynafen, acyclovir, ethylene glycol, protease inhibitors
Haeme pigment-induced toxicity (rhabdomyolysis) **: Cocaine, ethanol, lovastatin**
Hypersensitivity angiitis
Penicillin G, ampicillin, sulfonamides
Thrombotic microangiopathy/haemolytic-uraemic syndrome
Cyclosporine, oral contraceptives, mitomycin C, cocaine, quinine

Drug induced liver disease:

Cholestasis: Methyl testosterone, Erythromycin estolate, nitrofurantoin, rifampin, Carbamazine, Nifedipine, verapamil, Ezetimibe
Fatty liver: Amiodarone, Tetracycline (high-dose, IV), Valproic acid, Asparaginase, methotrexate, Dideoxynucleosides (e.g., zidovudine), protease inhibitors (e.g., indinavir, ritonavir)
Hepatitis: Halothane, Flutamide, Isoniazid, rifampicin, minocycline, pyrazinamide, Phenytoin, carbamazine, valproic acid, phenobarbital, imipramine, Ketoconazole, Methyldopa, captopril, Risperidone, Atomoxetine, acarbose
Mixed hepatitis/cholestasis: Amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole, Clindamycin, Terbinafine, Azathioprine, Nicotinic acid, lovastatin, ezetimide
Toxic (necrosis) : Acetaminophen, Carbon tetrachloride, *Amanita phalloides*
Granulomas: Quinidine, diltiazem, sulfonamides, carbamazine, phenylbutazone, Allopurinol

Tolerance: It refers to the requirement of higher dose of a drug to produce a given response

Tolerance is a widely occurring adaptive biological phenomenon

Types: Natural/Acquired
Acute/chronic

Acute tolerance (Tachyphylaxis): It refers to rapid development of tolerance when doses of a drug repeated in quick succession result in marked reduction in response

It is usually seen with indirectly acting drugs, such as ephedrine, tyramine, and nicotine

Mechanisms of tachyphylaxis:

i. Depletion of neurotransmitter stores in presynaptic nerve terminal
ii. Slow dissociation of the drug from its receptor
iii. Desensitization/internalization or downregulation of receptor
iv. Compensatory homeostatic adaptation

Adverse drug effects:

Adverse effect is'any undesirable or unintended consequence of drug administration'. It is a broad term, includes all kinds of noxious effect-trivial, serious or even fatal.

Types:

A – Augmented → Common, dose related, predictable **E.g:** Insulin causes hypoglycemia

B- Bizzare → less common, not dose related, unpredictable, more serious may require withdrawl of the drug

i. Drug allergy- E.g: Penicillin
ii. Idiosyncrasy- E.g: Dapsone causing hemolysis in G-6PD deficient patients

C- Chronic effects → E.g: Analgesic nephropathy

D- Delayed effects → Drug induced carcinogenesis E.g: Alkylating agents

E- End of treatment effects → Rebound hypertension with β-blockers

Pharmacovigilance:

It is the science & activities relating to the detection, assessment, understanding & prevention of adverse effects or any other drug related problems

Drug dependence:

It is a state in which use of drugs for personal satisfaction is accorded a higher priority than other basic needs, often in the face of known risks to health

Drug	Psychological	Physical dependence
Morphine	++	++
Barbiturates	++	++
Alcohol	++	++
Cocaine	++	+/-
Cannabis	++	+/-
Amphetamine	++	+/-

Teratogenecity: Usually occur if the drug is given to pregnant women in the phase of organogenesis (Between 18- 55 days of gestation)

Drug	Trimester	Effect
ACE inhibitors	All, especially second & third	Renal damage, Oligohydramnios
Carbamazepine	First	Neural tube defects
Valproic acid	All	Neural tube defects, cardiac and limb malformations
Diethylstilbestrol	All	Vaginal adenosis, clear cell vaginal adenocarcinoma
Isotretinoin	All	Extremely high risk of CNS, face, ear, & other malformations
Lithium	First, third	Ebstein's anomaly, neonatal toxicity after third trimester
Misoprostol	First	Mobius sequence
Penicillamine	First	Cutis laxa, other congenital malformations
Phenytoin	All	Fetal hydantoin syndrome
SSRIs	Third	Neonatal abstinence syndrome, persistent pulmonary hypertension of the newborn
Tetracycline	All	Discoloration and defects of teeth and altered bone growth
Thalidomide	First	Phocomelia (shortened or absent long bones of the limbs) and many internal malformations
Warfarin	First	Hypoplastic nasal bridge, chondrodysplasia
	Second	CNS malformations
	Third	Risk of bleeding. Discontinue use 1 month before delivery

1. In new drug designing , problem arises in **: (AIIMS 2012)**

a) Decreasing interaction of drug with target proteins
b) Increasing drug interaction with non-target proteins
c) Decreasing potency of drugs
d) Increased binding with target protein

2. All are true about structure based drug design system (**AIIMS 2011)**

a) Uses library of many structural drug designs
b) Screening of virtual drug structures become redundant
c) It removes the need to synthesize the lead compound
d) Depends on complete understanding of active sites and interacting molecules

3. Which of the following is wrong match in metabolizing (**AIIMS 2011)**

a) CCB – CYP3A
b) Carvedilol – CYP2 D6
c) Simvastatin – glucuronide conjugation
d) Digoxin – p glycoprotein

4. Drugs not used in pregnancy are all except? **(AIIMS 2011)**

a) Angiotensin converting enzyme inhibitors
b) Angiotensin receptor blockers
c) Aldosterone
d) Propylthiouracil

5. Pharmacovigilance is done for monitoring – **(AIIMS 2010)**

a) Drug price
b) Unethical practices
c) Drug safety
d) Pharmacology students

6. Pharmacovigilance is used for – **(AIIMS 2009)**

a) To monitor drug toxicity
b) To monitor unauthorized drug manufacture
c) Monitoring of students
d) Check costs

7. Which drug is not acetylated ?(**AIIMS 2008)**

a) INH
b) Dapsone
c) Hydralazine
d) Metoclopramide

8. Which is a prodrug? (**AIIMS 2008)**

a) Enalapril
b) Clonidine
c) Salmeterol
d) Acetazolamide

9. Which teratogen causes deafness? (**AIIMS 2008)**

a) Isotretinoin
b) Chloroquine
c) Alcohol
d) Warfarin

10. Loading dose depends on : (**AIIMS 2008**)

a) Volume of distribution
b) Clearance
c) Rate of administration
d) Half life

11. Which among the following is a Cyt. P450 inhibitor? (**AIIMS 2008)**

a) Ketoconazole

b) Rifampicin
c) Phenytoin
d) INH

12. Therapeutic drug monitoring is advised in all except (**AIIMS 2007**)
    a) Metformin
    b) Phenytoin
    c) Tacrolimus
    d) Cyclosporine

13. Good clinical practice (GCP) seen in all except (**AIIMS 2007)**
    a) Preclinical trials
    b) Phase I trials
    c) Phase II trials
    d) Phase IV trials

14. All of the following drugs are metabolized by acetylation except:(**AIIMS 2006)**
    a) INH
    b) Hydralazine
    c) Procainamide
    d) Metoclopromide

15. Loading dose depends upon (**AIIMS 2006)**
    a) Volume of distribution
    b) Half life
    c) Plasma clearance
    d) Route of administration

16. Which NSAID undergoes enter hepatic circulation (**AIIMS 2006)**
    a) Phenylbutazone
    b) Aspirin
    c) Ibuprofen
    d) Piroxicam

17. One of the following is a prodrug (**AIIMS 2006)**
    a) Enalapril
    b) Butorphanol
    c) Naltrexone
    d) Pralidoxime

18. Side effects of a drug arise due to the interactions of the drug to molecules other than the target. These effects of a drug can be minimized by its high –(**AIIMS 2005)**
    a) Specificity
    b) Affinity
    c) Solubility
    d) Hydrophobicity

19. Which of the following drugs has covalent interaction with its target –(**AIIMS 2005)**
    a) Aspirin
    b) Penicillin
    c) Nitric oxide
    d) Bosentan

20. Which of the following property of drug will enable it to be used in low concentrations –(**AIIMS 2005)**
    a) High affinity
    b) High specificity
    c) Low specificity
    d) High stability

<u>All India previous year question papers:</u>

1. Drug with a low therapeutic index whose blood levels need to be monitored include all of the following, except? **(AI 2012)**
    a) Lithium
    b) Cyclosporine
    c) Gentamicin
    d) Warfarin
2. A drug ‘A’ is already in use and drug B

needs to be introduced. The value of the new drug in relation to the old drug can be established by which phase of drug trial. **(AI 2012)**

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

3. The preferred method of drug designing is : (**AI 2012)**

a) Target – structure based
b) Hit and trial method
c) Molecular modeling
d) High throughout method

4. Mineral corticoid Receptors are found in all of the following, Except (**AI 2011)**

a) Liver
b) Colon
c) Hippocampus
d) Kidney

5. Narrow therapeutic index is seen with: **(AI 2010)**

a) Desipramine
b) Lithium
c) Penicillin
d) Diazepam

6. All of the following statements about phenytoin are true, except? (**AI 2010)**

a) Follows saturation kinetics
b) Is teratogenic
c) Is highly protein bound
d) Stimulates Insulin secretion

7. Which of the following teratogenic effects is incorrectly matched **(AI 2010)**

a) Phenytoin – Cleft lip / palate
b) Zidovudine – Skull defects
c) Valproate – Neural tube defects
d) Warfarin – Nasal Bone Dysplasia

8. Most common congenital anomaly associated with Lithium is (**AI 2010)**

a) Cardiac Malformations
b) Neural Tube Defects
c) Renal anomaly
d) Fetal Hydantoin Syndrome

9. Phase II in a clinical drug trial is done to assess: (**AI 2008)**

a) Therapeutic efficacy
b) Maximal tolerated dose
c) Maximal lethal dose
d) Toxicity

10. Therapeutic index is a measure of a drug's (**AI 2008**)

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

11. ED 50 is a measure of **(AI 2008)**

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

12. All of the following enzymes and their reactions are involved in the metabolism of Xenobiotics, Except: (**AI 2008**)

a) Cytochrome oxidase
b) Cytochrome p 450
c) Methylation
d) Hydroxylation

13. All of the following have receptors which are transcription factors, except? (**AI**

2007)

a) **Insulin**
b) Estrogen
c) Glucocorticoids
d) Vitamin D

14. Which of the following is a prodrug? (**AI 2007)**

a) Ticlopidine
b) Aspirin
c) **Clopidogrel**
d) Dipyridamole

15. 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

16. A highly ionized drug: **(AI 2005)**

a) **Is excreted mainly by the kidney**.
b) Can cross the placental barrier easily
c) Is well absorbed from the intestine
d) Accumulates in the cellular lipids

17. All of the following hormones have cell surface receptors except: (**AI 2005**)

a) Adrenaline
b) Growth Hormone
c) Insulin.
d) **Thyroxine**

18. A highly ionized drug: (**AI 2004)**

a) **Is excreted mainly by the kidneys**
b) Crosses the placental barrier easily
c) Is well absorbed from the intestine
d) Is highly protein bound

19. In which of the following phases of a clinical trial of drug ethical clearance is not required? **(AI 2004)**

a) Phase I
b) Phase II
c) Phase III
d) **Phase IV**

20. All of the following statements regarding bioavailability of a drug are true except: (**AI 2003)**

a) It is the proportion (fraction) of unchanged drug that reaches the systemic circulation
b) Bioavailability of an orally administered drug can be calculated by comparing the area under Curve (0 – α) after oral and intravenous (IV) administration.
c) **Low oral bioavailability always and necessarily mean poor absorption**
d) Bioavailability can be determined from plasma concentration or urinary excretion data.

21. Presence of food might be expected to interfere with drug absorption by slowing gastric emptying, or by altering the degree of ionization of the drug in the stomach. Which of the following statements is not correct example: **(AI 2003)**

a) Absorption of digoxin is delayed by the presence of food.
b) Concurrent food intake may severely reduce the rate of absorption of phenytoin.
c) Presence of food enhances the absorption of hydrochlorothiazide.
d) Antimalarial drug halofantrine is more extensively absorbed if taken with food

22. Haemorrhage secondary to heparin administration can be corrected by administration of : **(AI 2003)**
    a) Vitamin K
    b) Whole blood
    c) Protamine
    d) Ascorbic acid
23. Which of the following receptors are present intracellularly in muscle cells: **(AI 2003)**
    a) Insulin
    b) **Corticosteroid**
    c) Epinephrine
    d) Glucagon
24. 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)**
    a) pKa of a drug is the pH at which the drug is 50% ionized
    b) Small changes of pH near the pKa of a weak acidic drug will not affect its degree of ionization
    c) Knowledge of pKa of a drug is useful in predicting its behaviour in various body fluids.
    d) Phenobarbitone with a pKa of 7.2 is largely ionized at acid pH and will be about 40% non-ionized in plasma

Autonomic Nervous System (ANS)

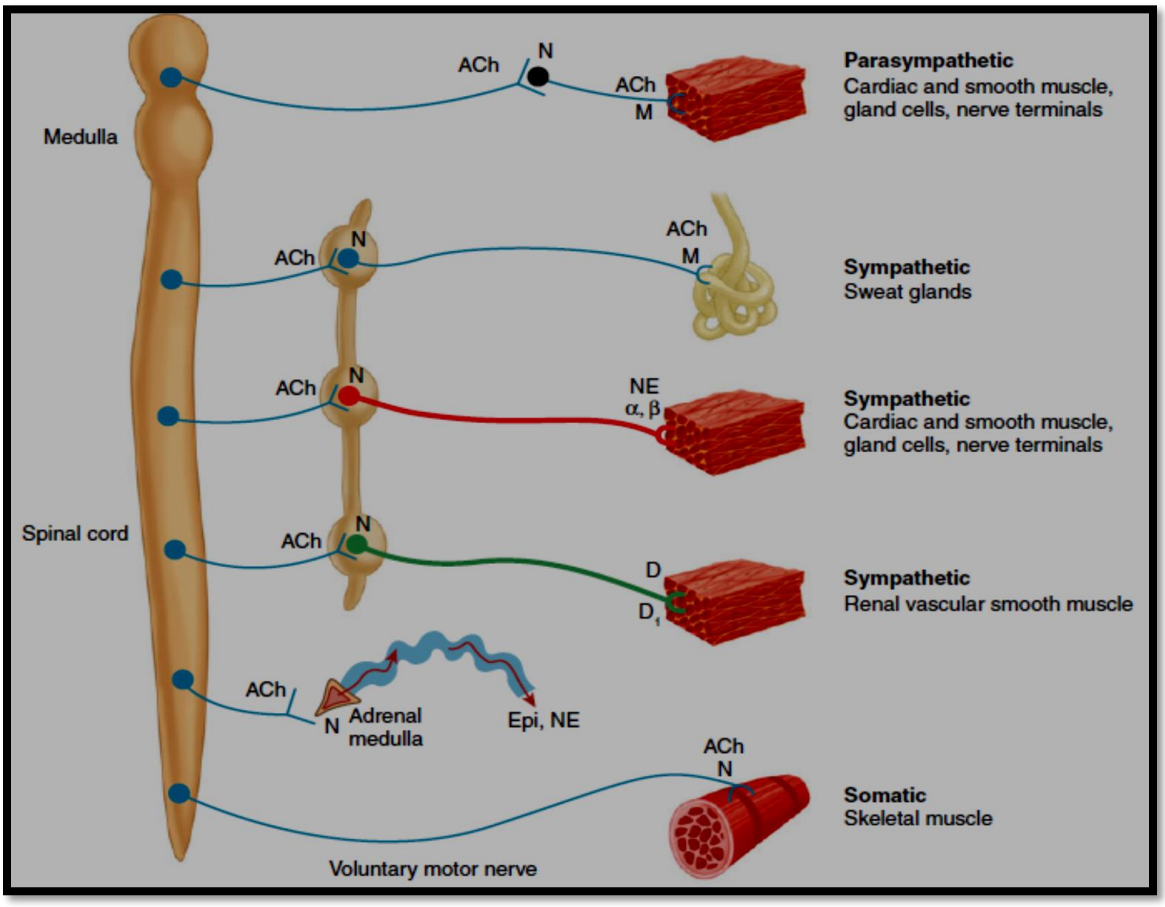
Autonomic Nervous System (ANS) is involuntary in nature and the activities of this system are maintained autonomically. In contrast to somatic nervous system, organs supplied by ANS do not atrophy even after section of an autonomic nerve (rather denervation supersensitivity of receptors occurs). ANS is divided into three main divisions; sympathetic, parasympathetic and 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 (NMJ) and N_N nicotinic receptors at 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 (S2,3,4) 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 or longer than preganglionic fibres whereas in parasympathetic system preganglionic fibres are much longer than postganglionic fibres (ganglia are closer to organs).

- Acetylcholine (ACh) is the principal NT at NMJ as well at all preganglionic fibres.
- In parasympathetic system, NT released at postganglionic fibres is also ACh.
- In sympathetic system, at most of post ganglionic 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)

Cholinergic receptors may be nicotinic (N_N, N_M) or muscarinic (M_1 through M_5) and adrenergic receptors are divided into α (α_1, α_2) and β (β_1, β_2, β_3) receptors.

Receptor	Major site of location
N_N	Ganglia, adrenal medulla
N_M	Neuromuscular junction
M_1	Gastric glands, autonomic ganglia and CNS
M_2	Heart
M_3	Smooth muscles, glands and endothelium
α_1	Smooth muscles and glands
α_2	Post-synaptic at vascular smooth muscles and brain, Presynaptic at nerve terminals
β_1	Heart and JG cells of kidney
β_2	Smooth muscles and heart
β_3	Adipose tissue and coronary vessels



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. Uptake of choline by 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.

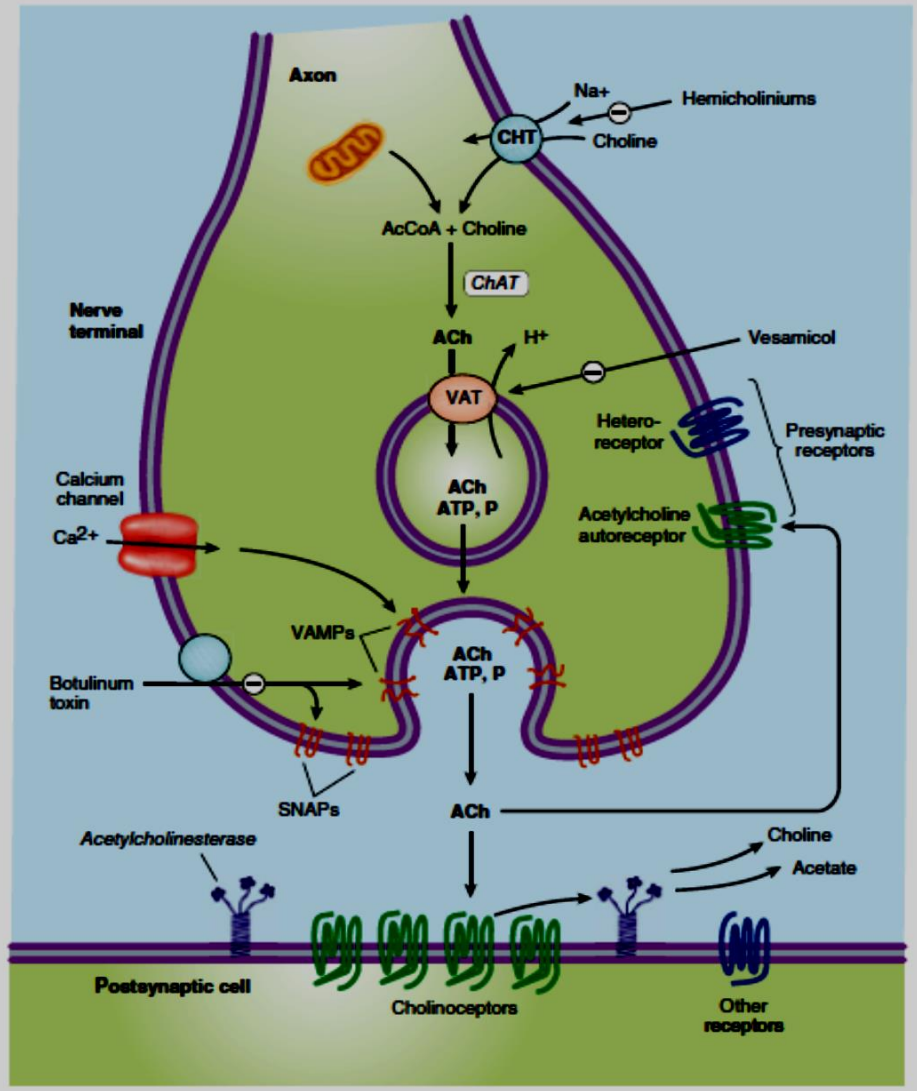


FIGURE 6–3 Schematic illustration of a generalized cholinergic junction (not to scale). Choline is transported into the presynaptic nerve terminal by a sodium-dependent choline transporter (CHT). This transporter can be inhibited by hemicholinium drugs. In the cytoplasm, acetylcholine is synthesized from choline and acetyl-CoA (AcCoA) by the enzyme choline acetyltransferase (ChAT). Acetylcholine is then transported into the storage vesicle by a second carrier, the vesicle-associated transporter (VAT), which can be inhibited by vesamicol. Peptides (P), adenosine triphosphate (ATP), and proteoglycan are also stored in the vesicle. Release of transmitter occurs when voltage-sensitive calcium channels in the terminal membrane are opened, allowing an influx of calcium. The resulting increase in intracellular calcium causes fusion of vesicles with the surface membrane and exocytotic expulsion of acetylcholine and cotransmitters into the junctional cleft (see text). This step can be blocked by botulinum toxin. Acetylcholine's action is terminated by metabolism by the enzyme acetylcholinesterase. Receptors on the presynaptic nerve ending modulate transmitter release. SNAPs, synaptosome-associated proteins; VAMPs, vesicle-associated membrane proteins.

Functions of cholinergic system

Sympathetic and parasympathetic system has 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

1. **Heart:** Parasympathetic system has inhibitory effect on the heart (M_2) and is responsible for negative chronotropic (decreased heart rate), ionotropic (decreased force of contraction) and dromotropic effects (decreased conduction). Anticholinergic drugs will stimulate the heart by decreasing the inhibitory effect of ACh on heart.
2. **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.
3. **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 eye and thus accommodation is possible. Anticholinergic drugs result in mydriasis and loss of accommodation (Cycloplegia).
4. **Glands:** Cholinergic system stimulates the secretion of glands and result in 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).
5. **Urinary bladder:** Cholinergic drugs stimulate detrussor and relax the trigone (sphincter) of urinary bladder resulting in increased micturition (M_3). Anticholinergic drugs may result in urinary retention.
6. **Gastro-intestinal tract**: Hydrochloric acid secretion in stomach (M_1 and M_3) is stimulated by parasympathetic system and thus increased risk of peptic ulcer disease. Peristalsis of GIT is increased and sphincters are relaxed by cholinergic drugs. Anticholinergic drugs can be used as spasmolytic agents for intestinal colic.
7. **Bronchus:** Cholinergic system causes bronchoconstriction (M_3) and anticholinergic drugs may lead to bronchodilation.
8. **Male sex organs:** Due to vasodilation, cholinergic system is responsible for erection of male organ.

Nicotinic actions: **PTO**

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

Drugs affecting muscarinic activity

1. Cholinergic or parasympathomimetic drugs
    - Direct acting (e.g. ACh, pilocarpine, cevimeline)
    - Indirect acting (e.g. Physostigmine, neostigmine)
2. Anticholinergic or parasympatholytics drugs
    - Non-selective antagonists (e.g. Atropine, hyoscine)
    - Receptor selective antagonists
        - M_1 blocker (e.g. Pirenzepine, telenzepine)
        - M_2 blocker (e.g. Gallamine)
        - M_3 blocker (e.g. Darifenacin)
    - Drugs acting by other mechanisms
        - Decrease choline uptake (e.g. Hemicholinium)
        - Decrease vesicular uptake of ACh (Vesamicol)
        - Decrease release of ACh (Botulinum toxin)

PARASYMPATHOMIMETIC DRUGS

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

1. 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 plasma and is not effective even by i.v. route.
- **M**ethacholine has maximum action on **m**yocardium.
- **B**ethanechol is mainly used for its action on urinary **b**ladder and has no nicotinic activity.
- **P**ilocarpine is used in glaucoma due to its **p**upillary constrictor (miotic) action. However because of its very short duration of action, intraocular tension may increase even if some doses are missed.

2. 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 and rivastigmine are 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. All other reversible anti-cholinesterases are synthetic quaternary compounds and are lipid insoluble. Due to high lipid solubility, physostigmine can be given 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 belladona (atropine) poisoning as a specific antidote.
- Neostigmine is preferred for the treatment of myasthenia gravis. It does not produce adverse effects in CNS (do 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 reversal of competitive skeletal muscle relaxants. Pyridostigmine is longer acting than neostigmine and can be used for all these indications.
- 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.

Irreversible anticholinesterases: This group includes organophosphates (Malathion, parathion, ecothiophate and diflos) and carbamates (carbaryl and propoxur).

- 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 poisoning are simply the extension of pharmacological actions of ACh and are manifested as pin-point pupil, salivation, lacrimation, sweating, bronchoconstriction, diarrhea, urination, bradycardia, hypotension and coma. Blood pressure 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 organophosphate poisoning but are contra-indicated in carbamate poisoning. The site on which oximes bind and reactivate the enzyme is occupied by carbamates whereas it is free in organophosphate poisoning. 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.

ANTICHOLINERGIC DRUGS

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

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

Actions of Antimuscarinic agents:

CNS: Atropine is a CNS stimulant whereas scopolamine causes CNS depression. Due to its amnesic and CNS depressant action, it induces "twilight sleep" and has been used as lie detector or truth serum in suspects. Transdermal patch of scopolamine (applied behind the pinna) is used for prevention of motion sickness. 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 agents for refraction testing and in iridocyclitis. Atropine has very long duration of action (3-5 days) in the eye whereas it has shorter action in other organs.

Tropicamide is the shortest acting mydriatic.

Anticholinergic agents are contra-indicated in glaucoma.

CVS: Atropine causes bradycardia initially due to inhibition of presynaptic muscarinic receptors but further 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.

Respiratory system: Anticholinergic drugs reverse the bronchoconstriction caused by stimulation of M_3 receptors. Ipratropium and tiotropium are selective M_3 receptor antagonists useful in the treatment of COPD and bronchial asthma. Glycopyrolate is used as a pre-anaesthetic medication to decrease the secretions and reflex bronchospasm during general anaesthesia.

GIT: Anticholinergic drugs decrease the motility, tone and secretions in gastrointestinal tract.

- Pirenzepine & telenzepine are selective M_1 blocker useful in peptic ulcer disease.
- Hyoscine, dicyclomine, propantheline, oxyphenonium and clidinium are useful as anti-spasmodic agents for the treatment of intestinal colic.
- Darifenancin is a selective M_3 blocker useful for irritable bowel syndrome and overactive bladder.

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 and renal colic. Tolterodine (selective M_3 antagonist) is also useful for urinary incontinence.

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

Other uses: Atropine is the drug of choice for early mushroom poisoning due to Inocybe species. (It is contra-indicated in poisoning due to Amanita muscaria). Thioctic acid is useful for late mushroom poisoning due to Amanita phalloides.

- It is also the drug of choice for organophosphate poisoning.
- It is used along with neostigmine (to decrease its muscarinic side effects) for the treatment of Mysthenia gravis.

Adverse effects: These include dry mouth, blurred vision (due to mydriasis & cycloplegia), urinary retention, constipation, hyperthermia, confusion, delirium and restlessness etc. It is 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 (**d**i hydr**o**xy **p**henyl**a**lanine). 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 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 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 vesicles (inhibited by cocaine and TCA) and partly by metabolism through MAO and COMT. Further conversion of NA to adrenaline (A) is carried out in adrenal medulla. This methylation step occurs in cytoplasm with the help of phenyl ethanolamine-N-methyl transferase. Adrenergic neurons lack this enzyme; therefore catecholamine synthesis is stopped at NA level.

NA remains stored in the vesicles. Stimulation of this neuron by 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).

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 α and β receptors directly whereas indirectly acting drugs increase the release 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 endogenous catecholamines whereas isoprenaline, dobutamine, dopexamine and fenoldopam are synthetic catecholamines. Non catecholamines 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 CNS. Metabolism in intestines (by MAO and COMT) and liver (by MAO) precludes their oral use.

ACTIONS OF SYMPATHETIC SYSTEM

1. Heart: Positive chronotropic, ionotropic and dromotropic effects are seen due to stimulation of β_1 receptors
2. 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 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 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 than other vascular beds.
3. 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 cholinergic neurons (heteroceptors) and results in decreased release of ACh.
4. Urinary system: Urinary retention can occur due to relaxation of detrussor by β_2 action and contraction of trigone (sphincter) by α_1 action.
5. Genital system: Pregnant uterus is relaxed by β_2 stimulation. Activation of α_1 receptors in vas deferens, seminal vesicle and prostate facilitates ejaculation.
6. 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.
7. Eye: Stimulation of β_1 receptors present on dilator pupillary muscle causes mydriasis. Ciliary vasodilation by stimulation of β_2 receptors increases the formation of aqueous humor whereas α_1 stimulation increases the outflow. Thus β blockers and α_1 agonists are useful in the treatment of glaucoma.

8. Glands: Secretion of salivary glands becomes thick due to vasoconstriction. Sweating is stimulated by sympathetic cholinergic receptors (M_3 action).
9. 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 elevation in blood glucose.
10. Other effects: Stimulation of β_1 receptors in kidney is responsible for renin release. β_2 stimulation can cause tremors.

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 & β_1) and isoprenaline possess little α activity (β_1 and β_2 only). Effect of these drugs on heart rate and blood pressure are given below:

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

Systolic blood pressure (SBP) is determined by cardiac output ($\beta_1$action) whereas diastolic BP 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 increase 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).

- 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. 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.
- Dopamine is the drug of choice for cardiogenic shock with oliguric renal failure. It causes renal vasodilation by acting on D_1 receptors and maintains renal perfusion and GFR. Other ionotropic 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 agonistic activity with NA reuptake inhibitory action.
- Fenoldopam is D_1 agonist useful in hypertensive emergencies.

Non Catecholamines

α_1 agonists: Phenylephrine, methoxamine, naphazoline, oxymetazoline and xylometazoline selectively activates α_1 receptors. All of these drugs can be used as nasal decongestants. Phenylephrine can also be used as mydriatic (does not cause cycloplegia).

- Phenylpropanolamine was banned due to risk of hemorrhagic stroke

α_2 agonists: Clonidine and α methyldopa 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.

Apraclonidine and brimonidine are selective α_2 agonists used topically for the treatment of glaucoma. Dexmedetomidine is an α_2 agonist used for sedation under intensive care circumstances & during anaesthesia. Guanfacine and guanabenz are α_2 agonists similar to clonidine and are rarely used now.

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), metaproterenol, terbutaline, pirbuterol, salmeterol and formoterol are selective β_2 agonists useful in bronchial asthma. Ritodrine and isoxsuprine are agonists useful as tocolytic (uterine relaxant) agents.

***Indirectly Acting Sympathomimetics*:** These drugs act by increasing the release of NA in the synaptic cleft. These agents enter the neuronal cytoplasm by same transporter that is responsible for 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 preferred drug for the treatment of attention deficit hyperkinetic disorder (ADHD). Other drugs used for this indication are amphetamines and pemoline.
- 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.

***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 cold remedies for nasal decongestant action. Ephedrine can also be used for treatment of bronchial asthma.

SYMPATHOLYTIC DRUGS

These drugs may act by blocking α and/or β 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 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).
- 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 selectively inhibits subtype of α_1 receptors present in prostate (α_{1A}) without affecting those present in blood vessels. It is therefore preferred for the treatment of BHP due to less chances of postural hypotension.
- Indoramin and urapadil are rarely used for hypertensive emergencies.

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

BETA BLOCKERS

Nonselective 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 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).
- Increased chances 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.

USES: **Cardiac**

- Hypertension
- Classical angina
- Myocardial infarction

- Supraventricular arrhythmias
- Chronic CHF
- Hypertrophic obstructive cardiomyopathy (DOC)

Extra cardiac

- Pheochromocytoma (after α blockade)
- Hyperthyroidism
- Performance anxiety
- Tremors
- Prophylaxis of migraine
- Glaucoma (timolol and betaxolol)
- Alcohol withdrawal

Limitations of non selective β blockers:

- Contraindicated in bronchial asthma due to bronchoconstrictor action.
- Hypoglycemia is commonly observed in diabetic patients (receiving insulin and oral hypoglycemic drugs) on beta blocker therapy. Symptoms of hypoglycemia (like tachycardia, sweating and tremors) are due to sympathetic stimulation that acts 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 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).

***β 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 patients prone to develop severe bradycardia with β blocker therapy. The drugs can be remembered as

COntain --- **C**eliprolol, **O**xprenolol

Partial ---- **P**indolol

Agonistic – **A**lprenolol

Activity ---- **A**cebutolol

Cardioselective (selective β_1) β blockers: These agents are preferred in patients with diabetes mellitus, bronchial asthma, peripheral vascular disease or hyperlipidemia. The drugs in this group are:

Beta ---- **B**etaxolol

Blockers --- **B**isoprolol

Action ---- **A**tenolol

At ---- **A**cebutolol

Exactly in – **E**smolol

Myocardium ---- **M**etoprolol

***β 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 risk of corneal anaesthesia. The drugs are:

Membrane --- **M**etoprolol

Local --- **L**abetalol

Anaesthetic – **A**cebutolol

Property -- **P**ropanolol (maximum),**P**indolol

***Lipid insoluble β blockers*:** These agents are mainly excreted by kidney and are therefore contraindicated in renal failure. These have long duration of action:

A – **A**cebutolol**A**tenolol

B – **B**etaxolol **,B**isoprolol

C – **C**eliprolol

No--- **N**adolol (longest acting β blocker)

Solution --- **S**otalol

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), and release of NO (nevibolol) or inhibition of Ca^{2+} channels.

COMBINED ALPHA AND BETA BLOCKERS

Labetalol and carvedilol are important drugs in this group. These are useful for control of hypertensive episodes in pheochromocytoma. Carvedilol is most commonly used beta blocker in chronic CHF due to its **antioxidant and antimitogenic properties.**

Questions:

1. All of the following are actions of muscarinic antagonists, except? **(AI 2011)**
   a. Decrease gastric secretions
   b. Decrease respiratory secretions
   c. Contract radial muscles of iris
   d. Facilitate AV conduction
2. Which of the following drugs is not used in acute angle closure glaucoma? **(AI 2009)**
   a. Pilocarpine
   b. Clozapine
   c. Fluphenazine
   d. Duloxetine
3. Mechansm of action of pralidoxime is: (**AI 2008)**
   a. Direct activation of Cholinergic receptors
   b. Reactivation of cholinesterase
   c. Inactivation of cholinesterase
   d. Inhibiton of acetyl choline
4. Ipratropium bromide is contraindicated in: **(AI 2008)**
   a. Asthma
   b. Urinary retention
   c. Hypertension
   d. Peptic ulcer
5. Tiotropium is used for: **(AI 2008)**
   a. Treating urinary retention
   b. Treating ileus
   c. Increasing salivation
   d. Treating asthma
6. All of the following drugs may be used to relive urinary spasms after urological procedures except? (**AI 2008)**
   a. Darifenacin
   b. Oxybutynin
   c. Tolterodine
   d. Tiotropium
7. All of the following may be associated with Beta $_2$ agonist treatment except? **(AI 2007)**
   a. Hyperkalemia
   b. Hyperglycemia
   c. Detrusor relaxation
   d. Relaxation of gut and bronchial muscles
8. All of the following may be associated with the use of Beta agonist in preterm labour except: **(AI 2007)**
   a. Hyper kalemia
   b. Hyperglycemia
   c. Tachycardia
   d. Relaxation of uterine muscles
9. All of the following are nonselective Beta blockers with additional actions except: **(AI 2007)**
   a. Carvedilol
   b. Betoxalol
   c. Cartelol
   d. Labetalol
10. The following drugs may be used in erectile dysfunction except? **(AI 2007)**
    a. Phenylephrine
    b. Apomorphine
    c. Alprostidil
    d. PGE1 analogues
11. The following drugs are used in obesity except**:(AI 2007)**
    a. Orlistat
    b. Sibutaramine
    c. Olestra
    d. Neuropeptide Y agonist

12. Which one of the following drugs increases gastrointestinal motility?

a. Glycopyrrolate
b. Atropine
c. Neostigmine
d. Fentanyl

13) Sympathomimetic drugs are useful in the therapy of all of the following conditions except?

a. Acute decompensated heart failure
b. Hypotension
c. Hypertension
d. Erectile dysfunction

14) Lid retraction is caused by –

a. Apraclonidine
b. Brimonidine
c. Latanoprost
d. Travaprost

15) Which is used in overactive bladder –
    a. Duloxetine
    b. Darfinacin
    c. Flavoxate
    d. Oxybutynin
16) All except, aggravates myasthenia gravis –
    a. Aazathioprine
    b. Phenytoin
    c. Tetracycline
    d. Aminoglycoside
17) Tolazoline is used as –
    a. As thrombin inhibitor in peripheral angiography
    b. As vasodilator in treating coronary artery stenosis during angio procedures
    c. As vasoconstrictor in the treatment of varices
    d. Antispasmodic during biliary spasm
18) All of the following drugs are useful in detrussor instability except –
    a. Solefenacin
    b. Tolterodine
    c. Flavoxate
    d. Duloxetine
19) Not used in erectile dysfunction?
    a. PGE_2
    b. Vardenifil
    c. Phenylephrine
    d. Alprostadil
20) All are endogenous catecholamine's except ;
    a. Epinephrine
    b. Norepinephrine
    c. Dopamine
    d. Dobutamine

CNS DRUGS

CNS

Alcohol

Alcohols are hydroxy derivatives of aliphatic hydrocarbons. Pharmacology of alcohol is important for its presence in beverages, alcoholism & for alcohol intoxication.

Alcohol is manufactured by fermentation of sugars. Fermentation proceeds till alcohol content reaches ~ 15%. Major source of commercial alcohol is *molasses*

- **Alcoholic beverages:**

I. **Malted liquors:** Obtained by fermentation of germinating cereals; are undistilled –alcohol content is low (3-6%)
E.g.: Beer, stout - Strong beers (up to 10%) are also available

II. **Wines:** Produced by fermentation of natural sugars as present in grapes & other fruits. These are also undistilled
Types: Light wines (Cider) → Alcohol content is 9-12% (max ≤ 15%)
Fortified wines (Port) → 16-22%
Effervescent wines (Champagne) → 12-16%

III. **Spirits:** These are distilled after fermentation E.g.: Rum, Gin, Whiskey, Brandy, Vodka, etc. Alcohol content of these can vary from 40-55%, in India for all licensed brands it is standardized to **42.8%** v/v or **37%** w/w

Other forms of alcohol:

Absolute alcohol: 99% w/w ethanol

Rectified spirit: 90% w/w ethyl alcohol produced from fermented from fermented molasses, by distillation

Methylated spirit: Also called denaturated spirit is produced by adding 5 parts of wood naphtha (methyl alcohol) to 95 parts of rectified spirit so as to render it unfit for drinking

Alcoholism:

A person is generally considered an alcoholic → when his or her lifestyle is dominated by the procurement and consumption of alcoholic beverages and when this behavior interferes with personal, professional, social, or family relations.

*A **light drinker*** generally is defined as one who consumes an average of one drink or less per day, usually with the evening meal

*A **moderate drinker*** is one who has approximately three drinks per day

*A **heavy drinker*** is one who has 5 or more drinks per day (or in the case of binge drinkers, at least once per week with 5 or more drinks on each occasion).

Important points on its effect on human body:

Central Nervous System: Ethanol primarily is a CNS depressant.

It acts by altering the levels of following neurotransmitters:

Neurotransmitter System	**Effects**
$GABA_A$	GABA release, ↑ receptor density
NMDA	Inhibition of postsynaptic NMDA receptors; with chronic use, up-regulation
DA	↑ Synaptic DA, ↑ effects on ventral tegmentum/nucleus accumbens reward
ACTH	↑ CNS and blood levels of ACTH
Opioid	Release of β-endorphins, activation of μ-receptors
5-HT	↑ in 5-HT synaptic space
Cannabinoid	↑ CB1 activity → changes in DA, GABA, glutamate activity

The CNS is markedly affected by acute alcohol consumption. Alcohol causes sedation, relief of anxiety and, at higher concentrations,slurred speech, ataxia, impaired judgment, and disinhibited behavior, a condition usually called **intoxication**

BAC	Clinical Effect

(mg/dL)	
50–100	Sedation, subjective"high", slower reaction times
100–200	Impaired motor function, slurred speech, ataxia
200–300	Emesis, stupor
300–400	Coma
> 400	Respiratory depression, death

Many countries permit mild degrees of intoxication, but beyond a certain statutory BAC, it becomes a culpable offence

E.g: In India, the statuatory limit has been fixed at **30 mg%**[Q]

CVS: Chronic alcoholism contributes to hypertension & can lead to cardiomyopathy (Dilated)[Q]

Atrial fibrillation & other cardiac arrhythmias may occur due to conduction defects & Q-T prolongation

Blood: Regular intake of small to moderate amounts of alcohol (1-2 drinks) has been found to ↑ HDL & ↓ LDL oxidation → 15-35% lower incidence of CAD

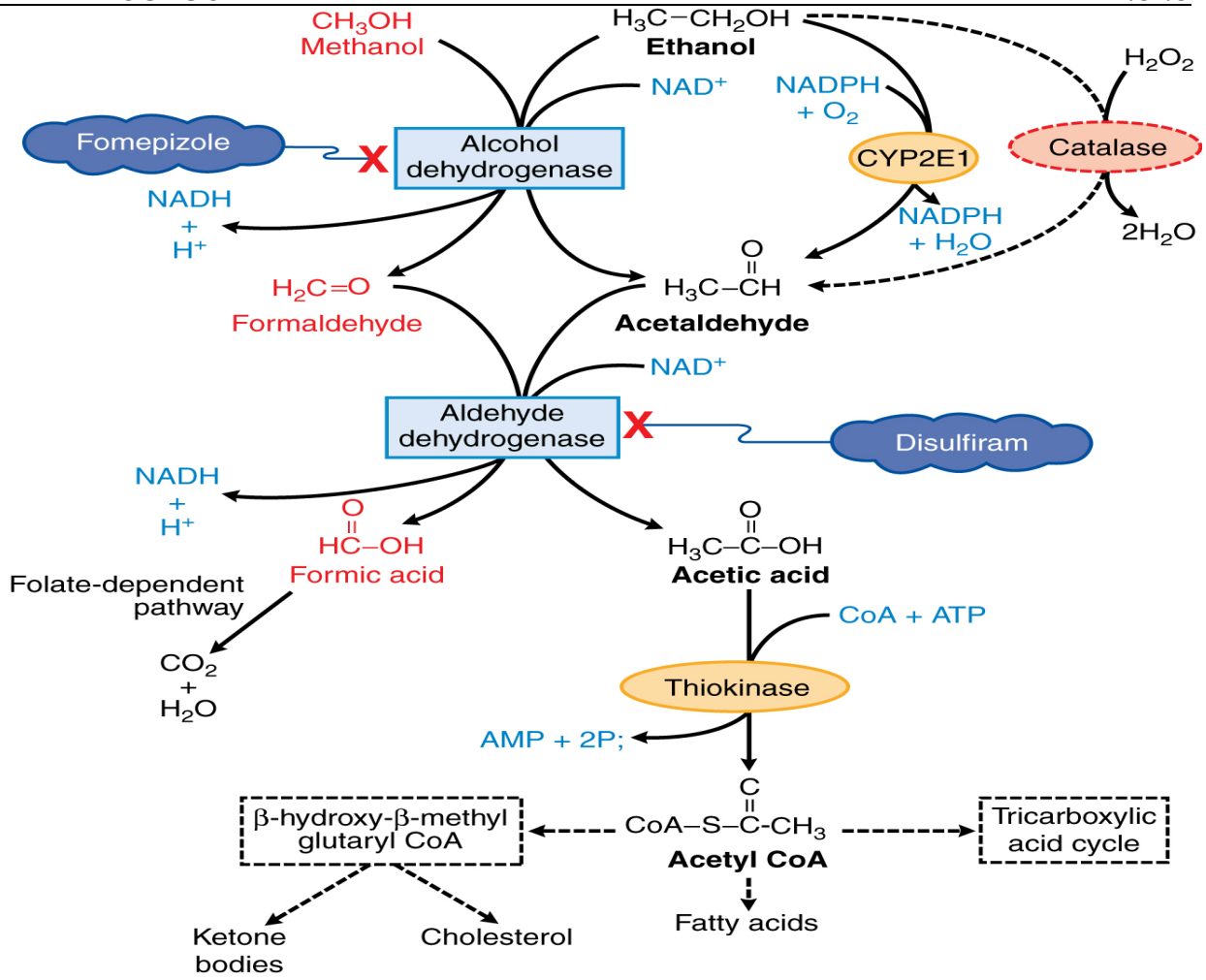
Risk reduction is greatest in high risk subjects & protection is lost if ≥3 drinks are consumed daily

Kidney: Diuresis is often noticed, i) Water ingested along with drinks

ii) Inhibition of ADH secretion

Pharmacokinetics: More than 90% of alcohol in the plasma is metabolized in the liver by three enzyme systems that operate within the hepatocyte. The remainder is excreted by the lungs and in urine and sweat

Metabolism of ethanol & methanol:



The metabolism of alcohol generally is said to follow zero-order pharmacokinetics. This can, in fact, be an oversimplification because at very high or very low concentrations of alcohol the metabolism can follow first-order pharmacokinetics

Drug interactions: Acute alcohol ingestion inhibits, while chronic intake induces CYP enzymes (especially CYP2E1)

Formation of toxic metabolite of paracetamol (NAPQI) is increased in chronic alcoholics

Individuals taking a sulfonylurea, cefoperazone or metranidazole have experienced bizzare, somewhat disulfiram-like reactions when they consume alcohol

Note: The CAGE questionnaire[Q] is a tool for detecting individuals more likely to be abusing alcohol and therefore at greater risk for alcohol withdrawal

Treatment: Alcohol-Related Disorders

Alcohol Withdrawal:

Treatment Regimens: i) Symptom-Triggered Therapy

ii) Fixed-Schedule Therapy

Pharmacologic Agents Used in the Treatment of Alcohol Withdrawal:

Drug	Dose per Day	Indication
Multivitamin	1 tablet	Malnutrition
Thiamine	50–100 mg	Deficiency
Crystalloid fluids (typically D5-0.45 NS with 20 mEq of KCl per liter)	50–100 mL/hr	Dehydration
Clonidine	0.05–0.3 mg PO Transdermal patch also	Autonomic tone rebound & hyperactivity
Labetalol	20 mg IV every 2 hours as needed	Hypertensive urgencies and above
Antipsychotics, haloperidol	2.5 mg to 5 mg every 4 hours	Agitation unresponsive to benzodiazepines, hallucinations or delusions
Antipsychotics, atypical **Quetiapine** **Aripiprazole**	5–200 mg 5–15 mg	Agitation unresponsive to benzodiazepines, hallucinations, or delusions in patients intolerant of conventional antipsychotics
Benzodiazepines: Lorazepam **Chlordiazepoxide Clonazepam** **Diazepam**	0.5–2 mg 5 mg–25 mg 0.5–2 mg 2.5–10 mg	Tremor, anxiety, diaphoresis, tachypnea, dysphoria, seizures
Alcohol oral		Prevent withdrawal
Alcohol IV		Prevent withdrawal

Pharmacologic Agents Used in the Treatment of Alcohol Dependence:

Drug	Dosage Range per Day	Indication
Disulfiram	**250 mg–500 mg**	**Deterrence**
Acamprosate	**999 mg–1,998 mg and higher (333 mg tablets)**	**Craving**
Naltrexone	**50 mg–100 mg**	**Craving**
Mood stabilizers (e.g., lamotrigine, topiramate, carbamazepine, valproic acid)	**Seizure disorder doses**	**Craving**
Antidepressants (e.g., clomipramine, bupropion, doxepin, maprotiline, fluoxetine)	**Depression doses**	**Craving, depression, anxiety**

Acute alcohol intoxication: Treatment

1. Maintenance of nutrition and electrolyte balance.
2. IV DNS – for hypoglycemia
3. IV thiamine – 100 mg
4. IV magnestium sulfate – 2-4 gram over 1-2 hours

Symptomatic treatment of alcohol witherawal:-

a. Maintenance of nutrition and electrolyte balance
b. IV DNS – for hypoglycemia.
c. IV thiamine – 100 mg
d. A-adrenegic agonist – clonidine – for its anticraving properties. 0.1 – 0.4 mg QID or atenolol 50-100 mg to combat autonomic hyperactivity.
e. Diazepam, Carbamazepine, chlordiazepoxide to prevent seizures.

Treatment of alcohol dependence:

1. Detoxification –
    a. Aversion therapy – disulfiram, citrated calcium cyanamide (CCC)
    b. Opioid antagonist – naltreoxone, nalmephene.
    c. Dopaminergic antagonists – tiapride
    d. Miscellaneous agents:- acramposate
    e. Supportive drugs – lithium, Carbamazepine, SSRI.

A. Disulfiram –
    a. MOA – inhibits aldehyde dehydrogenase – Acetaldehyde accumulates in tissues – various distressing symptoms like nausea, vomiting, flushing, burning sensation, throbbing headache etc. are seen. Inhibits dopa oxidase & can cause depletion of catecholamines.
    b. Rarely used due to possibility of severe reaction. Thus treatment should be given in hospitalized patients only. Severe hypotension can occur.
    c. Given in only dedicated patient – after overnight abstinence.Started with1000 mg and rapidly tapred to have maintenance dose 125 or 250mg.
    d. Irreversible inhibition of enzyme – effect lasts for 7 -14 days.
    e. Side effects – rashes, metallic taste, nervousness, abdominal upset.

B. Carbimide – shorter duration and fewer side effects.Leucocytosis and hypothyroidism are side effects.

C. Naltreoxone – blocks alcohol induced dopamine release at nuclease at mucleus accumbense & maintenance abstinence . 500 mg OD as long as 12 weeks.

D. Tiapride –D2 antagonist with neuroleptic and anxiolytic properties. Reduces symptoms of alcohol withdrawal.

E. Acamprosate- weak NMDA receptor antagonist with modest on $GABA_A$ receptor agonist effect. It reduces the relapse & used in Europe for maintenance of abstinence.

F. 5-HT3 antagonist ondansetron and topiramte also have some promoising effects on treating alcoholism.

2. Rehabilitation includes psychotherapy and institutional therapy.

Methanol poisoning:-

Methanol poisoning occurs due to ingestion of methylated spirit. It leads to CNS depression, acidosis and toxic effects of metabolites – formaldehyde and formic acid. Methanol is slowly oxidized & acidosis is slowly developing despite of initial alkaline correction. Thus patient has to be observed for many days in hospital.

1. Hospitalization, nursing care & nutrition.

2. Gastric lavage with activated charcoal.
3. Ethanol 10% IV – 0.6g/kg loading dose followed by 10g/hr in adults.
4. Treatment of acidosis – sodium bicarbonate IV to prevent retinal damage.
5. Treatment of hypokalemia – IV potassium chloride.
6. Folinic acid 1mg/kg (max up to 50mg) to accelerate the metabolism of formate.
7. Use of fomepizole – inhibitor of alcohol dehydrogenase. Also useful in treatment of ethyelence glycol. Rapid, prolonged effect with minimal side effects. 100 mg diluted in 250cc NS given over 45 mins.
8. Hemodialysis – esp. in severe cases.

Ethylene Glycol:-

Antifreeze in automobile radiators and many of industrial substances.

Ethylene glycol ---→Glycoaldehyde -→glycolic A→glycoxalic A → Oxalic A
Alcohol DH Aldehyde DH

Treatment is similar to methanol poisoning with additional use of diuretics, aikalinization and early hemodialysis.

OPIOIDS

These are 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 these receptors

M	κ	δ
Miosis	**D**ysphoria	Spinal analgesia
Analgesia	**M**iosis	Respiratory depression
Respiratory depression	**A**nalgesia	constipation
Constipation	**D**iuresis	
Euphoria	**S**edation	
Sedation		

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 (ORL_1)

Endorphin	μ
Dynorphin	κ
Enkephalin	δ
Nociceptin	N/OFQ

Pharmacokinetics:

- Sufentanil is most potent whereas meperidine (pethidine) and propoxyphene are 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 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. μ and κ mediates both types of analgesia whereas δ receptor is responsible for spinal analgesia.
   - μ receptor opioids have dependence producing actions due to euphoric action. κ receptors mediate psychomimetic effects (dysphoria)
   - 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, alfentanyl and sufentanil can result in truncal rigidity on rapid i.v. infusion. Fentanyl is responsible for post operative muscle rigidity whereas succinylcholine cause post operative muscle pain and fasciculations
   - 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 increases 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
   - These may aggravate bronchoconstriction in asthmatics by releasing histamine
   - Spinal or epidural administration of opioids may result in intense pruritus over lips and torse (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 analgesic and as alternative to methadone for the management of opioid withdrawal.
- Nalbuphine, pentazocine and dezocine are κ agonists with 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

***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
- i.v. morphine is useful in myocardial infarction as well as in acute pulmonary edema
- Codeine is used as an effective cough suppressant
- Loperamide and diphenoxylate can be used for treatment of non infective diarrhea
- Morphine is useful as pre anaesthetic medication whereas highly lipid soluble drugs (Like fentanyl, alfentanil, sufentanil etc) are used as an adjunct to other anaesthetic agents

***Routes of administration*:**

- Morphine can be administered by oral, rectal, i.v., i.m., intrathecal or eoidural routes

- Fentanyl can be applied as transdermal patch or by buccal transmucosal route
- Butorphanol is the only opioid available in nasal formulation

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 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 assessment of neurological function by masking the important papillary signs (causes miosis)
- These drugs used 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

IMPORTANT POINTS ABOUT SPECIFIC AGENTS

- Morphine, hydromorphone and oxymorphone are strong opioid agonists useful as analgesics
- Heroin (diacetylmorphine) is 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 ling t ½, development of dependence and tolerance is very slow making it useful for the treatment of opioid abuse. It is also useful for the therapy of opioid
- Pethidine possess anticholinergic activity (can result in tachycardia) and accumulation of its metabolite, norpethidine can produce seizures
- Levorphanol is similar to morphine in its actions
- Propoxyphene is low efficacy analgesic agent
- Diphenoxylate and its active metabolite difenoxin, as well as loperamide ais useful for diarrhea
- Nalbuphine exhibits ceiling effect to its respiratory depression
- 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
- Tramadol is 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 HT_3 antagonists like ondansetron. At high doses, it can lead to seizures.

OPIOID ANTAGONISTS: Naloxone, naltrexone and nalmefene are potent μ receptor antagonists with significant blocking action at κ and δ receptora also.

- Naloxone is given parenterally (ineffective orally) and is very short acting drug
- Nalmefene is also given parenterally but has a longer half life
- Naltrexone is long acting orally effective opioid antagonist

Action: 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 drug of choice foe acute opioid poisoning but it has to be repeated frequently
- Naltrexone is used as maintenance drug for opioid addicts. It is also used to decrease craving for alcohol in chronic alcoholics.

Sedatives & Hypnotics:-

Sedative is a drug that subdues excitement and calms the subject without inducing sleep, though drowsiness is produced.

Hypnotic is a drug that indues and maintains sleep, similar to normal arousable sleep.

Classification: -

1. **Barbiturates.**
   a. Long acting – Phenobarbitone
   b. Short acting – butobarbitone
   c. Ultra- short acting – thiopentone, methohexitone.
2. **Benzodiazepines**
   a. Hypnotics – Diazepam, flurazepam, nitrazepam, alprazolam, temazepam etc.
   b. Anti – anxiety- diazepam, chloradiazepoxide, oxazepam, lorazepam .
   c. Anti – convulsant – diazepam, lorazepam, clonazepam, clobazem.
3. **Newer non – BZD hypnotics** – zopiclone, zolpidem, zaleplon.
4. **Historical agents** - chloral hydrate, trichlophos, paraldehyde, glutethimide, methylprilone, metahqualone, laudanum, bromide, urethane, sulfonal and meprobamate.
5. **Others**
   a. -Antihistaminics – promethazine, diphenhydramine
   b. -Neuroleptic / antidepressants – chrlopromazine, amitriptyline
   c. -Anticholinergics – hyoscine
   d. -Opioids – morphine, pethidine.
6. Others – Ethanol, general anesthetics, antiepileptics like Phenytoin,
7. Newer different class drugs-
   a. Ramelteon
   b. Buspirone

Barbiturates:-

MOA: - act at GABA – BZD receptor Cl- channel complex. Potentiates gabaminergic inhibition by increasing the duration of chloride channel opening. Other actions:-

1. At high concentrations barbiturates directly increase chloride conductance.
2. Inhibits Ca+ dependent release of neurotransmitters.
3. Depress glutamate induced neuronal depolarization through AMPA channels.
4. At very high conc. Inhibit voltage sensitive NA+ & K+ channel.

Thus; due to these multitude of action; barbiturates are non – selective CNS depressants of varying grades.

Effects : - reversibly depress the activity of all exacitable tissues; most sensitive being CNS.

1. **CNS –** does dependant effects – sedation →sleep →anesthesia→coma.
    a. Sleep – disturbance of REM – NREM cycle. REM, stage 3 & 4 of NREM decreased.
    b. Sedative effect – smaller doses of longer acting agents.
    c. Hypnotic effect – higher doses of shorter acting agents.
    d. No selective anxiolysis, analgesia (Hyperalgesia is seen).
    e. Hangover – dizziness, distortions of mood, irritability and lethargy are seen.
    f. Tolerance is possible.
    g. At skeletal neuromuscular junctions, the blocking effects of both tubocurarine and decamethonium are enhanced during barbiturate anesthesia.
2. Respiration – depressed respiration esp. in higher doses in succession of neurogenic drive, hyperoapneic and hypoxic drive.
3. CVS – slight fall in BP & HR. toxic doses produce depression of vasomotor centre, ganglionic blockade & directly cardiac contractility.

Pharmacokinetics:-

1. Absorption – well absorbed through GIT,
2. Distribution – rapid – redistribution is a property of barbiturates – esp. with lipid soluble thiopentone.
3. Metabolism – in liver. They induce the metabolism of microsomal enzymes.
4. Excretion – long acting are excreted in urine. Alkalinization of urine increases excretion of barbiturates.
5. Increase lipid solubility decrease duration of action, decrease latency to onset of activity, accelerate metabolic degradation, and increase hypnotic potency.

Uses:-

1. Phenobarbitone in epilepsy.
2. Thiopentone in anesthesia.
3. Adjuvants in psychosomatic disorders and narcoanalysis – esp. amylobarbitone, pentobarbitone, thiopentone.
4. Congential non – heamolytic jaundice and kernicterus.
5. Other – sometimes to antagonize unwanted CNS – stimulant effects of various drugs, such as ephedrine, dextroamphetamine, and theophylline, although a preferred approach is adjustment of dosage or substitution of alternative therapy for the primary agents; Phenobarbital still is used to treat hypnosedative withdrawal.

Adverse Drug reaction: -

1. Side effects – nausea, vomiting, diarrhea and lassitude. Hang over, tolerance, dependence, mental confusion, impaired performance and traffic accident.
2. Idiosyncracy – excitement.
3. Anemia – megaloblastic anemia responds to folic acid.
4. Porphyria can be precipitated.
5. Hypersensitivity reaction – rashes, swelling of eyelids, lips etc.
6. Tolerance & dependence – both pharmacodynamic (cellular) and Pharmacokinetic (enzyme induction) tolerance is seen. Both physical and psychological dependence with withdrawal reactions are seen.
7. Paradoxical excitement – barbiturates may cause restlessness, excitement, and even delirium when given in the presence of pain and may worsen a patient's perception of pain.
8. Acute poisoning – fall in BP, respiratory depression and cardiovascular depression are seen. Treatment consist of –
    a. Gastric lavage with activated chardoal.

b. Supportive measures – airway, breathing, circulation (ABC), oxygen etc.
c. **Alkaline dieresis** – wit sodium bicarbonate 1 meq/ kg iv with or without mannitol – esp.in long acting barbiturates.
d. Heamodialysis and peritoneal dialysis – effective for both short & long acting agents.
e. **No specific anti** – dote.

Contraindications: -

a. Acute intermittent porphyria.
b. Liver and kidney disease.
c. Severe pulmonary insuddiciency – emphysema.
d. Obstructive sleep apnoea.

Interactiomns:-

a. Induce metabolism of warfarin, steroid, OC pills, tolbutamide, Griseofulvin, chloramphenicol, theophylline.
b. Additive action with other CNS depressants.
c. Sodium valproate increases plasma concentration.
d. Phenobarbitone competitively inhibits as well as induces Phenytoin and impramine metabolism.
e. Phenobarbitone decreases GIT absorption of Griseofulvin from GIT.

Benzodiazepines:-

MOA : - in GABAA receptor, the binding sites for GABA are located between adjacent $\square_1$ and $\square_2$ subunits, and the binding pocket for benzodiazepines (the BZ site of the $GABA_A$ receptor) is between a_1 and the g_2 subunit. Zolpidem, zaleplon, and eszopiclone bind more selectively because these drugs interact only with $GABA_A$- receptor isoforms that contain a_1 subunits.

GABA receptors: -

	$GABA_A$	$GABA_B$	$GABA_C$
	Cl-	K+	
Ion channel		Baclofen	
Selective antagonist	Bicucculine (competitive) Picrotoxin (Non – competitive) Flumazenil – Competitive at BZD site	Saclofen phaclofen	
Inverse agonist	DMCM – beta carboline		
Other drugs	Alcohol, GA gases, etomidate, propofol, barbiturates, BZD & non- BZD hypotics, Antiepileptics - gabapentin, vigabatrin, ivermectiv		

	Benzodiazepines	Barbiturates

MOA	1. Increase frequency of chloride channel. 2. Act at specific BZD site. 3. Need GABA for their action 4. No other different types MOA. 5. Specific CNS depressant	1. Increase duration of opening of Cl-channel. 2. Act at side different than BZD site on GABAA receptor 3. No need of GABA for their action. 4. Other different types of actions as well 5. Non- specific CNS Depressant.
Sleep	1. Less deformation of sleep architecture. 2. Less rebound phenomenon	1. Deformation of sleep architecture. 2. More rebound Phenomenon.
Selective Anxiolysis	Present	Absent.
Paradoxical excitement	-	Present–can caus hyperalgesia, Excitement, delirium in presence
		Of pain
Abuse liability	Low	High
Tolerance	Low	High
General safety	• Wide safety margin. • Less RS & CVS depression at hypnotic doses. • Intoxication only if used with other CNS depressants like alcohol. • Antagonist available-flumazenil	• Low safety margin • Marked RS & CVS depressions • Intoxication often Possible • No specific antidote available.
PK properties	Enzyme induction is less	Marked enzyme induction & drug – drug interactions.
Uses	Anxiolytic, skeletal muscle depressants, psychiatric uses, anti-epileptic, GA etc.	Congential hyperbilirubinemia, Narcoanalysis and psychoanalysis, GA & anti – epileptic
Side effects	Mild tolerated very well.	Many

Effects: - reversibly depress the activity of all excitable tissues; most sensitive being CNS.

1. CNS –

- Does not produce depression equivalent to barbiturates. Selective areas of brain are preferentially affected.

- Sleep - No disturbance of REM – NREM cycle. REM, stage 3 & 4 of NREM decreased while stage 2 is increased. Decrease the latency time, no effect on nocturnal secretion of GH, prolactin & LH and very less hangover symptoms.
- Selective anxiolytic effect is seen.
- Tolerance is possible ; though less likely than barbiturates.
- Some drugs like clonazebam, clobazem, diazepam, midazolam are having anti – epileptic properties.
- Skeletal muscle relaxant property.

2. Respiration – do not depress respiration except in persons consumed alcohol or other with obstructive sleep apnea etc airway disorders.
3. GIT – may improve anxiety related functional disorders.
4. CVS – slight fall in BP & HR.

Pharmacokinetic properties : - marked difference is attributable to changes in lipid solubility

1. Absorption : - rapid for some while slow for others.
2. Distribution : - widely distributed. Flurazepam – 10% while diazepam 99% protein bound.
3. Metabolism: - in liver by dealkylation and hydroxylation. Some exhibit enterohepatic circulation.
4. Elimination:- elimination half life may not be good predictor of duration of action due to wide distribution and presence of many active metabolites.
5. Drug-drug interactions :-
    a. Synergistic with other CNS depressants – barbiturates, alcohol.
    b. Drug displacement reactions are not significant.
    c. Ketoconazole, erythromycin etc. inihibitors of CYP3A4 may increase the drug concentrations.

Individual drugs:-

A. Slow elimation of parent drug or active metabolite – flurazepam
B. Relatively slow elimination but marked redistribution – diazepam, nitrazepam
C. Relatively rapid elimination and marked redistribution – alprazolam temazepam
D. Ultrarapid elimination – Triazolam, Midazolam.

Drug – Long acting-	Indication
A. Flurazepam B. Diazepam C. Nitrazepam	Chronic insomnia, short term insomnia Frequent nocturnal awakening, night before operation
Short acting	
A. Alprazolam, B. Temazepam, C. Triazolam	Individuals who react unfavorably to unfamiliar surroundings or unusual timings of sleep, sleep onset difficulties.

Indications :-

A. As hypnotic – non –BZD hypnotics like zolpidem, zopiclone etc. are drugs of choice than older hypnotics.
B. Anxiolytic and daytime sleepiness
C. Anticonvulsant – for status epilepticus, febrile seizures, tetanus etc.
D. Centrally acting skeletal muscle relaxants – in conditions like cerebral palsy, torticolis, tetanus

E. As preanesthetic medication
F. Before ECT – calming, amnestic, analgesic, skeletal muscle relaxant properties and relatively safety margin.
G. Alcohol withdrawal
H. Along with analgesics, NSAIDs, spasmolytics etc.

Side effects:-

- Dizziness, vertigo, ataxia, incoordination, disorientation, amnesia etc.

- Hangover is less common

- Weakness, blurring of vision, dry mouth.

- Impairment of judgement.

- Tolerance develops gradually.

- Cross tolerance to alcohol & other CNS depressants.

- Dependence liability is low and drug seeking behavior is not seen.

Flumazenil:- competitive antagonist at the BZD receptor for agonists as well as inverse agonists abolishses hypnogenic, psychomotor, cognitive effects of EEG.

Low bioavailability and not used orally, given IV – undergoes rapid metabolism. Tl/2 = 2 hrs.

Uses –

- To reverse BZD anesthesia
- In BZD overdose/ poisoning

Non-BZD Hypnotics:-

A. Zopiclone – agonist at subtype of BZD receptor. No alteration of REM sleep and increase in stage 3 of NREM. No disturbance of sleep architecture, hangover or withdrwal reactions on disocontinuation seen. Some next day morning impairment is seen. Mainly used to wean off BZDs nin chronic insomnia and short term use of insomnia. Metallic taste, psychological disturbances and dry mouth are rare side effects.
B. Zolpidem – acts on α1 subunit of BZD receptor – hypnotic effects pronounced. Metabolized in liver. Has all the advantages non –BZD hypnotic over BZD. One of most commonly prescribed hypnotic.
C. Zaleplon – shortest duration acting at α1 subunit of BZD receptor.Rapidly absorbed, 70% destroyed in I pass metabolism. Effective in only sleep onset insomnia; does not prolong sleep duration.
D. Advantages of newer NON- BZD drugs:-
- Realative less distortion of sleep architecture.
- Minimal daytime sleepiness or sedation.
- No / little rebound phenomenon.
- Low abuse liability
- Safety in overdose.
- Flumazenil can antagonize – zolpidem.

Newer agents –

1. **Melatonin** – for **Jet-lag**. Beneficial in shift workers to hasten the sleep, those with delayed sleep, improved sleep quality in elderly, helps to wean off the BZDs on chronic insomniacs. Lowering of

seizure threshold and psychiatric changes are blamed. Also marketed for disturbed biorhythum and degenerative disorders.

2. **Ramelteon –** agonist at $MT_1$and MT_2 melatonin receptors located in the suprachiasmatic nuclei of the brain for sleep onset insomnia.

Older agents:-

1. **Paraldehyde –** given as retention enema in patients with olive oil – tissue irritant and cannot be given orally. **Used in alcohol withdrawal – esp. delirium tremons, status epilepticus in children.**Acidosis, gastritis, fatty changes in liver are side effect.
2. **Ethchlorvynol –** older skeletal muscle relaxant with hypnotic properties similar to barbiturates and anti-epileptic properties.
3. **Meprobamate – gastric bezoars** is side effect.

Management of Insomnia –

1. **Short term insomnia –** for few days.
2. **Intermediate insomnia-** counseling, hypnotic in smallest possible dose, skin I dose after 2 nights of comfortable sleep followed by gradual discontinuation.
3. **Chronic insomnia –** psychotherapy, behavirol therapy and gradual discontinuation.

Non-pharmacological treatment –

- Avoid day time naps.
- Take moderate exercise – increase stage IV of NREM.
- Avoid alcohol, tobacco, caffeinated +-beverages at bedtime.
- Regular sleep – establish sleeping and awakening conditions.
- Don't use bed for eating reading TV watching.
- Change of mattress.
- Elderly should avoid night time fluid intake,
- Take warm milk- contains tryptophan – precursor for melatonin.
- Training on relaxation, meditation and yoga.

Drugs causing insomnia: -

I. **CNS stimulants –ephedrine, amhedrine, caffeine, nicotine, methyl phenidate.**
II. **Anorexiants and nasal decongestants.**
III. **Others –** bupropion, MAOI, SSRI, L-dopa, amantidine, Chloroquine, metronidazole, flouroquinolones, Diuretics and systermic steroids.

SK Muscle Relaxants:-

A. Peripherally acting:-

1. Non – depolarizing:

a. Longacting – d- tubocurarine, pancuronium, doxacurium, pipecurium
b. Intermediate acting – Vecuronium, atracuium, cistracurium, Rocuronium & rapacuronium.
c. Short acting – Mivacurium

2. **Depolorizing:**
   a. Succinylcholine, suxamethonium & Decamethonium

MOA:-

1. Competitive Blockers / Non-depolarizing blockers-has affinity but no intrinsic activity.
    a. Block N_M type of nicotinic receptors at NM junction. Normally binding of Ach with Nm receptor leads to opening of Na+ channel.
    b. Also block the presynaptic nicotinic receptors (Autoreceptors – excitatory in nature) – thus further release of ach is slowly reduced. "Fade phenomenon is seen".
2. Non-Competitive /Depolarizing block: succinylcholine has some intrinsic activity like Ach – first stimulation (thus fasciculations are seen) followed by persistent depolarizing block. Later Na+ channel associated with NMJ gets inactivated. Thus even with further Ach release – no muscle contraction. Flaccid paralysis occurs.

Sr. No		Competitive blockers – d-TC	Depolarizing blockers – Sch
1	Paralysis in mam	Flaccid	Fasciculation – flaccid
2	MOA	Ach antagonists	Ach PA
3	Human neonates	More sensitive	More resistant
4	Tetanic stimulation during partial block	Poorly sustained contraction	Well sustained contraction
5	Post- tetanic potentiation	Present	Absent
6	Neostigmine	Antagonizes block	No effect
7	Train of Four Phenomenon (Ratio)	< 1 (suggests fade phenomenon)	= 1 (no fade phenomenon)
8	Fade phenomenon	Present	Absent
9	Ether ansthesia	Synergistic	No effect
10	Order of paralysis	Fingers, eyes – limbs – neck – face & trunk	Neck, limbs – face, trunk – respiratory
11	Effect of lowering temperature	Reduces block	Intensifies block

Actions

1. Skeletal muscle Relaxant feect – fade followed by flacdid paralysis is seen with competitive blockers while fasciculation followed by flaccid paralysis is feature of non- competitive blockers.
2. Autonomic ganglia – some degree of ganglionic blockade is seen.
3. Histamine release- d- TC release histamine from mast cells – also by Sch, mivacuronium & to lesser extent by long acting agents.
4. CVS – Hypotension – due to histamine release, ganglionic blockade & reduced venous return. HR increases due to vagal blockade. Newer agents have very less effects on BP & HR. Sch causes bradycardia.
5. GIT – post – operative paralytic ileus.

1. d-TC = prominent histamine release, ganglionic blockade & CVS action – not used now.

2. Sch = muscle fasciculations, decrease BP & HR, arrhythmia, histamine release & K+ efflux From muscles →hyperkalemia are the side effects. Used for tracheal intubations within 5 mins. Risky in children (require higher dose, hyperkalemia & arrhythmia) & elderly (risk of regurgitation & aspiration)
3. Pancuronium – good CVS stability – little ganglionic blockade, bronchospasm or arrhythmias. Longer duration of action –requires reversal. Used for prolonged operations like neurosurgery.
4. Pipecuronium – Slow onset & longer duration of action for porolonged surgeries. Elimination through both kidney & liver
5. Vecuronium – short duration for action – rapid distribution & Faster metabolism. Most commonly used SKMR for routine surgery .
6. Atracurium – shorter actng ; no reversal required – " Hoffman elimination" & degradation by cholinesterases. Safe in liver, Kidney disease patients. Hypotension due to histamine release may occur.
7. Cisatracurium – no degradation by cholinesterases. Safe in liver, Kidney disease patients. No hypotension due to No histamine release.
8. Rocuronium – rpid onset & intermediate duration, CVS safety. Versatile action - can be used for tracheal intubation & also as Skeletal muscle relaxant – Fascilitates mechanical ventilation in ICUs. Mild vagolytic action increases HR. Precise onset of action & no need of reversal.

9. Mivacurium – shortest acting SKMR while Doxacurium is longest acting.

Drug interactions: -

1. GA – potentiate competitive blockers – either, isoflurance potentiate most & Nitrous oxide to least extent.
2. Flourinated anesthetics prediscope to Phase II blockade by Sch.
3. Maligant hyperthermia is more common with sch & halothane or isoflourance used concomitantly.
4. Amnticholinesterase – reverse competitive blockers. Neostigmine is used.
5. Antibiotics – Aminoglycosides reduce Ach release – Potentiate block.
6. CCBs - Verapamil – potentiate SMKRs.
7. Diuretics – hypokalemia can enhance block.

Uses –

1. Adjuvant to GA – adequate muscle relaxation for surgery.
2. Assisted ventilation in ICU patients
3. Convulsion & trauma – ECT Prophylaxis
4. Severe cases of Tetanus & status epilepticus.

Directly acting agents: -

1. Dantrolene – acts on RyR – Ryanodine receptors of calcium channel on skeletal muscle & prevents it blockade. Intracellular release of calcium which is required for exciation contraction coupling is blocked. Used for malignant hyperthermia, spasticity due to upper motor neuron lesion, cerebol palsy & multiple sclerosis. Some benefit in neurolept malignant syndrome as well.
2. Quinine – for nocturnal leg cramps.

Centrally acting agent : uses

- Baclofen – $GABA_B$ receptor agonist
- BZD – diazepam
- Tizanidine – central $\alpha 2$ agonist.
- Mephensine group of drugs – Mepahensine, carisoprodol, Chlorzoxazone, chlormezanone & methocarbamol
- Others – Eperisone, Tolperisone, Thiocholcicoside

1. Acute muscle spasma – overstreching of muscle, fibrositis, rheumatic disorder & sparin.
2. Torticollis, lumbago, backache, neuralgias
3. Anxiety & tension
4. Spastic neurological disease
5. Tetanus
6. ECT
7. Orthopedic manipulations.

Anti- epileptics:-

1. Epilepsy :- group of disorders of seizures, convulsions, other sensory or psychiatric phenomenon.
2. Convulsion - motor manifestation of seizure.
3. Seizure - type of abnormal activity of neuron or group of neurons.
4. Types of epilepsies
    1. Generalized -
        a. Generalized tonic clonic
        b. Absence seizures
        c. Atonic seizures
        d. Myoclonic seizures
        e. Infantile spasms
    2. Partial seizures
        a. Simple partial
        b. Complex partial
        c. Simple or complex with secondary generalization.

Experimental animal models :- due to lack of perfect models, older models which shed light the process of epileptogenesis are still used.

a. Maximal electroshock seizures – maximal electric shock is given to produce condition like seizure
b. PTZ models – injection of PTZ (pentylenetetrazole) in rats produce seizures mimicking absence seizures.
c. Chronic focal seizures – focal seizures due to applications at particular site of brain of an irritant – alumina craem.
d. Kindled seizures – brief burst of weak electrical impulses will produce chronic seizures.

Classification of anti – epileptics :-

Selection of antiepileptic Drugs:-			
Primary generalized tonic-clonic	**Partial**	**Absence**	**Atypical Absence, Myoclonic, Atonic**
First - Line			
Valproic acid Lamotrigine Topiramate	Carbamazepine Phenytoin Lamotrigine Oxcarbazepine Levetiracetam	Valproic acid Ethosuximide	Valproic acid Lamotrigine Topiramate
Alternatives			
Zonisamide[b] Phenytoin Carbamazepine Oxcarbazepine Phenobarbital Primidone Felbamate	Valproic acid Topiramate[b] Tiagabine[b] Zonisamide [b] Gabapentin [b] Phenobarbital Primidone	Lamotrigine Clonazepam	Clonazepam Felbamate

	Felbamate		

[b]As adjunctive therapy. [α] includes simple partial, complex partial, and secondarily generalized seizures

Drugs	Plasma concentration
Phenobarbitone	10-30 μg/ml
Phenytoin	10-20
Carbamazepine	5-10
Valproate, ehtosuccimide, Clonazepam	Levels poorly correlate.

Classification based on structure:-

1. Barbiturates - phenobarbitone, primidone
2. Hydantoin – phenytoin, phosphenytoin.
3. Iminostilbene – carbamazepine, oxcarbamazepine.
4. Succimide – ethosuccimide
5. Aliphatic carboxylic acid – valproate and divalproex.
6. BZDs – diazepam, clonazepam, lorazepam, clobazem
7. Newer drugs – lamotrigine, gabapentine, vigabatrin, topiramate, tiagabine, zonisamide, levetiracetam
8. Others – acetazolamide, trimethadione and phenacemide – not used.
9. **Newer drugs – lacosamide (enhances slow sodium channel inactivation), levetiracetam- SV2A synaptic vesicle protein, Rufinamide – for lennox gastuat syndrome & trimethadione – first oxazolidinedione.**

Classification based on mechanism of action:-

a. Prolongation of sodium channel activation – phenytoin. Phenobarbitone, valproate, lamotrigine, topiramate and zonisamide
b. Facilitation of GABA mediated chloride channel opening – barbiturate, benzodiazepines, vigabatrin, valproate, gabapentin and tiagabine.
c. Inhibiton of T type of ca+2 currents – ethosuccimide, valpraoate, trimethadione.
d. NMDA receptor antagonist – felbamate.
e. AMPA receptor antagonist – phenobarbitone, Topiratmate
f. Carbonic anhydrase inhibitor – Acetazolamide, zonisamide

Wide spectrum AED – phenobarbitone, valproate, lamotrigine and topiramate.

Phenobarbitone-

- Barbiturate with higher anti –convulsant :hypnotic dose.
- GABA fascillitatory, GABAmimetic, anti –glutamate, Ca+ entry inhibiting etc. many effects – generalized CNS depressant → broad spectrum anticonvulsant effect.
- Sedation is major drawback. Rashes, megaloblastic anemia, osteomalacia etc. are other side effects.
- Uses:- GTS, partial seizures – simple and complex & status epilepticus.

Primidone-

- In liver converted to phenobarbitone and PEMA – active metabolite. Used as adjuvant to phenytoin or carbamazepine rarely.

- Few cases of myoclonic epilepsy respond.
- ADRs – similar to phenobarbitone with additional anemia, psychiatric reactions and lymphadenopathy.

Phenytoin :-

- Not a CNS depressant : though sonie sedation is seen.
- Blocks sodium channel in inactivated state – a phase which governs repolarization phase. (similar to local anesthetics – which block in inactivated state to prolong repolarization and in contrast to anti – arrhythmic which close in open state).

- Does not interfere with kinding as seen with phenobarbitone.
- PK-
    - Absorption – slow by oral route, BA is crucial point for monitoring treatment. Not advisable to change brand of drug.
    - Wide distribution and 80 – 90% plasma protein bound – Drug displacement reactions are common.
    - Kinetics is capacity limited – first follow first order kinetics which changes to zero order kinetics at higher doses →small changes in dose leadsd to larger change in concentrations.
    - Metabolized in liver & eliminated in kidney – 1 monthly monitorining of dose is required.
- ADRS –
    - At therapeutic levels
        - Gum hypertrophy – commonest (20%) overgrowth of gingival collagen. Oral hygiene can prevent it.
        - Hirsuitism, coarsening of facial features – not started in young girls.
        - Acne
        - Hypersensitivity reactions – rashes, DLE, lymphadenopathy- pseudolymphoma, neutropeia – may require discontinuation of therapy.
        - Megaloblastic anemia – due to increase in excertion and decrease in absorption of folate.
        - Hyperglycemia – inhibit insulin release.
        - Osteomalacia – desensitization of vitamin D targets & interference with calcium metabolism.
        - Foetal – hydantoin syndrome – cleft lip, cleft palate, hare lip and microcephaly are important features.
    - At toxic levels –
        - Cerebellar & vestibular manifestations – ataxia, diplopia, vertigo, nystagmus
        - Drowsiness, mental confusion, behavioral alteration, hallucinations
        - Epigastric pain, nausea and vomiting – minized by taking drugs with meals .
        - Fall in BP and cardiac arrhythmias – with IV injection.

- Drug interactions:-
    - CBZ & Phe induce metabolism of each other
    - Valproate displaces from protein binding\
    - Chloramphenicol, INH, cimitedine, warfarin – inhibit metabolism & toxicity can be seen.
    - Inhibits warfarin metabolism
    - Induces metabolism of OC pills, digoxin, doxycycline and theophyline.
- Uses:-
    - Epilepsies – GTCS, status epilepticus.
    - Trigeminal Neuralgia.
    - Cardiac arrhythmias.

Phosphenytoin - water soluble congener of phenytoin. Converted to phenytoin in body (can be given in NS & DNS – phenytoin cannot be given in glucose). Mainly used for status epilepticus.

Carbamazepine –

- Carbamazepin modifies maximal elextroshock seizures as well as raises threshold for PTZ seizure.
- Antimaniac effects – like lithium ; antidiuretic effect & useful in neuralgias.
- PK – active metabolites , inducer of CYP enzymes & Autoinduction is seen.
- ADRs – does related neurotoxicity – sedation, dizziness, vertigo, diplopia and ataxia. Acute intoxication is associated with coma,CVS Collapse and convulsions.
- Hypesensitivity – lupus like syndrome, hepatitis, agranulocytosis and aplastic anemia.
- Water retention and hyponatremia – enhances ADH action.
- Uses – trigeminal and related neuralgias, complex partial seizures – most effective drug.GTCS & SPS – I line drug and MDP, acute mania and bipolar disorders – alternative to lithium.

Oxcabazepine :-

- Newer congener which is converted to active metabolite – better tolerated than CBZ.
- Autoinduction, enzyme induction, toxic effects due to arenoxide metabolite of CBZ are less; but hyponatremia can be more.

Trimethadione:- reduces PTZ currents – reduces T type of thalamic Ca+2 current – useful in absence seizure. Methadione, paramethadione & diemthadione (t1/2 = 246 hrs). sedatio is the main side effect .

Ethosuccimide:-

- Effective only in absence seizures – raises PTZ induced seizures than MES.

MES or kindling. Aplastic anemia, GIT intolerance & skin rash are side effects.

Valproate

- Broad spectrum AED which raise threshold of PTZ induced seizures than MES.
- Effective in partial, GTCS as well as absence seizures – phenytoin like na+ prolongation of inactivation, inhibit T type of Ca+ current as well as augmentation of GABA mediated inhibition.
- ADRs-
  - Generally low, anorexia, nausea, heart burn are common;
  - Drowsniess, ataxia and tramor are dose related ADRs;
  - Rashes & thrombocytopenia represent hypersensitivity reactions.
  - Alopecia, fulminant hepatitis can be seen. Pancreatitis can be seen. PCOD and menstrual irregularities.
  - GIT intolerance, wt gain, hypermmonemia etc can be seen.
  - Spina bifida & other neural tube defects are common if the drug is used in pregnancy.
- Uses - drug of choice of absence seizures, alternative for GTCS, SPS & CPS; myoclonic and atonic seizures;mania & bipolar disorders and migraine prophylaxia.

Divalproex:- it is co – ordination compound of valproic acid and sodium valproate in 1:1 ratio with similar efficacy and well tolerated nature.

BZDs: clonazepam blocks PTZ induced seizures with little sedation. Thus it is primarly employed in the treatment of absence seizurs, as adjuvant to myoclonic seizures & akinetic seizures. They may afford some benefit in infantile spasms.

Clobazem:- sedation and psychomotor retardation are less prominent. Used as adjuvant to other AED like phenytoin in treatment of refractory epilepsy.

Diazepam :- used for emergency control of status epilepticus, tetanus, eclampsia etc. it can be given by **rectal route of administration for febrile seizures in children.**

Lamotrigine :- broad spectrum AED with multitude of action like carbamazepine and further also inhibits release of excitatory neurotransmitters – aspartate & glutamate. It is preferred as add on therapy to refractory partial or GTCS; though effective as monotherapy. Absence, myoclonic and akinetic epilepsy is also treated effectively. ADRs –sleepiness, dizziness, diplopia, ataxia and vomiting.

Gabapentin – GABA derivative which increases GABA release, modifies PTZ &MES seizures. Used as add on to drugs of partial seizures with or without generalization.

Other uses – **first line for diabetic & other neuropathies, postherpatic neuralgia & prophylactic in migraine.**

Vigabatrin:- inhibitor of GABA transaminase enzyme which degrades GABA. The drawbacks are visual side effects, pyschosis, depression &alteration of behavioral changes.

Topiramate:- weak carbonic anhydrase inhibitor, prolongs sodium channel in inactivated state, antagonism of glutamate receptor as well as GABA potentiation. Approved for prophylaxis of migraine as well as supplementing primary antiepileptic drug in refactory SPS, CPS and GTCS. Sedation paresthesia, fatigue, renal stones, wt loss & glaucoma etc can be seen.

Tiagabin:- depressed GABA transporter – GATI & thus reuptake of GABA →increase in synaptic concentration of GABA. It is added as add on therapy for partial seizures with or without secondary generalization.

Zonisamide :- acetazolamide derivative – modifies MES & kindling phenomenon. It is approved as add – on for refactory partial epilepsy.

Levetiracetam - suppresses kindling without effect on MES or PTZ seizures. Used as adjuvant medication in refractory partial seizures with or without secondary generalization.

Rufinamide:- indicated in lennoux Gastaut syndrome & resistant types

Lacosamide :- slow inhibition of sodium current. Indicated for partial epilepsy with or without II generalization above 16 yrs of age.

Drugs which can induce seizures-

1. Lignocaine, tramadol, pethidine
2. GA – Ether, halothane, ketamine & isoflurance
3. Phenothiazine anti-psychotics, few antihistaminics – haloperidol & some anti – depressants
4. Alkylating agents – busulfan, chlorambucil
5. Antimalarials
6. Radiocontrast
7. CNS stimulants – ephedrine, amphetamine, terbutaline, cocaine and aminophylline, theophylline.
8. Antibacterials – penicillin, INH, imipenam.
9. Methotrexate, cyclosporine, muromonab OkT3,
10. Alcohol or other substance withdrawal.

Drugs used for the management of status epilepticus:-

1. Lorazepam
2. Phosphenytoin

3. Valproate
4. Phenobarbital
5. Propofol
6. Midazolam
7. pentobarbital

Anti –parkinsonian Drug:-

Classification:-

1. Drugs affecting brain dopaminergic system
    a. Dopamine precursor – levo- dopa, Etilevodopa,a Droxidopa, Melevodopa
    b. Peripheral DC inhibitor – carbidopa, benserazide
    c. Dopaminergic agonists
        i. Ergot derivatives – bromocriptine, cabergoline, pergolide
        ii. Non-ergot derivatives – Ropinirole, pramipexol & Rotigotine
    d. MAO -B inhibitors - selegelline, Rasagelline, Ladostigil, lazabemide, mofegiline,pargyline.
    e. COMT inhibitor – entacapone, tolcapone
    f. Dopamine facilitator –amantidine
2. Drug affecting brain cholinergic system
    a. Central anticholinergics – trihexyphenydyl, procyclidine, biperiden
    b. Antihistaminics – orphenadrine, promethazine.

Levodopa:-

- Inactive precursor of dopamine acts on brain (1 – 2% of remaining dose) and peripheral side (remaining portion of dose).
- CNS –
    - No effect on normal individuals.
    - Hypokinesia, rigidity followed by tremor followed by secondary features like gait and posture, speech, facial expression, mood & self care improve.
    - Excitement, frank psychosis & 'general alerting behaviour' in some individuals.
    - Sexual excitement, non – specifica awakening in hepatic coma etc seen.
    - D1 & D5 receptors – excitatory – increase C_{AMP}. GPCR.
    - D2 like D2, D3 & D4 – inhibitory – inhibit adenyl cyclase, opening K+ channels.
- CVS- tachycardia – acts on β-adrenergic receptors. Postural hypotension due to central action- NA & DA decrease the sympathetic tone. Tolerance develops.
- CTZ – lies out of blood brain barrier – elicits nausea & vomiting. Tolerance develops.
- Endocrine – inhibit prolactin release and on somatotrophe to increase GH.
- PK – rapidly absorbed from GIT, undergoes high first pass metabolism. Delay in Gastric emptying will reduce the amount reaching to brain.
- Amino acids compete for absorption.
- Pyridoxal increases the rate of metabolism of DA.

ADR :-

A. At initiation of therapy – minimized by starting at low dose. Tolerance develops.
   a. Alteration in taste
   b. Postual hypotension
   c. Cardiac arrhythmia
   d. Exacerbation of angina.

B. After prolonged therapy –
   a. Abnormal movements – facial tics, grimacing, tounge thrusting, choreoathetoid movements. No tolerance develops, dose reduction will reduce severity of symptoms. May be disabling more than disease.
   b. Behavioral effects – depression, mania, anxiety, nightmares, mental confusion, frank psychosis.
   c. Fluctuations of motor response-
      i. End of dose / wearing off – deterioration seen as plasma concentrations fall down.
      ii. Switches / on – off phenomenon – rapid fluctuation seen with changes in plasma concentration. Abnormal movements may add to worsening even in 'ON' phase – sr.conc. are sufficient to reduce PD symptoms. Patient is almost disabled in 'OFF' phase – as sr. conc. Of levodopa fall. Increase in dose frequency & decrease in dose may help it.
      iii. Caution in elederly with IHD, CAD, stroke, Psychosis, hepatic or renal disease.

Drug interactions:-

- B6 – pyridoxine – reduces therapeutic efficacy by accelerating metabolism.
- Phenothiazines, butyrophenones, metoclopramide reverse its effects by blocking DA receptors.
- Domeperidone blocks levodopa induced nausea & vomiting without affecting therapeutic efficacy.
- Reserpine reverses by preventing DA entry into synaptic vesicles.
- Non- selective MAOI – hypertensive crisis can be precipitated – no degradation of NA & DA
- Antihypertensives – postural hypotension can be aggravated.
- Atropine other anticholinergics – additive antiparkinsonian effect ; but delay levodopa absorption.

Peripheral dopa Decarboxylase inhibitors:-

e.g. carbidopa & benserazide – reduce the peripheral metabolism of levodopa & make more of it available to brain. Themselves do not cross to blood brain barrier have no effect on brain DA levels.

Benefits of combination:

→ Plasma half life prolonged & dose can be reduced to ¼ th.

→ systemic conc. Of DA reduced – systemic side effects reduced.

→ cardiac complications reduced.

→ pyridoxine reversal does not occur – B6 can be given.

→ 'On – off phenomenon' is reduced.

→ degree of improvement may be higher – some non-responders may respond.

Problems no resolved / accentuated –

→ Involuntary movements

→ Behavioral symptoms

→ Postural hypotension.

Red / Pink	
Daunorubicin or doxorubicin	Heparin
Ibuprofen	Methyldopa
Phenothiazines	Phenytoin
Phenylbutazone	Rifampin
Salicylates	Senna

Amantidine – antiviral influenza A2 which is rapidly acting lower efficacy drug used in milder cases, or in short courses to supplement levodopa for advanced cases. Originally introduced as an antiviral agent, it was appreciated to also have antiparkinsonian effect that are now thought to be due to NMDA – receptor antagonism. While some physicians use amantadine in patients with early disease for its mild symptomatic effects, it is most widely used as an antidyskinesis agent in patients with advanced PD. Indeed, it is the only oral agent that has been demonstrated in controlled studies to reduce dyskinesia while improving parkinsonian features, although benefits may be relatively transient. Tolerance may develop. In advanced cases serves to suppress motor fluctuations and abnormal movements.

Livedo reticularis and edema of ankles are side effects.

Centrally acting anticholinergics- they act by reducing unbalanced cholinergic excessive activity in brain.

Enzymes Inhibits	AChE	AChE, BuChE	AChE	AChE, BuChE
Mechanism	Noncompetitive	Noncompetitive	Competitive	Noncompetitive
Typical Maintenance dose	10 mg once daily	9.5 mg/24h (transdermal)	8-12 mg twice daily (immediate – release)	20 mg, four times daily
		3-6 mg twice daily (oral)	16-24 mg / day (extended – release)	
FDA- approved Indications	Mild –severe AD	Mild- moderate AD,	Mild – moderate AD	Mild – Moderate AD
		Mild – moderate PDD[d]		
Metabolism[e]	CYP2D6, CYP3A4	Esterases	CYP2D6, CYP3A4	CYPIA2

Tremor f/b rigidly f/b hypokinesia are improved. Sialorrhea is improved due to peripheral only class effective in **Drug induced parkinsonism**

Other Neurodegenerative disease :-

1. **Alzheimer's disease.**
   - **a.** Memantine – NMDA receptor antagonist
   - **b.** Anti – cholinesterase – tacrine- not used due to hepatotoxicity. Galantamine, Rivastigmine are others. Commonest used – donepezil – less peripheral effects & longer acting – BD dosage.
   - **c.** Nootropics – agents which selectively increase the cognition without affecting other functions of cerebral cortex e.g.piracetam & pyrinitol
   - **d.** Codergocrine – dinydroergotoxine
   - **e.** Gingkgo – Biloda
   - **f.** Others – non-approved – ApoE4 injections, Estrogen, NSAIDs, statins etc.

Mematine is used either as an adjunct or an alternative to cholinesterase inhibitors in AD, and is also commonly used to treat other neurodegenerative dementias. Mematine is a noncompetitive antagonist of the NMDA – type glutamate receptor. It interacts with the Mg^{2+} binding site of the channel to prevent excessive activation while sparing normal function. Memantine significantly reduces the rate of clinical deterioration in patients with moderate to severe AD. Whether this is due to a true disease – modifying effect, possibly

reduced excitotoxicity, or to a symptomatic effect of the drug is unclear. Adverse effects of memantine include headache or dizziness, but are usually mild and reversible. The drug is excreted by the kidneys, and dosage should be reduced in patients with severe renal impairment.

2. **Restless leg syndrome – pramipaxole, ropinirole**

1. Dopamine agonists such as ropinirole, pramipexole, carbidopa/levodopa or pergolide. Rotigotine is delivered by a transdermal patch for early stage parkinson's disease; it is not yet approved for RLS in the US. The Neupro patch has been withdrawn from the US market due to problems with the medication delivery system. Rotigotine is for not only advanced stage parkinson's disease but also for RLS. There are, however, issues with the use of dopamine agonists. Dopamine agonists have caused augmentation. This is a medical condition where the drug itself causes symptoms to increase in severity and/or occur earlier in the day. Dopamine agonists may also cause rebound, when symptoms increases as the drug wears off. In may cases, the longer dopamine agonists are used the higher the risk os augmentation and rebound as well as the severity of the symptoms.
2. Gabapentin enacarbil, a non-dopaminergic treatment for moderate to severe primary RLS.
3. Opioids particularly methadone is a particularly effective treatment for the symptoms of severe RLS and does not have the negative side – effects (augmentation and rebounding) of dopamine agonist
4. Benzodiazepines, such as diazepam, which often in addition to symptom relief assist in staying asleep and reducing awakenings from the movements
5. Anticonvulsants, such as carbamazepine, help people who experience the RLS sensation as painful.

3. **Huntingtons disease – Haloperidol**
4. **Amyotrophic lateral sclerosis- Riluzole – NMDA antagonis.**
5. **Multiple sclerosis**
   a. Treatment – methylprednisolone
   b. Prophylaxis
      i. Glatiramare acetate
      ii. Immunosuppressants – Azathioprine etc.
      iii. Natalizumab – anti- intergrin antibody
      iv. Interfereon – β- for relapsing – remitting type.
   c. Symptomatic therapy

6. Essential tremors – beta blockers

Antipsychoits:-

Classification :-

1. **Phenothiazines**
   a. Aliphatic chain – chlorpromazine (CPZ), trifluopromazine
   b. Piperadine chain – thioridazine, mesoridazine
   c. Piperazine side chain – trifluoperazine, fluphenazine
2. **Butyrophenones** – haloperidol, trifluoperazine, fluphenazine
3. **Thioxanthens** – Flupenthixol
4. Other heterocyclics – pimozide, Loxapine
5. Atypical neuroleptics – clozapine, olanzapine, quetiapine, aripiprazole, ziprasidone.

Pharmacological action:-

1. **CNS –**

a. **Normal person -** psychomotor slowing, emotional quitening, paucity of thought & indifference to surrounding – called as "neuroleptic" effect. (previously also **called as Major tranquillizer** – a drug which reduces mental tension, produces calmness without inducing sleep or depressing mental faculties – e.g. CPZ, reserprine. Minor tranuillizers were sedative & hypnotics).
b. **Psychotic**

i. Reduces irrational behavior, calms patient and relives anxiety.
ii. Aliphatic and piperazine side chain compounds have more sedation, less potency & tolerance liability, piperazine & butyrophenones are more potent & produce side effects like EPR & hyperprolactinemia.
iii. Performance, intelligence are unaffected while vigilance is impaired.
iv. Extra-Pyaramidal reaction – correlate with potency of compound & least with thioridazine, clozapin and other atypical anti- psychotics.
v. CPZ lowers seizure threshold – effect less with piperazine side chain compounds.
vi. Temperature control knocked off – polikilothermia.
vii. Potent anti- emetic effect exceptthioridazine – through CTZ.
viii. Condition A voidance reflex (CAR) – is blocked without blocking unconditioned reflex. (in sedative, hypnotics, skeletal muscle relaxants both are blocked).

2. **ANS-**

a. α adrenergic blockade –postural hypotension can be seen. Effect graded as CPZ > thiroidazine > clozapine > fluphenazine > haloperidol > pimozide – more potent comounds will have lesser α blockade.
b. Anticholinergic property – Thioridazine > CPZ > trifluoperazine = haloperidol
c. Weak anti – H1 property – esp. phenothiazine
d. Anti-5-HT action – esp. phenothiazines- antiemetic action.
3. **Local anesthetic action –** CPZ potent as procaine.Weak membrane stabilizers.
4. **CVS** – postural hypotension – central as well as peripheral action, partial tolerance with chronic use and reflex tachycardia**. QT prolongation – arrhythmia – esp. with thioridazine.** CPZ exerts anti- arrhythmic action.
5. **Skeletal muscle** – anti-spastic action acting centrally at basal ganglia or medulla oblongata.
6. **Endocrine** – galactorrhea, gyneacomastia, reduce gonadotropin secretion, rarely amenorrhea and infertility. ACTH levels Fall – rise of corticosteroids in stress is reduced. Decrease in ADH, leads to increase in urine volume.
7. **Tolerance & dependence – sedative & hypotensive action within few days/weeks.**
8. **Withdrawal phenomenon – physical dependence is rarely present; but withdrawal symptoms can be seen.**

MOA :- Dopamine theory –

- Dopamine excess causes psychosis.
- Drugs with dopamine blockade have anti-psychotic property – esp. **central D2 receptor blockade.**
- Counteracting excess of dopamine in limbic is responsible for anti – psychotic effects while counteracting DA at basal ganglia leads to extrapyramidal effects.

Pharmacokinetics

1. Absorption – oral CPZ – less & unreliable bioavailability. Better absorption after IM/IV.
2. Distribution – high penetration in brain ; highly tissue as well as plasma protein bound.

3. Metabolism – liver mainly CYP2D6 into many metabolites – few may be active
4. Elimination – no. of metabolites are excreted.

Other Anti –psychoticcs

- Triflupromazine – mainly used as anti – emetic. Acute muscle dystonia; esp in children.
- Thioridazine – most anticholinergic effect, low EPRs. Cardiac arrhythmia & male sexual dysfunction are common. Blindness; retinitis pigmentosa like syndrome is peculiar side effect; dose > 1 g/d not given.
- Trifluoperazine/ fluphenazine – piperazine side chain compounds with minimal autonomic side effects, lesser hypotension, sedation & seizure threshold lowering capacity. Less likely to cause jaundice and hypersensitivity.
- Haloperidol – potent anti-psychotic with lesser automatic side effects, less epileptogenic, no wt. gain or jaundice. Indicated for –
  - Acute schizophrenia
  - Huntington's disease.
  - Gillles de la tourette syndrome.
  - Penfluridol- long acting used for chronic schizophrenia, affective withdrawal and social mal- adjustment.
- Pimozide – specific DA agonist with little α adrenergic or cholinergic blockade. Long acting → used for maintenance therapy; psychomotor agitation is prominent. Risk of arrhythmia present. Gilles de la tourett's syndrome and ticks are other indications.
- Loxapine – DA blocking property with short and rapid action.
- Clozapine –
  - Atypical agent with weak D2 blockade - No/few extrapyramidal side effects and less galactorrhea (less prolactinemia)
  - Suppress both positive and negative symptoms, atypical patients also respond.
  - Relatively selective D4 receptor, 5 – HT2, αsdrenergic and significant H1 blockade
  - **Agranulocytosis** is chief side effect – weakly monitoring of WBC is required.
  - **Reserve drug in resistant schizophrenia**.
- **Risperidone** - combination of D2 & 5 – HT2 blockade receptor with additional α1, 2 & H1 receptors. Postural hypotension is side effect. At higher doses EPRs and prolactin level rise are seen. Increased risk of stroke in elderly.
- **Olanzapine** – D2, 5 – HT2, α1 & 2 as well as muscarinic and H1 receptors. Both positive and negative symptoms are controlled – broad spectrum schizo – affective disorders are seen. Dry mouth, constipation are side effects due to muscarinic blockade. Increased stroke, no agranulocytosis.
- **Quetiapine** – short acting with 5- HTIA, 5-HT2, D2, α1 & 2 ans H1 blockade. Sedation, postural hypotension, urinary retatnion, wt gain, rise in blood sugar are seen; but EPRs are less common. No effect in negative symptoms, but mania/ bipolar disorders are other indications.
- **Aripiprazole** – partial D2 & 5- HTIA blocker, 5 – HT2 antagonist. Minimal sedation, EPRs, hyperprolactinemia, hypotension & QT prolongation are not significant. Little wt gain. Long acting dose should be halved in ketoconazole, quinidine & doubled with CPZ. Also used in mania& bipolar disorder.
- **Ziprasidone** – D2, 5 – HT2A/C H1, α1 blocking activity, 5-HT1 blockade, moderately potent inhibition of reuptake of 5- HT & NA, agonis at 5- HTIA with antidepressant effect. Less propensity to cause EPR & hyperprolactinemia. QT prolongation can be seen. Used in mania as well.

- EPRs-
  - Parkinsonism – rigidity, tremor, hypokinesia, mask like facies, shuffling gait and rabbit syndrome – perioral tremor. Levodopa not effective, centrally acting anticholinergic.

- Acute muscular dystonia – bzarre muscle spasms, linguo – facial muscle grimacing, tounge thrusting, torticolis locked jaw etc. within few hours. Children less than 10 years. Hydroxyzine, central anticholinergic, promethazine IM clears reaction within 10 – 15 min.
- Akathasia – restlessness, feeling of discomfort, apparent desire to move, within 1 -8 wks of therapy – 20% of incidence. Central anticholinergic may reduce. Most cases require dose reduction or alternative drug.
- Malignant neuroleptic syndrome – marked rigidity, immobility, tremor, fever, semiconsciousness, fluctuating BP and heart rate. Last 5 -10 min after drug withdrawal & may be fetal . IV dantrolene may benefit. Bromocriptine in large doses may be useful.
- Tardive dyskinesia – late in therapy, menifests as purposeless involuntary facial and limb movements, constant chewing, puffing, lip licking etc. accentuated by anticholinergic & temporarily suppressed by high doses of neuroleptic. No satisfactory solution.

- CNS - drowsiness, lethargy, mental confusion, increased appetite, wt gain, aggravation of seizures.
- CVS – postural hypotension, palpitation, of ejaculation, due to α adrenergic blockade. QT prolongation and cardiac arrhythmias are risk of thioridazine, primozide & ziprasidone.
- Anticholinergic – dry mouth, blurring of vision, urinary hesitancy – highest with thioridazine
- Endocrine – hyper – prolactinemia – D2 blockade – loss of dopaminergic inhibition leads to increase in PRL. Amenorrhea, infertility, galactorrhea and gyneacomastia.
- Miscellenious reactions – wt gain, diabsetes (with clozapine), blue pigmentation, retianal degeneration.
- Hypersensitivity reactions –
  - Cholestatic jaundice
  - Skin rash, urticaria, contact dermatitis, photosensitivity & myocarditis.

Uses-

a. Psychosis
b. Anxiety
c. Antiemetic
d. Other
   i. To potentiate hypnotics, analgesics, anesthetics
   ii. Tetatus
   iii. Intractable cough
   iv. Alcoholic hallucinations
   v. Huntingtons disease
   vi. Gilles de la tourette's syndrome
   vii. Neurolept analgesia'pre- operative sedation.

<u>Antimaniac : Mood stabilizing</u>

1. <u>Lithium carbonate</u>
   - Suppreses mania and to exert a prophylactic effect in biopolar manic depressive illness without any further CNS effect.
   - CNS – no effect in normal person, neither sedative nor eruphoriant – mood stabilization after prolonged administration.
   - Li+ partly replaces body Na+ - effects ionc fluxes & modify membrane properties.
   - Decrease NA & DA in the brian of treated animal without affecting 5 – HT → correction of monoamine imbalance in CNS

- Inhibits hydrolysis of inositol – 1 – phosphate → free inositol production is reduced which is required for synthesis of IP3 & DAG.
- Inhibits ADH effect on distal tubules – diabetes insipidus.
- Leukocyte count increased by lithium theory.
- Reduces thyroxine synthesis by interfering with iodination of tyrosine.
- PK – slow oral absorption, gradual CNS penetration, eliminated unchanged by kidney in a way much similar to sodium. Renal clearance of Li+ = 1/5 th of creatinine clearance .
- Marked inter – individual variation in Li+ excertion.
- Sr. Li+ levels are measured 12 hrs after last dose predict the stady state concentration – normally 0.5 – 0.8 Meq/L. Toxic manifestations begin at levels more than 1.5 Meq/L
- Secreted in breast milk – mothers on lithium should not breastfed.
- ADRs-
  - Nausea, vomiting, mild diarrhea – start with lower doses.
  - Thirst, polyurea – later clears
  - Fine tremors – rarely seizures.
  - CNS – Coarse tremors, giddiness, ataxia, motor incoordination, slurred speech, hyperreflexia are features. At acute intoxication – muscle twitches, drowsiness, delirium, coma and convulsion.
  - No specific antidote, osmotic dieresis with sodium bicarbonate to promote Li+ secretion. At plasma levels more than 4 MEq/L – Hemodialysis is required.
  - Goiter on long term use – contra in pregnancy – foetal goiter, cardiac abn- ebsteins syndrome are seen. It inhibits iodination of tyrosine – thyroxine treatment required.
  - Diabetics insipidus
  - Contraindicated in sick sinus syndrome.
- Interaction
  - Plasma levels rise with diuretics like thiazides, furosemide.
  - Tetra, NSAIDs, ACEI – cause lithium retention.
  - Reduces pressor response to NA.
  - Succinylcholine and pancuronium – prolonged paralysis in pt with Li+ treatment.
  - Increases sulfonylurea induced hypoglycemia.
- Uses-
  - Acute mania – though effective slow to start & control of plasma levels is difficult.
  - Most prefere a BZD like clonazepam or lorazepam to control the episode & then start lithium
  - Prophylaxis of bipolar disorder – proven efficacy. Relapse likely after discontinuation.
  - Also prophylaxis of recurrent unipolar depression.
  - Recurrent neuropsychiatric illness, cluster headache, adjuvant to antidepressants in resistant major depression.
  - Cancer chemotherapy with leucopenia / agranulocytosis – to increase count.
  - SIADH – tends to counteract water retention.

2. <u>Other drugs</u> - carbamazepine, valproate, lamotrigine, topiramate, atypical anti – psychotics – olanzapine, ripesridone & atypical agents.

a. Carbamazepine :- prolongs remission in bipolar disorder. Effficacy in mania is equal to lithium. Relapsers or rapid cyclers are put on the combination of CBZ + Lithium. May also be used for firstline / adjunctive treatment for acute mania as well as bipolar disorders.

b. Valproate :- first line treatment in acute mania – high doses act faster than lithium. Also used in non-responders & rapid cyclers. Combination with lithium may be useful for resistant cases.

c. Lamotrigine :- Approved for bipolar; but not used for acute mania. Useful in rapid cyclers.

<u>Antidepressants:-</u>

<u>Classification:-</u>

1. **RIMAs –** (**R**eversible **I**nhibitors of **M**AO –**A**) – Moclobemide, Clorgylline.
2. **Tricyclic Antidepressants (TCA)** – imipramine, Amitryptylline, Trimipramine, Doxepine, Dothiepine, clomipramine.
3. Selective serotonin Reuptake Inhibitors (SSRIs) : - Fluoxetine, Fluvoxamine, Paroxetine, sertraline, citalopram, Escitalopram.
4. **Other Atypical Agents**:- Trazodone, nefazodone,
5. **Presynaptic α2 blocker** – Mianserine,
6. NaSSA- Non- adrenergic, specific serotoninergic antidepressant – Mirtazapine,
7. SNRI- serotonin & Nor- epinephrine neuptake inhibitors (Dual reuptake inhibitors) – Milnacifran, venlafaxine, Duloxetine,
8. SSRE – selective serotonin reuptake enhancer – Tianeptine, Amineptine and
9. DNRI – DA & NE reuptake inhibitor – Bupropion

RIMAs – MAO- monoamine oxidase are mitochondrial enzymes involved in the oxidative metabolism of biological amines. There are 2 types -

	Type A	Type B
	De- aminates 5 – HT, NA	Preferentially deaminates phenylethylamine
	Inhibited Clorgylline, Mocobemide	Selegelline
	Peripheral adrenergic nerve endings, Intenstinal mucosa & human placenta	Certain areas of brain – serotoninergic areas & platelet.

Dopamine metabolized by both & liver has both enzymes.

1. Non – selective agents : - tranylcypromine, phenlezine, isoxcarbazide, INH & ipraniazide.
2. Selective MAO –A : - moclobemide, clorgylline
3. Selective MAO – B :- selegelline (non – selective at higher does)

Interactions-

a. Cheese reaction – varieties of cheese, beer, wine, pikled meat, yeast contining large quantities of tyramide – accumulate 0069n pts on non-selective MAOI →indirectly acting sympathimimetic agent → large displacement of NA → hypertensive crisis, cerebrovascular accidents → IV phentolamine, prazosin or chlorpromazine (α blocker) is given.
b. Cold & cough remedies – contain ephedrine or other sympathomimetics - Hypertensive reaction can occur.
c. Reserpine, Guanethidine, TCA – excitement, HTN & hyperthermia can occur – due to initial NA releasing action.
d. Levodopa – excitement & hypertension can occur due to increase in DA & NA.
e. Antiparkinsons medications – hallucinations & belladonna poisoing features.
f. Barbiturates, alcohol, opioids & antihistamanics – action is intensified – respiration fails.
g. Pethidine - high fever, sweating, excitement, delirium & convulsion can occur due to accumulation of nor-pethidine.

Selective MAO –A inhibitor : - Clorgylline & moclobemide – reversible & selective MAO –A inhibitors, efficacious as TCAs except in severe cases. It lacks anticholinergic, sedative, congnitive psychomotor & cardiovascular adverse effect of typical TCA.

Adverse effects are nausea, vomiting, headache, insomnia, headache and rarely liver & renal impairment.

Moclobemide emerged as a well tolerated alternative to TCAs in mild to moderate depression and in social phobia. It is particularly useful for elderly with cardiac problems.

TCA : - Imipramine selectively benefited depressed, but not agitated psychots. Thus it was used in depression.

CNS – in normal individuals it induces peculiar clumsy feeling, tiredness, light-headedness, sleepiness, difficulty in concentrating, thinking and unsteady gait. In depressed individuals, first sedation is produced followed by gradual mood elevation after 2-3 weeks. They are not euphoriants. Other properties are-

- Sedation –
- Lowering of seizure threshold - clompiramine, maprotiline & bupropin are highest in this regard.
- Respiratory depression

MOA : - inhibit NA & 5 – HT reuptake into their neurons. Most of them don't inhibit DA reuptake. Amphentamine & cocaine are strong CNS stimulants which are DA reuptake inhibitor. TCAs indirectly facilitate dopaminergic transmission in forebrain – which is claimed for the mood elevating effect. The other mechanism claimed is stimulation followed by desensitization of presynaptic autoreceptors – α 1, 5 – HT1A & 5- HT1D → the net effect is enhanced NA & 5- HT transmission.

ANS ; - anthicholinergic – dry mouth, blurring of vision, constiapation & urinary hesitation.

Antihistaminic – slight H1 blockade – amitryptylline, doxepine, trimipramine.

CVS :- therapeutic window – optimal antidepressant & hypotensive effects.

PK - therapeutic window – optimal antidepressant effect is exerted in narrow therapeutic range. TCA orally absorbed, wide distributed & demethylation is chief way of metabolism. Metabolites are excreted in urine over 1 –2 week.

ADRs:-

1. Anticholinergic effect – dry mouth, bad taste, constipation, epigastric distress etc.
2. Sedation, mental confusion & weakness.
3. Increased appetite and wt gain is noted with most TCAs.
4. Switch over to mania.
5. Sweating & fine tremors
6. Seizure threshold is lowered.
7. Postural hypotension.
8. Cardiac arrhythmias
9. Rashes & jaundice due to hypersensitivity
10. Mianserin is hepatotoxic.

Acute poisoning – belladonna like poisoning features. Excitement, delirium & anticholinergic side effects are seen. Fall in temp, BP, tachycardia, ECG changes & arrhythmias are seen. Treatment is with diazepam for control of convulsion & delirium. Propranolol & lidocaine are given for cardiac arrhythmias. Class I A & C anti – arrhythmics & lidocaine as well as digoxin are contraindicated. Physostigmine may reverses many central & peripheral anticholinergic & sometimes cardiac effects.

Interactions : -

- Sympathomimetics – potentiate directly acting agents while attenuate indirectly acting agents.
- Abolish gunethidine & clonidine by preventing their transport in neurons.
- Phenytoin, phenylbutazone, aspirin & CPZ can displace TCAs from protein binding sites & can cause toxicity.
- SSRis – inhibit metabolism of TCAs.
- TCAs Delay gastric emptying & retared the absorption of themselves & many other drugs except digoxin & tetracyclines (where absorption is increased).
- MAO Inhibitors – dangerous hypertensive crisis can occur.

Amoxapine – tetracyclic compound with neuroleptic & antidepressant properties – blocks D2 & inhibit reuptake of NA. risk of extrapyramidal reactions & seizures is there. Used for psychotic depressed pts.

Reboxetine – newer selective NA reuptake blocker – NARI. Antimuscarinic and proerpteis are less.

<u>SSRI :- selective Serotonin Reuptake Inhibitors</u>

Advantages over TCAs :-

- No anticholinergic effect.
- No α1 blockade / post- hypotension and are thus suitable in elederly.

- No sedation, congnitive impairment.
- No seizure precipitating threshold
- No interference with cardiac conduction - no risk of cardiac arrhythmia.
- Weight gain is less common.
- Good patient acceptability.
- Risk of switching over to mania is less – preferred in recurrent depression.
- More no. of patients respond.
- Reduced lag time – time between onset of treatment and onset of effects.

Disadvantages of SSRI –

1. Serotonin syndrome - with any of serotoninergic agents – like non-selective MAO inhibitors. It manifests as agitation, restlessness, seating, teitching followed by convusion etc.
2. Enzyme inhibition - CYP 2 D6 & CYP 3A4 – TCA, haloperidol, clozapine, terfenadine, astemizole, beta blockers, warfarin, BZD, CBZ are seen.
3. New ADRs like nervousness, restlessness, anorexia, insomnia etc. are seen.
4. 5 – HT3 stimulation –nausea & vomiting – tolerance develops.
5. Discontinuation — paresthesia, bowel upset, bosyache, agitation and sleep disturbances are seen as withdrawal reactions.

The efficacy of SSRI is similar to TCAs except in severe depression.

1. Fluoxetine – bicyclic compound, prototype of SSRi, longest acting with active metabolite which remain effective for 7 – 10 days, given in children > 7 years or older for depression or OCD.
2. Fluvoxamine - shorter acting SSRI with h 18 hrs half life. Nausea, vomiting is more as well as agitation and discontinuation reactions.
3. Paroxetine – short acting SSRI, without active metabolite.
4. Sertraline – longer acting metabolite present.
5. Citalopram – less drug reaction
6. Escitalopram – active 0 metabolite. Safe & effective.

Other uses of SSRI:-

1. Obcessive – Compulsive disorders.
2. Panic disorders,
3. Scodial phobia
4. Eating disorders – buliama
5. Premenstrual dysphoria.
6. Compulsive buying
7. Kleptomania
8. Postmyocardial infarction

Atypical Agents : -

1. Trazadone – less efficient 5 – HT uptake, prominent α blocking as well as weak 5 – HT2 antagonistic effect. Sedative, non-anticholinergic, causes bradycardia & less prone to cause arrhythmia – better suited for elderly. Mild anxiolytic – effective for OCD. Priapism & α1 blockade (postural hypotension) are seen. Short acting.

2. Mianserine – blocks α2 adrenregic receptors (NARI) which increases release of NA. Antagonist at 5 – HT1C, 5-HT2 as well as H1 receptor. Sedative, relieves anxiety, suppresses panic attacks.seizure is overdose. Blood dyscrasias and liver dysfunction seen.
3. Tianeptine - increases rather than inhibiting 5 – HT uptake (SNRE), neither sedative nor stimulant. Anxiodepressive states with psychosomatic symptoms is indication & endogenous depression. Dryness of mouth, epigastric pain, drowsiness, insomnia, tremor & headache are side effects.
4. Aminptine – another SNRE with antidepressant property. Has naticholinergic side effects, tachycardia, confusion, delirium, postual hypotension, conduction disturbance and arrhythmias are seen.
5. Venlafaxine – SNRI – serotonin & Noradrenergic reuptake inhibitor. Inhibits 5 – HT & NA without affecting other seceptors. No sedation, faster onset of action. Raises BP – safe in overdose. Nausea, sweating, anxiety, dizziness & impotence.
6. Duloxetine - newer SNRI. Nor sedative, nor anticholinergic agent. Blocks α2 autoreceptors and heteroreceptors – 5 – HT receptors – enhancing both attacks, diabetic neuropathic pain, stress incontinence in women.
7. Mirtazapine – NaSSa – noradrenergic and selective serotoninergic agent. Blocks α2 autoreceptors and heteroreceptors – 5-HT receptors – enhancing both NA & 5 – HT release. H1 blockade → seation, but no anticholinergic or antidopaminergic properties.
8. Bupropion – inhibitor of NA & DA reuptake. Excitement, seizures are seen. Metabolized into amphetamine like compound. Used for smoking abstinence and quitting as well as to reduce the symptoms of nicotine withdrawal. Insomnia, agitation, dry mouth and nausea are side effects.

Uses of antidepressants:-

1. **Endogenous (Major) depression –**
   a. **SSRI** – currently drugs of firs choice for depression – due to better tolerability.
   b. **TCA** – in non-responsive or resistant cases; severe depression.
   c. **Moclobemide** – for elderly & patients with cardiac disease.
   d. **Atypical agents** – for depressive illnesses.
   e. **ECT** – severly depressed patients
   f. **TCA /SSRI with lithium OR SSRI with atypical antipsychotic –** Bipolar depression.
2. Obsessive – compulsive disorders – SSRI are DOC. Clomopramine in OCD & panic disorders. Also in eating disorders like bulimia, body dysmorphic syndrome, kleptomania, compulsive buying and kleptomania are side effects.
3. Anxiety Disorders – SSRI – esp. for post – traumatic stress disorders
4. Neuropathic pain – imipramine and amitryptylline reduces the intensity of post- herpatic neuralgia.
5. Attention deficit hyperactivity disorder in children – TCA like imipramine, nortryptylline, amoxapine are DOC.
6. Enuresis – imipramine
7. Migraine – amitriptylline in prophylaxis.
8. Pruritus – topical doxepin.

Anti – anxiety drugs:-

Classification:-

1. Benzodiazepines – clonazepam, alprazolam, lorazepam, oxazepam, diazepam.
2. Azapirones – buspirone, Gepirone, Ipsapirone
3. Sedative antihistaminic –Hydroxyzine
4. B – blocker – propranolol.

Other drugs like SSRI are used in OCD, phobias, panic and many types of severe generalized anxiety disorders.

Buspirone:-

- No sedation, congnitive impairment of functional impairment.
- Does not interact with BZD receptor or modify GABA minergic transmission.
- Does not suppress BZD or barbiturate withdrawal.
- No muscle relaxant or anticonvulsant effects.
- Relieves mild – moderate anxiety, not effective in severe disease, OCD, panic disorders.
- Therapeutic effect on 5 –HT1A. stimulate presynaptic 5 – HT1A autoreceptor – reduces activity of dorsal raphe serotoninergic neurons. After chronic treatment adaptive reduction in cortical 5 – HT2 receptors is seen. Weak D2 blockade – noanti – psychotic or extrapyramidal effects.
- Nausea, headache, light headedness & rarely excitement are side effects.
- Rise in BP – pt with MAOI; does not potentiate CNS depressants.

BZD – some members produce anxiolysis without significant CNS depression. Selecting taming effect – specific effect on limbic system (no generalized CNS depression like barbiturates).

1. At this dose; CVS, RS depression is also minor.
2. Less abuse liability & withdrawal reaction - due to their long half life.
3. Relative safety over other agents even in gross overdose.

    a. Chlordiazepoxide – first BZD used clinically – slow & longer acting. Poor anticonvulsant effect.
    b. Diazepam – quick absorption, biphasic effect – first strong effect followed by longer, milder effect. V. long half life due to active metabolites. Preferred anxiolytic with organic disease.
    c. Oxazepam – no active metabolite – preferred in elderly & those with liver disease. Shorter duration of action.
    d. Alprazolam – prominent anxiolytic & mood elevating effect. Good efficacy in the panicky disorders. Long half life.
    e. Clonazepam
    f. Etizolam
    g. Lorazepam – slow oral absorption . no active metabolite it is quite sedative & produces amnesia. Can be given by IM route.

Other drugs:-

1. Bblockers – masks the symptoms of anxiety like palpitation, tremor, GIT hurrying etc.
2. Hydroxyzine – ant H1 antihistaminic with sedative, anti – emetic, anti – muscarinic & spasmolytic properties.
3. Opioid

Alagesia – (pain) – unpleasant sensation evoked due to noxious stimuli.

Analgesia – drug that selectively relives pain without altering consciousness.

Non – steroidal anti – inflammatory drug

Nonsteroidal anti-inflammatory drugs, usually abbreviated to NSAIDs or NAIDs, but also referred to as nonsteroidal anti-inflammatory agents /analgesics (NSAIAs) or nonsteroidal anti- inflammatory medicines (NSAIMs), are drugs with analgesic and antipyretic (fever reducing) effects and which have, in higher doses, anti – inflammatory effects.

Most NSAIDs act as nonselective inhibitors of the enzyme cyclooxygenase (COX), inhibiting both the cyclooxygenase – 1 (COX-1) and cyclooxygenase – 2 (COX-2) isoenzymes. COX catalyzes the formation of prostaglandins and thromboxane from arachidonic acid (itself derived from the cellular phospholipid bilayer by phospholipase A_2) . prostaglandins act (among other things) as messenger molecules in the process of inflammation. The relatively selective COX-2 selective inhibitors, coxibs, the newest clsaa of NSAIDs, can be considered as true COX-2 selective inhibitors, and include celecoxib, rofecoxib, valdecoxib, parecoxib and etoricoxib. Rofecoxib however, which has since been withdrawn, had been shown to produce significantly fewer gastrointestinal ADRs compared with naproxen.

Aspirin covalently modifies COX-1 and COX-2, irreversibly inhibiting COX activity. This is an important distrinction from all the NSAIDs because the duration of aspirin's effects is related to the turnover rate of COXs in different target tissues. The duration of effect of non-aspirin NSAIDs, which inhibit the active sites of the COX enzymes competitively. Relates to the time course of drug disposition. The importance of enzyme turnover in recovery from aspirin action is most notable in platelets, which, being anucleate, have a markedly limited capacity for protein synthesis. Thus, the consequences of inhibition os platelet COX-1 (COX-2 is

expressed in megakaryocytes and perhaps immature platelet forms) last for the lifetime of the platelet. PGs have long been implicated in the maintenance of patency of the ductus aeteriosus, and indomethacin, ibuprofen, and other tNSAIDs have been used in neonates to close the inappropriately patent ductus. Conversely, infusion of PGE2 maintains ductal patency after birth.

The effects of salicylates on uric acid excretion are excretion are markedly dependent on dose.

Low doses (1 or 2 g/day) may decrease urate excretion and elevate plasma urate concentrations; intermediate doses (2 or 3 g/day) usually do not alter urate excretion.

Large doses (>5 g/day) induce uricosuria and lower plasma urate levels

Hearing impairment, alternations of perceived sounds, and tinnitus commonly occur during high – dose salicylate therapy.

Some Drugs that Cause Ototoxicity	
• **Type**	• **Examples**
Antibiotics	Aminoglycosides
	Vancomycin
Chemotherapeutic drugs	Platinum – containing drugs (eg,
Diuretics	Ethacrynic acidSome
	Furosemide
Other	Quinine
	Salicylates

High therapeutic doses of salicylate are associated with a primary respiratory alkalosis and compensatory renal acidosis. Subsequent changes in acid – base status generally occur only when toxic doses of salicylates are ingested by infants and children or occasionally after large doses in adults. The phase of primary respitory alkalosis rarely is recognized in children with salicylate toxicity. They usually present in a state of mixed respiratory and renal acidosis, characterized by a decrease in blood pH, a low plasma bicarbonate concentration, and normal or nearly normal plasma Pco_2.

N – acetylcysteine is indicated for those at risk of hepatic ijury. NAC therapy should be instituted in suspected cases of acetaminophen poisoning before blood levels become available, with treatment terminated if assay results subsequently indicate that the risk of hepatotoxicit is low. NAC functions by detoxifying NAPQI. It both repletes GSH stores and may Conjugate directly with NAPQI by serving as a GSH substitute. Ther is some evidence that in cases of established acetaminophen toxicity, NAC may protect against extrahepatic injury by its anti – oxidant and anti – inflammatory properties.

Rheumatoid arthritis

Pharmacological treatment of RA can be divided into disease – modifying antirheumatic drugs (DMARDs), anti- inflammatory agents and analgesics.

Chemically synthesised DMARDs; azathioprine, ciclosporin (cyclosporine A), D –penicillamine, gold salts, hydroxychloroquine, leflunomide, methotrexate (MTX), minocycline, sulfasalazine (SSZ)

Cytotoxic drugs: Cyclophosphamide

The most important and most common adverse events relate to liver and bone marrow toxicity (MTX, SSZ, leflunomide, azathioprine, gold compounds, D- pencillamine), renal toxicity (cyslosporine A, parenteral gold salts, D-penicillamine), pneumonitis (MTX), allergic skin reactions (gold compounds, SSZ), autoimmunity (D- penicillamine, SSZ, minocycline) and infections (Azathioprine, cyclosporine A).

Biological agents

- Biological agents (biological) include:
  - Tumor necrosis factor alpha (TNFα) blockers – etanercept, infliximab, adalimumab, certolizumab pegol, golimumab
  - Interleukin 1 (IL – 1) blockers – anakinra

- Monoclonal antibodies against B cells – rituximab

- T cell costimulation blocker- abatacept

- Interleukin 6 (IL-6) blockers – tocilizumab (an anti – IL-6 receptor antibody)

- T- cell co – stimulation inhibitor (binds B7 protein on antigen – presenting cell) - abatacept

Drug	Seious Toxicifies	Other common side Effects	Initial Evaluation	Monitoring
Hydroxychloroquine	Irreversible retinal damage Cardiotoxicity Blood dyscrasia	Nausea Diarrhea Headache Rash	Eye examination If > 40 years old or prior ocular disease	Funduscopic and visual field testing every 12 months
Sulfasalazine	Granulocytopenia Hemolytic anemia (with G6PD deficiency)	Nausea Diarrhea Headache	CBC, LFTs G6PD level	CBC every 2-4 weeks for first 3 months, then every 3 months
Methotrexate	Hepototoxicity Myelosupression Infection Interstitial pneumonitis Pregnancy category X	Nausea Diarrhea Stomatitis/mouth ulcers Alopecia Fatigue	CBC, LFTs Viral hepatitis panel* Chest X-ray	CBC, creatinine LFTs every 2-3 months
Leflunomide	Hepototoxicity Myelosupression Infection Pregnancy category X	Alopecia Diarrhea	CBC, LFTs Viral hepatitis panel*	CBC, creatinine LFTs every 2-3 months
TNF-Inhibitors	Risk bacterial fungal infection Reactivation of laten TB Lymphoma risk (controversial) Drug induced lupus Neurologic deficits	Infusion reaction LFTs	PPD skin test	LFTs periodically
Abatacept	Risk bacterial, viral infections	Headache Nauusea	PPD skin test	Monitor for infusion reactions
Anakinra	Risk bacterial, viral infections Reactivation of latent TB Neutropenia	Injection site reaction Headache	PPD skin test CBC with differential	CBC every month for 3 months, then every 4 months for 1 year Monitor for injection site reactions
Rituximab	Risk bacterial, viral	Rash	CBC viral	CBC at regular

			hepatitis panel*	intervals

Drug	Serious Toxixities	Other Common side Effects	Intial Evaluation	Monitoring
	Infections Infusions reaction	Fever		
	Cytopenia Hepatitis B reactivation			
Toclilzumab	Risk of infection Infusion reaction LFT elevation Dyslipidemia cytopenias		PPD skin test	CBC and LFTs at regular intervals

Antigout

Uricosuries	Primary: Probenecid sulfinpyrazone Benzbromarone isobrominidione Secondary : Amlodipine Atorvastatin Fenofibrate Guaifenesin Losartan
Xanthine oxidase inhibitors	Purine analogues: Allopurinol Oxypurinol Tisopurine Other : Febuxostant inositols (phytic axccid, Myo – inositol)
Mitotic inhibitors	Colchicines
Other	Cinchophen NSAIDs except aspirin sevelamer URate oxidase (Rasburicase, Pegloticase)

Colchicine- Colchicine is neither analgesic nor antiinfalmmatory, but it specifically suppresses gouty inflammation. It does not inhibit the synthesis or promote the excretion of uric acid . thus, ift has no effect on blood uric acid levels.

An acute attack of gout is started by the precipitation of urate crystals in the synovial fluid. They start an inflammatory response, chemotactic factors are produced -+ granulocyte migration into the joint; they phagocytose urate crystals and release a glycoprotein which aggravates the inflammation by :

i. Increasing lactic acid production from inflammatory cells -+ local pH is reduced -+ more urate crystals are precipitated in the affected joint.
ii. Releasing lysosomal enzymes which causes joint destruction.

Colchincine does not affect phagocytosis of urate crystals but inhibits release of the glycoprotein. And the subsequent events. By binding to fibrillar protein tubulin, it inhibits granulocyte migration into the inflamed joint and thus interrupts the vicious cycle. Other actions of colchicines are:

a) Antimitotic; causes metaphase arrest: binding to microtubules of mitotic spindle was tried for cancer chemotheraphy but abandoned due to toxicity. It is used to produce polyploidy in plants.

b) Increases gut motility through neural mechanism

It has antimitotic effects, arresting cell division in G_1 by interfering with microtubule and spindle formation (an effect shared with vinca alkaloids) colchinic may later neutrophil motility in ex vivo assays. Colchicine decreases the crystal – induced secretion of chemotactic factors and superoxide anions by activated neutrophils. It also limits neutrophil adhesion to endothelium by modulating the expression of endothelium by modulating the expression of endothelial adhesion molecules. Higher concentrations inhibit IL- 1β processing and release from neutrophils in vitro.

Colchicines inhibits the release of histamine – containing granules from mast cells. The secretion of insulin from pancreatic βcells,and the movement of melanin granules in melanophores. These processes also may involve interference with the microtubular system, but whether this occurs at clinically relevant concentrations is questionable.

Colchicines also exhibits a variety of other pharmacological effects. It lowers body temperature, increases the sensitivity to central depressants, depresses the respiratory center, enhances the response to sympathomimetic agents, constricts blood vessels, and induces hypertension by central vasomotor stimulation. It enhances GI activity by neurogenic stimulation but depresses it by a direct effect, and alters neuromuscular function. Clochicine dramatically relieves acute attacks of gout.

Allopurinol inhibits xanthine oxidase and prevents the synthesis of urate from hypoxanthine and xanthine.

Febuxostat is a non-purine inhibitor of xanthine oxidase. While oxypurinol, the active metabolite of allopurinol, inhibits the reduced form of the enzyme, febuxostat forms a stable complex with both the reduced and oxidized enzyme and inhibits catalytic function in both states.

Rasburicase is a recombinant urate oxidase that catalyzes the enzymatic oxidiation of uric acid into the soluble and inactive metabolite allantoin.

Uricosuric agents increase the rate of excertion of uric acid. Probenecid inhibits the reabsorption of uric acid by organic anion transporters, principally URAT – 1. Uric acid is the only important endogenous compound whose excertion is known to be increased by Probenecid. The uricosuric action of Probenecid is blunted by the co – administration of salicylates.

SUMMARY – CNS PHARMACOLOGY

DRUGS FOR CENTRAL NERVOUS SYSTEM DISEASES

1. Diazepam is MC used sedative & hyponotic with t\1\2-100; it is DOC for status epileptics, febrile seizures, drug induced hyperactivity, picrotoxin poisoning, prevention of seizures due to lidocaine, emergence deliverium due to ketamine, drug induced EPS or excitement of mania- flumazenil is antidote of diazepam
2. Lorezepam, estazolam, oxazapam are water-soluble benzodiazepines.
3. Lorazepam & oxazepam – doesn't undergo hepatic metabolism – can be used in elderly & in patients with liver disease.
4. Benzodiazepines cause anterograde amnesia (head injury causes retrograde amnsia).
5. Cholordiazepoxide (high dose) is DOC for alcohol withdrawal from alcohol – as it is longer acting. Many times diazepam is also used.
6. Flunitrazepam is date rape drug & causes night mares.
7. Alprazolam has anxiolytic as well mood elevating properties.
8. Clonazepam, alprazolam. Diazepam, lorazepam & oxazepam are used ffor anxiolysis
9. Clonazepam, Midazolam, diazepam & clobazepam are used anti – epileptic.
10. Diazepam is centrally acting skeletal muscle relaxant.
11. Distrurbance of sleep architecture = barbiturates & older sedatives & hypnotics >BZD> non- BZD like Zolpidem (most commonly used sedative used for insomnia).
12. Modafinil is approved for narcolepsy & also used for call centre workers, night residents, night shift workers etc.
13. Melatonin & its M1 receptor agonist Ramelteon are used for Jet – Lag.
14. Amobarbitone is sometimes used for "Psychoanalysis"
15. Thiopentone has "Redistribution"
16. Phenobarbitone is used for epilepsy & status epilepticus.
17. Hemodialysis is useful for barbiturate poisoning – alkaline dieresis (not for BZD – flumazenil)
18. Flumazenil is GABA –A receptor antagonist – useful BZD poisoning or reversal.
19. Phenytoin – MC side effect is gum hyperplasia; others are hirsutism (thus not recommended in adolescent girls), hypocalcemia, osteomalacia, megablastic anemia (do MCV testing), pseudolymphoma and hypersensitivity (discountinue the drug) commonest symptom of toxicity is nystagmus. TDM levels = 10 -20 mcg/ml.
20. Carbamazepine is DOC for all kind of neuralgias (trigeminal\ glossopharyngeal) & partial seizure; MC side effect is rash (10%) , leucopenia and hepatitis. Hyponatremia.
21. Oxcarbazepine – lesser hepatitis & hepatic enzyme induction. Hyponatremia same with CBZ.
22. Valproic acid is broadest spectrum antiepelipetic drug; DOC for GTCS, akinetic, atonic, myclonic & mixed epilepsies; causes hepattocity mainly in children, weight gain.
23. Divalproate – better bioavailability & lesser side effects.
24. Other broad spectrum AED = lamotrigene, phenobarbitone & topiramate.
25. Phenobarbitone is CI in acute intermittent porphyria; DOC for hemolytic anemia, jaundice in newborn, epilepsy following febrile seizures, & epilepsy in pregnancy. Also useful in status.
26. Lamotrigene has steven – johnson's syndrome is the side effect.
27. Topiramate causes weight loss & psychiatric symptoms. Used in migraine when β blockers are contraindicated – bronchial asthma, COPD etc.
28. Zonisamide has carbonic anhydrase inhibiting activity – renal stones are the side effects.
29. Lavetiracetam, brevetiracetam act by inhibiting presynaptic vesicle protein – prevents its fusion with nerve membrane – prevents release. Useful for refactory seizures.
30. Felbramate is NMDA receptor antagonist – causes aplastio anemia.
31. Vigabartrin is GABA trans – aminase inhibitor.
32. Tiagabine – GAT-1 (reuptake protein for GaBA) inhibitor.
33. Gabapentine, pregablin (pre- synptic α2delt subunit of calcium channel inhibitor) – used for diabetic & other peripheral neuropathies.
34. Newer AED are mainly used as add on to refctory partial epilepsy with or without secondary generalization.
35. Buspirone is a non- sedative anxiolytic drug that is devoid of properties possessed by diazepam such as muscular relaxation, amnesia, sedation, anti – convulsant action etc. its main drawback is that it takes two

weeks to start its action therefore is used in mainte (presynaptic receptor) nance of patients with generalized anxiety disorders rather than in acute phase. 5 – HT1A partial agonist.

36. Alprazolam is the drug with anxiolytic & mood elevating properties.
37. Donepazil is the DOC for Alzhiemer's disease.
38. Memantine is NMDA receptor antagonist used in Alzheimer's disease.
39. Riluzole is used in Amyotrophic lateral Sclerosis.
40. Interferon β is used in relapsing remitting type of multiple sclerosis – others are glathmare acetate; natalizumab (anti – integrin antibody) & immunosuppressive agents.
41. Levodopa is most effective anti-parkinson drug, only drug that lowers mortality
42. Amantidine (also an antiviral drug – influenza A2) enhances dopamine transmission (MC side effect is ankle edema)-CI in renal failure and epilepsy. Livedo reticularis is characteristic side effect.
43. Behavioral side effects are aggravated with addition of carbidopa.
44. Pramipaxole & ropinirole are used in restless leg syndrome as well.
45. Rasagellline is useful for toxin induced PD.
46. Selegelline has antioxiodant properties.
47. Pergolide & cabergoline can cause valvular heart disease. All ergot derivatives are contraindicated in HTN, PVD, peptic ulcer.
48. Tolcapone & entacapone are COMT inhibitors. Tolcapone is associated with hepatotoxicity.
49. In drug / disease / trauma induced PD – DOC are centrally acting anticholinergics like benztropin, benzhexol etc.
50. Morphine was isolated by serturner from poppy plant it is analgesic and antitussive
51. Pethidine is synthetic opioid that has anticholinergic property (causes mydriasis) while other opioids cause meiosis. Pethidine can cause seizures (due to nor – pethidine; esp. with non- selective MAO inhibitors).
52. Pethidine gets accumulated in renal failure causing hyperreflexia; this is known as norpethidine syndrome
53. Buprenorphine is the longest acting opioid that has alcohol anti – craving properties (methadone is DOC for opioid detoxtification
54. Naloxone (most potent opioid antagonist) doesn't reverse the overdose of Buprenorphine due to its ceiling effect
55. Morphine is DOC for acute pulmonary edema, Tetralogy of Fellot's
56. Opioids don't have anti- inflammatory properties but are useful in severe pain of visceral origin as they work by reducing the release of substance P from spinal cord's substantia gelatinososa
57. Tramadol has additional NE & 5 – HT inhibiting property – best suited drug for short term management of mild – moderate pain. Nausea, vomiting & dizziness are main side effects.
58. Pentozocine, nalorphine & butorphenol are κanalgesics = associated with side effect of dysphoria. Pentozocine causes tachycardia & HTN – not used in hypertensive, /ami pts.
59. Bupreorphiue is DOC as analgesics in ICU – safe in cardiac patients. It is kappa receptor antagonist & μ receptor agonist.
60. Methadone is DOC for opioid maintainence therapy in withdrawal – enzyme inducers like rifampin & phenytoin precipitate withdrawal syndrome in such patients.
61. Morphine stimulates CTZ (causing nausea) at therapeutic doses while at toxic doses it suppresses it.
62. Morphine stimulates vagal center, edinger westphal nucleus & CTZ.
63. Morphine suppresses RS center, vasomotor center, cough center & temperature regulation center.
64. For billiary colic by morphine – DOC is nitrate.
65. Codeinc anti-tussive while loperamide & diphenoxylate are anti – secretory.
66. Naltreoxone is indicated in opioid poisoning, newborn asphyxia, diagnosis of opioid addict & in treatment of opioid overdose.
67. Fentanyl is short acting, lipid soluble, more potent than morphine used in transdermal patch for cancer pt & also in obstretic analgesia.'
68. Histamine's maximum amount is found in lung mast cells (90% of body's histamine is present there)
69. Astemazole is longest acting newer antithistaminic and citirizine, although a member of newer of newer non-sedative family; out of newer drugs it produces maximum sedation
70. Older anti-histaminics are better for urticaria and itching due to their anticholinergic effects while newer ones are better for sneezing and common cold etc.
71. Fexofenadine (allergra), a newer analogue of hepatotoxic and cardiotxic drug terfenadine is not associated with torsa de depointes

72. Citrizine is a metabolite of promethazine but is devoid of sedative effect at usual therapeutic doses (in some it produces sedation)
73. Promethazine (phenargan) iis DOC for drug induced extrapyramidal disturbances
74. Sumatriptan, a 5-HTib/jd partial agonist is the DOC for acute attack of migraine; propranolol is DOC for prevention of migraine
75. Sumatriptan can cause vasospasm, therefore is contraindicated in hypertension, angina and peripheral vascular disease patients
76. Alcohol is must prevalent neurotoxin in our environment
77. Disulfiram (metronidazole has dilsufiram like effect) has is alcohol dehydrogenase inhibitor and is DOC for alcohol detoxification.
78. Drugs having disulfiram reaction – gresiofulvin, metronidazole, procarbazine, cefoperazone & chlorpropamide.
79. Clonidine is anti – craving drug for alcohol.
80. Topiramate, Acamproset & naltreoxone are other anti-craving drugs for alcohol withdrawal.
81. Fomepizole – is aldehyde dehydrogenase inhibitor used for methanol poisoning.
82. Legal limit of alcohol is 80mg\dl in most nations and levels above 400mg\dl are uniformly fatal; it follows zero order kinetics (phenytoin, tolbutamide, theophylline, warfarin, aspirin, caffeine) also follow zero – order kinetics (fixed amount is metabolized)
83. Ethylene glycol poisoning shows presence of oxalate crystals in urine
84. Foepizole/ethanol are DOC for methylalcohol poisoning (causes blindness due to optic atrophy)
85. SSRI are drug of choice – sertraline and escitalopram are most chosen one for depression. They are bets tolerated, good response rate, faster onset and less drug interactions. But they are not effective in severe depression – TCAs are useful.
86. SSRI are also used for Post-traumatic stress disorder, anxiety & panic disorders, eating disorders, Phobias etc.
87. SNRI – venlafaxine, desvenlafaxine, dulaxetine
88. Duloxetine is also used for neuropathes.
89. Mirtazapine – NaSSa – nor-adrenergic selective serotoninergic antidepressant – useful in depression with somatic symptoms like insomnia, GIT disorders.
90. Reboxetine is NRI – NE reuptake inhibitor.
91. DNRI – bupropione – useful for nicotin withdrawal – others are Varenacline (Nn type partial agonist) Rimonabant (CB1 – cannabinoid type I receptor antagonist), nicotine transdermal patches & clonidine as anticraving agent.
92. Mianserine is presynaptic $\alpha 2$ receptor blocker.
93. Trazodone & nefazodone are serotonin receptor blockers as well reuptake inhibitor - $\alpha 2$ blockade is associated with priapism as side effects.
94. Amritryptylline is udes for neuropathies, ADHD & severe depression.
95. Doxepine is useful as anti-pruritic agent.
96. SSRI have peculiar side effect like serotonin syndrome, withdrawal reactions & some enzyme inhibiting property.
97. Amoxapine is tetracyclic compound useful in depression with pscyhosis
98. Alprazolam is useful in anxiety with depression
99. For psychosis – SGA – second generation anti-psychotics – esp, Risperidone & Olanzepine are considered to be drug of choice.
100. Risperidone is associated with Extrapyramidal side effect & olanzepine can cause carbohydrate intolerance, precipitate the type II diabetes & weight gain is also seen as side effect.
101. Haloperidol is useful for acute severe type of schizophrenia.
102. Clozapine is used for resistant schizophrenia – has agranulocytosis & seizures as side effects. It is also useful for negative synptoms.
103. Thioridazone has less EPR; but prominent arrhythmias, anti-cholinergic effect – can precipitate acute angle closure glaucoma, retinal damage at dose>1000mg/day.
104. Fluphenazine is available as long acting 1 month depot preparation.
105. Lithium is useful for suppression of manic episode as well as for prophylaxis of manic disorders at doses when other CNS side effect are not seen.
106. Ataxia is the main side effect of lithium.
107. Goiter, DI (antagonizes ADH receptor) teratogenicity (Ebstein's anomaly), CNS toxicity & GIT side effect seen.

108. Lithium is used for acute mania, prophylaxis of bipolar disorder, recurrent psychiatric illness, cluster headache, SIADH & cancer chemotherapy induced leukoepnia are the main side effects.
109. Carbomazepine is the drug of choice for pregnancy with BPD.
110. AED like carbamazepine, Valproate (for acute disease as well as for rapid cyclers), lamotrigie topiramate & gabapentine are used in BPD.
111. SGA like risperidone, olanzepine are now considered to be first line drugs for acute mania.
112. Ephedrine is DOC for hypotension induced by spinal anesthesia.

Sr. No		Competitive blockers – d-TC	Depolarizing blockers Sch
1	Tetanic stimulation during partial block	Poorly sustained contraction	Well sustained contraction
2	Post-tetanic potention	Present	Absent
3	Neostigmine	Antagonizes block	No effect
4	Train of four phenomenon (ratio)	< 1 (suggests fade phenomenon)	= 1 (No fade phenomenon)
5	Fade phenomenon	Present	absent

113. Mivacurium – shortest acting SKMR while Doxacurium is longest acting.
114. Atracuronium undergoes "Hoffman elimination"
115. Dantrolene (for malignant hyperthermia) & quinine (for nocturnal leg cramps) are directly acting skeletal muscle relaxants.
116. Baclofen - $GABA_B$ receptor agonist, BZD – diazepam. Tizanidine – central α2 agonist, mephensine group of drugs – Mephensine, carisoprodol, chlorzoxazone, chlorzoxazone, chlormezanone & methocarbamol & others – Eperisone, tolperisone, Thiocholcicoside are centrally acting skeletal muscle relaxants used for spastic neurological conditions – tetanus, hemiplegia etc.
117. LA act by blocking neuronal sodium channels in inactivated stage.
118. Prilocaine causes methamoglobinemia Bupivacaine has cardiotoxicity & tetracaine is PABA derivative.
119. Eutectic mixture of LA – lignocaine & prilocaine increases the penetration of lignocaine in tissue
120. Lower the solubility of drug reapid is onset as well as reversal
121. Mean alveolar concentration (MAC):- indicates the potency of anesthetic gas
122. Nitrous oxide – second gas effect & diffusional hypoxia, poor Skeletal muscles relaxants property, good analgesia & Euphoriant.
123. Halothane – potent anesthetic; but not a good analgesic nor a muscle relaxant, cardiac toxicity, malignant hyperthermia, hepatitis & safe in asthmatics.
124. Enflurane – seizures.
125. Sevoflurane – safe in pediatric patients – rapid onset & recovery – OPD basis anesthesia.
126. Thiopentone – re-distribution – rapid onset & recovery, requires prior atropinization – to prevent laryngospsm.
127. Ketamine – dissociative anesthesia – rise in all pressure in body – HTN, intracranial, intra-abdominal etc. bronchodilator – preffered for asthmatics.
128. Fentanyl – droperidol = neurolept analgesia.

RESPIRATORY DRUGS

Expectorants	Althea root. Antimony pentasulfide. Creosote . Guaiacolsulfonate. Guaifenesin. Ipecacuanha (Syrup of ipeacac). Levoverbenone. Potassium Iodide. Senega. Tyloxapol
Mucolytics	Acetylcysteine. Ambroxol. Bromhexine. Carbocisteine. Domiodol. Dornase Alfa. Eprazinone. Erdosteine. Letosteien. Mesna. Neltenexine. Sobrerol. Stepronin. Tiopronin.

Cough soppressants	Opium alkaloids, opioids, And derivatives	Acetyldihydrocodeine. Benzylmorphine. Codeine. Dextromethorphan. Diacetylmorphine. Dihydrocodeine. Dimemorfan. Droxypropine. Ethylmorphine. Hydrocodone. Hydromorphone. Isoaminile. Laudanum. Levomethadone . levopropoxyphene. Methadone. Nicocodeine. Nicodicodeine. Normethadone. Noscapine. Pholcodine. Thebacon. Tipepidine. Zipeprol.
	Other	Benzonatate . Benproperine. Bibenzonium Bromide. Butamirate. Clobutinol. Clofedanol. Cloperastine. Diphenhy dramine. Dibunate. Dimethoxanate. Dropropizine . Fedrilate. Glaucine . Levodropropizine. Meprotixol . Morclofone . Nepinalone . Oxolanide. Oxeladin. Pentoxyverine. Pipazetate. Prenoxdiazine. Piperidione.

Mucokinetics are a class of drugs which aid in the clearance of mucous from the airways, lungs, bronchi, and trachea. Such drugs can be further categorized by their mechanism of action.

- Expectorants
- Mucolytic agents
- Wetting agents / hypoviscosity agents
- Abhesives / surfactants

An expectorant (from the Latin expectorare, to expel from the chest) works by signaling the body to increase the amount or hydration of secretions, resulting in more yet clearer secretions and as a byproduct lubricating the irritated respiratory tract. A mucolytic agent is an agent which dissolves thick mucus and is usually used to help relieve respiratory difficulties. It does so by dissolving various chemical bonds within secretions, which in turn can lower the viscosity by altering the mucin – containing components.

Management of asthma –

Asthma medications are generally divided into 2 categories:

- Quick relief (also called reliever medications)
- Long-term control (also called controller medications)

Quick relief

Quick relief medications are used to relieve acute asthma exacerbations and to prevent exercise – induced asthma (EIA) or exercise – induced bronchospasm (EIB) symptoms. These medications include short – acting beta agonists (SABs), anticholinergics (used only for severe exacerbations), and systemic corticosteroids, which speed recovery from acute exacerbations.

Long – term control

Long-term control medications include inhaled corticosteroids (ICSs), cromolyn sodium, nedocromil, long-acting beta agonists (LABAs), combination inhaled corticosteroids and long – acting beta agonists, methylxanthines, and leukotriene antagonists. Inhaled corticosteroids are considered the primary drug of choice for control of chronic asthma, but unfortunately the response to this treatment is characterized by wide variability among patients.

Beta2-adrenergic agonist agents

Short –acting beta2 agonists

Salbutamol, levosalbutamol, terbutaline, pirbuterol, procaterol, metaproterenol, fenoterol, bitolterol mesylate, ritodrine

Long-acting beta$_2$ agonists

- Sameterol, formoterol, bambuterol, clenbuterol

Ultra – long-acting beta$_2$ agonists

- indacaterol

Class Summary

Beta$_2$ agonists (salbutamol, pirbuterol acetate, levalbuterol) relieve reversible bronchospasm by relaxing the smooth muscles of the bronchi. These agents act as bronchodilators and are used to treat bronchospasm in acute asthmatic episodes and to prevent bronchospasm associated with exercise-induced asthma or nocturnal asthma. Occupation of β_2 receptors by agonists results in the activation of the G_s-adenylyl cyclase – cAMP-PKA pathway, resulting in phosphorylative events leading to bronchilal smooth muscle relaxation.

Effects of β-Adrenergic Agonists on Airways
Relaxation of airway smooth muscle (proximal and distal airways)
Inhibition of mast cell mediator release
Inhibition of plasma exudation and airway edema
Increased mucociliary clearance
Increased mucus secretion
Decreased cough
No effect on chronic inflammation

Clinical Use

B_2- agonists are usually given by inhalation to reduce side effects. Short – acting β_2-agonists (SABAs) such as salbutamol and terbutaline have a rapid onset of bronchodilation and are, therefore, used as needed for symptom relief. Increased use of SABAs indicates that asthma is not controlled, they are also useful in preventing EIA if taken prior to exercise Long-acting β_2-agonists (LABAs) include salmeterol and formoterol, have replaced the regular use of SABAa, but LABAs should not be given in the absence of ICS therapy as they do not control the underlying inflammation. They do, however, improve asthma control and reduce exacerbations when added to ICS, which allows asthma to be controlled at lower doses of corticosteroids.

Side effects

Side Effects of β_2 Agonists

Muscle tremor (direct effect on skeletal muscle β_2 receptors
Tachycardia (direct effect on atrial β_2 receptors, reflex effect from increased peripheral vasodilation Via β_2 receptors)
Hypokalemia (direct β_2 effect on skeletal muscle uptake of K^+
Restlessness
Hypoxemia (increased V/Q mismatch due to reversal of hypoxic pulmonary vasoconstriction)

Tolerance

Tolerance is a potential problem with any agonist given chronically, but while there is down-regulation of β_2-receptors, this dose not reduce the bronchodilator response as there is a large receptor reverse in airway smooth – muscle cells.

Anticholinergic Agent

Muscarinic receptor antagonists such as ipratropium bromide, prevent cholinergic nerve- induced bronchoconstriction and mucus secretion. They are much less effective than β_2 – agonists in asthma therapy as they inhibit only the cholinergic reflex component of bronchoconstruction, whereas β_2 - agonists prevent all bronchoconstrictor mechanisms. Anticholinergics are, therefore, only used as an additional bronchodilator in patients with asthma that is not controlled by other inhaled medications. High doses may be given by nebulizer in treating acute severe asthma but should only be given following β_2 - agonists, as they have a slower onset of bronchodilation.

Side effects are not usually a problem as there is little or no systemic absorption. The most common side effect is dry mouth; in elderly patients, urinary retention and glaucoma may also be observed.

Methylxanthines

Theophylline is a methylxanthine similar in structure to the common dietary xanthenes caffeine and theobromine. Doxofyllineis less active as an adenosine antagonist and may have a more favorable side- effect profile. Mechanisms of action have been proposed:

- Inhibition of phosphodiesterases. Theophylline is a nonselective PDE inhibitor. PDE inhibition and the concomitant elevation of cellular cAMP and cyclic guanosine monophosphate (cGMP) almost certainly account for the nonbronchodilator effects of theophylline that are seen at lower concentrations. Inhibition of PDE should lead to synergistic interaction with β agonists through an increase in cAMP. Several isoenzyme families of PDE have now been recognized and those important in smooth muscle relaxation include PDE3, PDE4, and PDE5. Theophylline is a weak inhibitor of all PDE isoenzymes. Other PDE inhibitors are-

Phosphodiesterase inhibitors	
PDE1	Vinpocetine
PDE2	EHNA
PDE3	Amrinone. Anagrelide. Bucladesine. Cilostamide. Cilostazol. Enoximone. Milrinone. Quazinone. Siguazodan.Trequinsin. Vesnarinone.Zardaverine
PDE4	Arofylline. Cilomilast. Denbutylline. Drotaverine. Etazolate. Filaminast. Glaucine. Ibudilast. Irsogladine. Luteolin. Mesembrine. Roflumilast. Rolipram.
PDE5	Acetildenafil.Aildenafil. Avanafil. Dipyridamole. Icariin. Lodenafil. Microdenafil.

	Sildenafil.Sulfoaildenafil.Tadalafil. Udenafil. Vardenafil
PDE6	Zaprinast
PDE10	Papaverine . Tofisopam
Nonselective	Caffeine. Doxofylline. Pentoxifylline. Propentotylline. Theophylline

- Adenosine receptor antagonism. Theophylline antagonizes adenosine receptors at therapeutic concentrations. Adenosine antagonism is unlikely to account for the anti-inflammatory effects of theophylline but may be responsible for serious side effects, including cardiac arrhythmias and seizures through the antagonism of A_1 receptors.
- Interleukin – 10 release. IL-10 has a broad spectrum of anti-inflammatory effects, and there is evidence that its secretion is reduced in asthma. IL-10 release is increased by theophylline.
- Effects on gene transcription. Theophylline prevents the translocation of the pro-inflammatory transcription factor NF-κB into the nucleus, potentially reducing the expression of inflammatory genes in asthma and COPD.
- Effects on apoptosis. Theophylline also induces apoptosis in T lymphocytes, reducing their survival; this effect appears to be mediated via PDE inhibition.
- Histone deacetylase activation. Recruitment of histone deacetylase – 2 (HDAC2) by glucocorticoid receptors switches off inflammatory genes. Therapeutic concentrations of theophylline activate HDAC, thereby enhancing the anti- inflammatory effects of corticosteroids.
- Other effects. Several other effects of theophylline have been described, including an increase in circulating catecholamines, inhibition of calcium influx into inflammatory cells, inhibition of prostaglandin effects, and antagonism of tumor necrosis factor (TNF)α. These effects are generally seen only at concentrations of theophylline that are above the therapeutic range in asthma and are therefore unlikely to contribute to the anti-inflammatory actions of theophylline observed in asthmatics.

Factors Affecting Clearance of Theophylline
Increased clearance
Enzyme induction (mainly CYP1A2) by co-administered drugs (e.g., rifampicin, barbiturates, ethanol)
Smoking (tobacco, marijuana) via CYP1A2 induction
High-protein, low – carbohydrate diet
Barbecued meat
Childhood
Decreased clearance
CYP inhibition (cimetidine, erythromycin, ciprofloxacin, allopurinol, fluvoxamine, zileuton, zafirlukast)
Congestive heart failure
Liver disease
Pneumonia
Viral infection and vaccination
High- carbohydrate diet
Old age

Side Effects of Theophylline and Mechanisms

SIDE EFFECT	**PROPOSED MECHANISM**
Nausea and vomiting	PDE4 inhibition
Headaches	PDE4 inhibition
Gastric discomfort	PDE4 inhibition
Diuresis	A_1 receptor antagonism
Behavioral distrurbance (?)	?
Cardiac arrhythmias	PDE3 inhibition, A_1 receptor antagonism
Epileptic seizures	A_1 receptor antagonism

There is a close relationship between improvement in airway function and serum theophylline concentration. Below 10 mg/L, therapeutic effects in terms of bronchodilation are small;above 20 mg/L additional benefits are outweighed by side effects, so that the therapeutic range was generally taken to be 10-20 mg/L(55-110µM). Even within that range, toxicity can be observed, making theophylline a difficult drug to use. However, recent studies suggest that theophylline has anti- asthma effects other than bronchodilation below 10mg/L, so the therapeutic range is now taken as 5-15 mg/L.

Corticosteroid,

Corticosteroids are used intravenously (hydrocortisone or methylprednisolone) for the treatment of acute severe asthma, although several studies now show that OCS are as effective and easier to administer. A course of OCS (usually prednisone or prednisolone 30-45 mg once daily for 5-10 days) is used to treat acute exacerbations of asthma; no tapering of the dose is needed.

Side Effects of inhaled corticosteroids
Local side effects
Dysphonia
Oropharyngeal candidiasis
Cough
Systemic side effects
Adrenal suppression and insufficiency
Growth suppression
Bruising
Osteoporosis
Cataracts
Glaucoma
Metabolic abnormalities (glucose, insulin, triglycerides)
Psychiatric disturbances (euphoria, depression)
pneumonia

5- lipoxygenase Inhibitor

Class Summary

Like leukotriene receptor antagonists, 5-lipoxygenase inhibitors (Zileuton) act on leukotrienes.

Zileuton inhibits leukotriene formation, which, in turn, decreases neutrophil and eosinophil and eosinophil migration, neutrophil and monocyte aggregation, leukocyte adhension, capillary permeability , and smooth muscle contractions.

Mast cell stabilizers

Class Summary

These agents (cromolyn sodium) block early and late asthmatic responses, interface with chloride channels, stabilize the mast cell membrane, and inhibit the activation and release of mediators from eosinophils and epithelial cells. They inhibit acute responses to cold air, exercise, and sulfar dioxide. Cromolyn sodium inhibits the release of histamine, leukotrienes, and other mediators from sensitized mast cells exposed to specific antigens. It has no intrinsic anti-inflammatory, antihistamine, or vasoconstrictive effects.

Monoclonal Antibody

Omalizumab is a recombinant, DNA – derived, humanized IgG monoclonal antibody that binds selectively to human IgE on the surface of mast cells and basophils. It reduces mediator release, which promotes an allergic response. It is indicated for moderate – to – severe persistentasthma in patients who react to perennial allergens in whom symptoms are not controlled by inhaled corticosteroids.

Leukotriene Receptor Antagonist

Cysteinyl-leukotrienes are potent bronchoconstrictors, cause microvascular leakage, and increase eosinophilic inflammation through the activation of cys-LT_1 –receptors. These inflammatory mediators are produced predominantly by mast cells and, to a lesser extent, eosinophils in asthma. Antileukotreenes such as montelukast and zafirlukast, block cys- LT_1 –receptors and provide modest clinical benefit in asthma. They are less effective than ICS in controlling asthma and have less effect on airway inflammation, but are useful as an add-on therapy in some patients not controlled with low doses of ICS, although they are less effective than LABAs. They are given orally once or twice daily and are well tolerated. Zafirlukast is a selective competitive inhibitor of LTD4 and LTE4 receptors.

Novel Classes of Bronchodilators

- Magnesium sulfate (MgSO4) is useful as an additional bronchodilator in patients with acute severe asthma.
- K^+ channels are involved in recovery of excitable cells after depolarization and are important in stabilization of cells. K^+ channel openers such as cromakalim or levcromakalim (the levo – isomer of cromakalim) open ATP-dependent K^+ channels in smooth muscle, leading to membrane hyperpolarization and relaxation of airway smooth muscle, this suggests that K^+ channel activators may be useful as bronchodilators.
- Atrial natriuretic peptide (ANP) avtivates membrane – bound guanylyl cyclase and increases cellular cyclic GMP, leading to bronchodilation by mechanism similar to those of NO on smooth muscle.

KIDNEY

DIURETICS

Diuretics mainly exert their effect by the inhibition of renal tubular reabsorption of sodium and water.

Major Segments of the Nephron and Their Functions.

Segment	Functions	Water Permeability	Primary Transporters and Drug Targets at Apical Membrane	Diuretic with Major Action
Glomerulus	Formation of glomerular filtrate	Extremely high	None	None
Proximal convoluted tubule (PCT)	Reabsorption of 65% of filtered Na^+/ K^+/ CA^{2+}, and Mg^{2+}; 85% of NaHCO3 , and nearly 100% of glucose and amino acids. Isosmotic reabsorption of water.	Very high	Na/H^1 (NHE3), carbonic anhydrase	Carbonic anhydrase inhibitors
Proximal tubule, straight segments	Secretion and reabsorption of organic acids and bases, including uric acid and most diuretics	Very high	Acid (eg, uric acid) and base transporters	None
Thin descending limb of Henle's loop	Passive reabsorption of water	High	Aquaporins	None
Thick ascending limb of Henle's loop (TAL)	Active reabsorption of 15–25% of filtered Na^+/ K^+/ Cl^-; secondary reabsorption of Ca^{2+} and Mg^{2+}	Very low	Na/K/2Cl (NKCC2)	Loop diuretics
Distal convoluted tubule (DCT)	Active reabsorption of 4–8% of filtered Na^+ and Cl^-; Ca^{2+} reabsorption under parathyroid hormone control	Very low	Na/Cl (NCC)	Thiazides
Cortical collecting tubule (CCT)	Na^+ reabsorption (2–5%) coupled to K^+ and H^+ secretion	Variable[2]	Na channels (ENaC), K channels,[1] H transporter,[1] aquaporins	K^+-sparing diuretics

Medullary collecting duct	Water reabsorption under vasopressin control	Variable[2]	Aquaporins	Vasopressin antagonist

[1]Not a target of currently available drugs

CLASSIFICATION:

Diuretics may be classified according to 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.

1) **DIURETICS ACTING ON THE PROXIMAL TUBULE (PT)**

Carbonic anhydrase inhibitors and osmotic diuretics act by inhibiting reabsorption in the proximal tubular portion of the nephron.

a) **Carbonic anhydrase (CA) inhibitors**

Luminal membrane of proximal tubules contain Na^+–H^+ antiporter which helps in the excretion of H^+ in exchange with absorption 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, net effect of carbonic anhydrase is to cause absorption of sodium and bicarbonate. Inhibitors of this enzyme result in the excretion of sodium and bicarbonate in the urine. Due to urinary excretion of bicarbonate, metabolic acidosis ensues that result in less filtration of HCO_3^- at the glomerulus. Therefore, action of these diuretics is self limiting.

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 more 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 its use in absence seizures). Acetazolamide can be used orally for 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 liver disease due to risk of precipitation of hepatic coma. In liver disease, NH_3 is not converted to urea and if present in excess, can cross blood brain barrier resulting in encephalopathy. It is excreted through kidney after conversion to NH_4^+ (combines with H^+ in nephron). CA inhibitors decrease excretion of H^+ resulting in more reabsorption of ammonia (it is in non ionized form in alkaline medium) and thus more toxicity.

b) **Osmotic diuretics**

Mannitol, glycerol and isosorbide are inert drugs that can cause osmotic diuresis. When given i.v., mannitol increases osmotic pressure in blood vessels and consequent removal of excess fluid from cells (basis of its use in glaucoma and raised intracranial tension) resulting in 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). Again due to osmotic effect, fluid is retained in the lumen of PT (responsible for the diuretic effect). It also inhibits reabsorption in ascending limb of loop of Henle by an unknown mechanism. Along with water, excretion of all cations and anions is increased. Properties for a substance to act as an ideal osmotic diuretic are:

1) It should exert osmotic effect.
2) It should be pharmacologically inert.
3) It should be freely filtered at the glomerulus.
4) 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 raised intracranial tension. It can also be used to maintain GFR in 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 because in this situation, mannitol can leak from ruptured cerebral blood vessels resulting in increased ICT (more fluid retention due to osmotic effect in the cells). If given orally, mannitol can result in osmotic diarrhea. Isosorbide and glycerol can be used orally for glaucoma and raised intracranial tension.

2) **DIURETICS ACTING ON THE LOOP OF HENLE**

These are also known as loop diuretics and act by causing inhibition of $Na^+ K^+ 2Cl^-$ symporter present at the luminal membrane of ascending limb of loop of Henle. Furosemide, torsemide, bumetanide, ethacrynic acid 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 tubular lumen through secretion (by organic anion transporter) in PT. Loop of Henle is responsible for maintaining 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).

Lop 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 urine). Loop diuretics also changes 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 diuretics of choice in presence of moderate to severe renal failure.

- Furosemide possesses vasodilatory action which is responsible for quick relief in LVF and pulmonary edema (used i.v.).
- Bumetanide is most potent loop diuretic and produces less adverse effects than furosemide.
- Ethacrynic acid is highly ototoxic with steep DRC.
- Mersalyl like organomercurials are not used now because of risk of kidney damage.

Uses: Main use of loop diuretics is to remove 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 more excretion whereas thiazides cause hypercalcemia by decreasing its excretion. Ethacrynic acid can cause ototoxicity.

3) DIURETICS ACTING ON DISTAL TUBULES AND CD

a) **Thiazides**

Drugs in this group include chlorthiazide, hydrochlorthiazide, benzthiazide, hydroflumethiazide, chlorthalidone, metolazone and indapamide. These drugs act by inhibiting Na^+-Cl^- symporter at the luminal membrane of early DT. This part of DT is 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 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 doesn't increase appreciably with increase in dose). These drugs tend to reduce GFR, therefore are not indicated in renal failure patients.

- 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 natriuretic effect.

Uses: Thiazides are used as first line antihypertensive drugs. These are also used to mobilize edema fluid in mild to moderate heart failure. Paradoxically, these drugs decrease urine output in diabetes insipidus.

Thiazides reduce 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.

Interactions

- Thiazides and loop diuretics enhances digitalis toxicity by causing hypokalemia.
- 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 in PT).
- Resistance to loop diuretics can be reversed by addition of thiazides and resistance to latter can be decreased by adding potassium sparing diuretics.

b) **Potassium sparing diuretics**

These diuretics act in 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 which inhibit the epithelial Na^+ channels or the actions of aldosterone will cause decreased reabsorption of Na^+ (diuretic effect) and less excretion of K^+ (potassium sparing effect) and H^+.

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 traveling through lumen, these drugs reach its site of action i.e. late DT and CD. Important members of this group are amiloride and triamterene. Amiloride is more potent and longer acting than triamterene. Triamterene is less often used because of incomplete absorption, photosensitivity and impairment of glucose tolerance. Amiloride decreases Mg^{++} and Ca^{++} excretion and increases urate excretion.

Lithium is absorbed through epithelial Na^+ channels in 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 secretions in cystic fibrosis.

b. **Aldosterone antagonists**

Spironolactone and epleronone antagonize the action of aldosterone and produce effects similar to amiloride. These drugs act from interstitial site of tubular cell (all other drugs 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. Spironolactone can be used for the treatment of hirsutism because of its anti-androgenic action.

Adverse effects and interactions: Spironolactone can cause gynaecomastia and impotency. Hyperkalemia, abdominal pain and aggravation of peptic ulcer can also occur. ACE inhibitor and potassium supplements increase the risk of hyperkalemia, if used along with these agents.

ANTIDIURETICS

The drugs that decrease urine volume are called antidiuretics. Primary indication of antidiuretics is diabetes insipidus (DI). 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 V1, V2 and V3.

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 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 release of NO) has also been demonstrated.
- ADH is also involved in the release of vWF and factor VIII from endothelium. This action is also mediated by V_2 receptors.

USES

- Major indication of ADH is central DI. DI is the 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 used orally or intranasally.
- Desmopressin can also be used for nocturnal enuresis (in adults) and bed wetting in children.
- 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.
- 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.

ADVERSE EFECTS 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 patients with ischemic heart disease and hypertension.

OTHER ANTIDIURETICS

THIAZIDES

These drugs are used as diuretics but in DI, these exert paradoxical effect (decrease urine formation). This paradoxical effect is believed to be due to increased formation of cAMP in the distal tubules. These are low efficacy antidiuretics but are beneficial in both central as well as nephrogenic DI.

CHLORPROPAMIDE and CARBAMAZEPINE

These drugs increase the action of ADH on kidney and are useful only in central DI.

AMILORIDE

It is the agent of choice for treatment of Lithium induced DI.

HEMATOLOGY

HAEMATINICS

These are agents required in formation of blood and treatment of anemia. Main haematinics include iron, folic acid and vitamin B12. Others substances like copper, pyridoxine etc are also required in small quantities for formation of blood.

Iron:

Daily requirement of iron is 1 mg in adult male, 2 mg in menstruating female and 3-5 mg in pregnancy. 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 form of ferrous (Fe^{2+}). Heme contains the iron in ferrous form and most of inorganic iron is in ferric form (Fe^{3+}). 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, the 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 increases 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 parentral 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 (app. 325 mg TDS) daily. 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. Major adverse effects of oral iron that result in poor compliance are gastro intestinal problems like epigastric pain, nausea, vomiting and metallic taste etc. These are related to elemental iron content in the iron preparation.

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, which can cause iron toxicity due to more free iron. 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 POISONING: Acute iron poisoning can occur in children due to accidental intake of large number of 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 deferipirone is preferred.

Folic Acid

It consists of pteridine, paraaminobenzoic acid (PABA) and glutamic acid. Dietary folic acid is in form of polyglutamates and these are cleaved off in 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 homocystiene 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 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. 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, meet, 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 homocystiene 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). 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 factors 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 thrombopoetin and IL-11. Erythropoietin is secreted from kidney and help in formation of red blood cells. Recombinant human erythropoietin (Epoietin) is mainly useful for anemia due to chronic renal failure, and also due to bone marrow suppressing drugs like Zidovudine and anticancer drugs. Major adverse effect is polycythemia and hypertension. Recombinant G-CSF is Filgrastim and recombinant GM-CSF is Sargramostim. These are used for leucopenia induced by cancer chemotherapy and also useful for harvesting peripheral blood stem cells (these substances results 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. Oprelvekin is the drug, which is recombinant IL-11 and is used for prevention and treatment of thrombocytopenia induced by cancer chemotherapy.

COAGULANTS

Main Coagulant in the body is vitamin K. It is of three types K1 (Phytonadione), K2 (Menaquinone) and K3 (Menadione). 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. Main indications of using of 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 K1 is used. Menadione (K3) is contra-indicated in patient with G-6-PD deficiency (causes hemolysis) and in newborn (more chances of kernicterus by competitive inhibition of glucuronidation of bilirubin and its displacement from plasma protein binding sites).

ANTICOAGULANTS

Three major groups of anticoagulants are used in vivo; oral anticoagulants (warfarin group), indirect thrombin inhibitors (heparin group) and direct thrombin inhibitors. Heparin can be used both in vivo as well as in vitro.

ORAL ANTICOAGULANTS:

Drugs in this group includes 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 is required for this activity. Oral anticoagulants prevents this regeneration, 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. Protein C has shortest half life, so it is first to decline and its deficiency may lead to dermal vascular necrosis and hyper coagulation (protein C is anti-clotting) as early appearing 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 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 treatment of choice but specific antidote will be 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 (growth retardation, hypoplasia of nose and hand bones etc.) if used during pregnancy (therefore contra-indicated). Prothrombin time is used to adjust the dose of warfarin (because it mainly affects the intrinsic 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.

$$INR = (PT \text{ of patient}/PT \text{ of reference})^{ISI}$$

Where ISI is international sensitivity index that depends on the sensitivity of reference thromboplastin to WHO standard thromboplastin.

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, Griesofulvin etc) and oral contraceptives (increase clotting factors) decrease the effect and thus require increase in dose of warfarin.

INDIRECT THROBIN INHIBITORS

This group includes unfractionated heparin, low molecular weight heparin (Enoxaparin, dalteparin) and Fondaparinux. 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 intestines. 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 induces 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. 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). It does not cross the placenta and is thus anticoagulant of choice during pregnancy. At higher doses, heparin also exerts antiplatelet action. Bioavailability of unfractionated heparin is inconsistent after s.c. route and the effect is monitoring by testing aPTT (at low doses it selectively affects the intrinsic pathway). LMW heparin and fondaparinux have long half lives and consistent absorption; therefore do not require monitoring and once daily s.c. doses are sufficient. 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). Other adverse effects include thrombocytopenia, alopecia, osteoporosis and hypersensitivity reactions. Thrombocytopenia may occur due to formation of antibodies against platelets that can result in paradoxical thrombosis. Warfarin is contraindicated in such a case and also LMW heparin or Fondaparinux should not be used. Anticoagulant of choice for this situation is direct thrombin inhibitors like Lepirudin.

	HEPARIN	**ORAL ANTICOAGULANTS**

1. Route of admin 2. Onset of action 3. Activity 4. MOA 5. Monitor 6. Antagonists 7. Placental barrier 8. Use	Parenteral, (I/V, SC) Rapid In vitro and in vivo Activates Antithrombin III aPTT Protamine sulphate Does not cross placenta To initiate therapy	Oral Delayed (1-3 days) In vivo only ↓ activation of II, VII, IX, X PT Vit. K1 (Phytonadione) Fetal warfarin syndrome For maintenance

DIRECT THROMBIN INHIBITORS

This group includes hirudin, Lepirudin, bivalirudin, argatroban, melagatran and Ximelagatran. Ximelagatran is pro drug of melagatran and 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.

USES OF ANTICOAGULANTS

These drugs 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).

CONTRA-INDICATIONS OF ANTICOAGULANTS

All anticoagulants are contra-indicated in the conditions having increased risk of bleeding like in 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 in inactivated by circulating antiplasmins. Fibrinolytics are the drug which activates Plasminogen to form plasmin and thus helps 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, Urokinase, Alteplase and reteplase. Streptokinase is obtained from beta hemolytic streptococci. It activates fibrin bound as well as circulating plasminogen (other drugs of this group activate selectively

fibrin bound 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. Urokinase is isolated from human urine and is not antigenic. Alteplase and reteplase are recombinant tPA. These are not antigenic and are more efficacious than streptokinase but incidence of hemorrhage is similar to streptokinase and Urokinase. Main indication of these drugs is treatment of acute myocardial infarction, for which these should be given i.v. within 12 hours preferably within first 3-6 hours. These are also indicated in severe, life threatening pulmonary hemorrhage. These drugs are also contra-indicated in the conditions where risk of bleeding is more. Epsilon amino caproic acid (EACA) and tranexaemic acid are specific antidotes for overdose of fibrinolytic agents.

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, TXA_2, serotonin and other substances that promote further aggregation by activating Gp IIb/IIIa receptors on the platelet surface. PGI_2 (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 formation of prostacyclins. The net effect is inhibition of TXA2 synthesis leading to anti-aggregatory effects. Aspirin inhibits thromboxane synthesis but do not inhibit the enzyme thromboxane synthetase (dazoxiben is inhibitor of this enzyme). For antiplatelet action lowest doses of aspirin are required (60-325 mg). it has no effect on platelet survival time and their adhesion to vessel wall. Dipyridamole is another drug which acts by inhibiting phosphodiesterase (which breaks down cAMP) resulting in increased cAMP that potentiates prostacyclins and thus anti-aggregation. Ticlopidine and clopidogrel acts as 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. Both of these drugs are prodrugs and are converted to active metabolite in the liver. Ticlopidine causes thrombocytopenia and thus less commonly used, whereas clopidogrel is better tolerated. Gp IIb/IIIa antagonists are strongest antiplatelet drugs as they block aggregation induced by all agonists. Abciximab is monoclonal antibody against this receptor and is not antigenic. 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).

GIT

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).

The main strategies employed for treatment of peptic ulcer disease and gastritis is to:

a) Neutralize gastric acid by antacids.

1. ANTACIDS

These drugs are weak bases that neutralize gastric acid (do not decrease the volume of acid secreted).

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 doesn't 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 water repellant, pharmacologically inert anti foaming agent. It reduces gastric 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).

b.Decrease secretion of acid in stomach.

1. DRUGS DECREASING ACID SECRETION

i) ***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.

PPIs are given orally in early morning empty stomach (just before breakfast). Pantoprazole is the only PPI that 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 drug of choice (DOC) for PUD due to any etiology (even NSAID induced). These are also the drugs of choice for gastroesophageal reflux disease (GERD) and Zollinger Ellison Syndrome (ZES). In stress induced gastric bleeding, H2 blockers are preferred over PPIs.

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.

Note:

- Lansoprazole is most potent PPI.

- Pantoprazole can be given i.v.

ii) ***H2 receptor antagonists*:** These drugs competitively inhibit H_2 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 H_2 blockers. Drugs in this group are cimetidine, ranitidine, famotidine, roxatidine, nizatidine and loxatidine.

These drugs are more effective for reducing basal acid secretion than stimulated acid secretion. These drugs can be used for GERD, PUD, ZES and prevention of stress induced ulcers. Cimetidine is not used routinely because:

1) It can cross blood brain barrier and result in mental state changes.
2) It inhibits binding of dihydrotestosterone to androgen receptors that can manifest as impotence in males.
3) It inhibits metabolism of estradiol and increases serum prolactin levels on long term use, thus can cause gynaecomastia (in males) and galactorrhoea (in females).
4) It is potent inhibitor of CYP enzymes and can increase plasma concentration of warfarin, theophylline and many other drugs.
5) It is least potent PPI.

Note:

- Famotidine is most potent H_2 blocker
- Loxatidine is a non-competitive blocker of H_2 receptors.
- Nizatidine also possess anti-AChE activity and can cause bradycardia and enhanced gastric emptying.

iii) ***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 M_1 blockers that are preferred antimuscarinic agents for peptic ulcer disease as these are devoid of anticholinergic adverse effects.

C.Increase protective factors like mucus and bicarbonate.

2. DRUGS INCREASING PROTECTIVE FACTORS

PGE_1, PGE_2 and PGI_2 act as anti-ulcer drugs by increasing the release of mucus and bicarbonate and by increasing the mucosal blood flow. PGs also inhibit H^+K^+ ATPase and decrease the acid production. Misoprostol (PGE_1 analogue) is MOST SPECIFIC drug for treatment and prevention of NSAID induced peptic ulcers (DOC is PPI). Enprostil and rioprostil (PGE_2 analogue) are other drugs in this group. Commonest side effect of PG analogues is diarrhea and colicky abdominal pain.

3. 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.

i) **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).
ii) **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).

4. ULCER HEALING DRUGS

Carbenoloxone is obtained from the roots of liquorice. 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.

5. ANTI H. PYLORI DRUGS

H. pylori infection can be detected by "urea breath test". It is responsible for relapse of PUD. Drugs used for H pylori include:

Regimens Recommended for Eradication of *H. Pylori* Infection	
Drug	**Dose**
Triple Therapy	
1. Bismuth subsalicylate*plus*	2 tablets qid
Metronidazole*plus*	250 mg qid
Tetracycline[a]	500 mg qid
2. Ranitidine bismuth citrate *plus*	400 mg bid
Tetracycline*plus*	500 mg bid
Clarithromycin or metronidazole	500 mg bid
3. Omeprazole (lansoprazole) *plus*	20 mg bid (30 mg bid)
Clarithromycin*plus*	250 or 500 mg bid
Metronidazole[b] *or*	500 mg bid
Amoxicillin[c]	1 g bid
Quadruple Therapy	
Omeprazole (lansoprazole)	20 mg (30 mg) daily
Bismuth subsalicylate	2 tablets qid
Metronidazole	250 mg qid
Tetracycline	500 mg qid

These are used as three drug combination (triple therapy) for 2 weeks (one week regimen is less effective). US-FDA approved regimen is lansoprazole (30 mg) + amoxicillin (1000 mg) + clarithromycin (500 mg) for 2 weeks. Four drug regimens (including bismuth compounds) can also be used.

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 ($5HT_3$)

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 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 drug) 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
- D_2 blockers although effective should not be used due to their teratogenic potential

CHEMOTHERAPY INDUCED VOMITING

- 5 HT_3 blockers like ondansetron, granisetron and dolasetron are DOC for this condition.
- Dolasetron is most potent 5 HT_3 blocker but it may prolong QT interval
- Efficacy of these drugs increases if used along with antihistaminics, D_2 blockers or dexamethasone.
- D_2 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 former condition is $5HT_3$ blocker whereas for the latter condition, DOC is aprepitant (substance P antagonist).

POST OPERATIVE VOMITING:

5 HT_3 antagonists are preferred over other drugs.

OTHER DRUGS FOR VOMITING

- Steroids like dexamethasone can be used as anti emetic agents in chemotherapy induced vomiting
- Dronabinol (a cannabinoid) also possesses anti emetic properties and acts by stimulating CB_1 receptors

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 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 don't 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-HT_4) as well as inhibitory ($5HT_3$, D_2) presynaptic receptors.

Thus D_2 and $5HT_3$ antagonists and 5 HT_4 agonists will increase the release of ACh and stimulate the GI motility.

Metoclopramide: It possesses central as well as peripheral D_2 blocking action. Central D_2 blocking action is responsible for its anti emetic effects.

- It is also a prokinetic drug due to agonistic action at $5HT_4$ receptors (main mechanism) and antagonistic action at $5HT_3$ 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 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.)
- D_2 blocking action can result in extrapyramidal side effects (muscle dystonia, Parkinsonism etc.) and hyperprolactinemia. Latter may lead to gynaecomastia (in males) and galactorrhoea (in females).

Domperidone: It is a D2 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.

5 HT4 AGONISTS: Cisapride, mosapride, renzapride, prucalopride and tegaserod are 5-HT_4 agonistic drugs with no action on D2 receptors (no anti emetic 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 enzymes inhibitors like ketoconazole and erythromycin (increased chances of torsades de pointes, an arrhythmia with QT prolongation). Mosapride and renzapride don't prolong QT interval. Tegaserod can be used for constipation dominant irritable bowel syndrome.

OTHER PROKINETIC DRUGS:

- Levosulpiride is a newer D_2 blocker having prokinetic activity.
- Loxiglumide is CCK_1 receptor antagonist.

DRUGS FOR 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.
- *For diarrhea dominant IBS, drugs that can be used are*
- Loperamide or diphenoxylate
- New κ opioid receptor antagonist- Fedotozine
- Reserpine analog – Mebeverine
- 5 HT_3 antagonist – Alosetron (also reduces pain)
- Clonidine (also reduces distension induced pain)

- *For constipation dominant IBD, drugs effective are*
- 5 HT4 agonists (tegaserod, prucalopride)
- Loxiglumide

CONSTIPATION

High fibre diet, adequate fluid intake and regular exercise are best measures to prevent constipation. Patients not responding to these medications may require laxatives. These can be classified as

1) Bulk forming laxatives e.g psyllium and methylcellulose
2) Stool softeners e.g docusate, glycerin
3) Osmotic laxatives like milk of magnesia, lactulose and polyethylene glycol
4) Stimulant purgatives e.g. senna,cascara, phenolphthalein and castor oil

- Chronic use of antaraquinone derivatives (like sena and cascara) may lead to melanosis coli (brown pigmentation of colon)
- Phenolphthalein is not used now due to risk of cardiotoxicity

DIARRHOEA

Diarrhea can be treated by antibiotics effective against the causative organism. In non infective diarrhea, various drugs are useful

Opioids: loperamide is non addictive over the counter anti diarrheal drug. Diphenoxylate 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.

Octeotide: this long acting somatostatin analog can be used to decrease secretory diarrhea and other symptoms of carcinoid syndrome and VIPoma. In higher doses, it is also useful for the treatment of diarrhea due to vagotomy, short bowel syndrome and AIDS.

Hydration must be maintained to prevent fluid depletion and shock. It is mostly accomplished by the institution of oral rehydration solution.

Oral Rehydration Solution (ORS): 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 diarrheas. Trisodium citrate is added to prevent acidosis. Composition of ORS used previously and now is as follows:

	WHO 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

TABLE 2

In new formula WHO-ORS, concentration of NaCl and glucose as well as total osmolarity is decreased because

- WHO standard fomula 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 nowadays 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.

INFLAMMATORY BOWEL DISEASE

Ulcerative colitis and Crohn's disease are two distinct disorders classified under inflammatory bowel disease. (IBD)

1) *Aminosalicylates*: 5-aminosalicylic acid (5-ASA) is the main anti inflammatory compound that acts topically in the colon. When given alone by oral route, more than 80% is absorbed in proximal intestines and very little reaches the diseased site i.e. colon. To decrease the aborption it may be associated with some inert compound. Sulfasalazine (5-ASA + sulphapyridine), 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 stomach and the combination reaches the colon where the bacteria cleaves the azo bond to free 5-ASA for action. 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 first line treatment for treatment of 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 stimulate a secretory diarrhea.

2) *Glucocorticoids*: prednisone, prednisolone, hydrocortisone and budesonide are used in the treatment of moderate to severe ulcerative colitis and Crohn's disease.

3) *Purine analogs*: azathioprine and 6-MP are important agents in induction and maintenance of remission of ulcerative colitis and Crohn's disease.

4) *Methotrexate*: it is used in induction and maintenance of remission of Crohn's disease but not ulcerative colitis.

5) *Anti TNFα therapy*: infliximab and etanercept are useful in Crohn's disease. Efficacy in ulcerative colitis is doubtful.

SUMMARY Drugs Used Primarily for Gastrointestinal Conditions

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
DRUGS USED IN ACID-PEPTIC DISEASES				
• Proton pump inhibitors (PPIs), eg, omeprazole, lanso prazole	Irreversible blockade of H^+, K^+-ATPase pump in active parietal cells of stomach	Long-lasting reduction of stimulated and nocturnal acid secretion	Peptic ulcer, gastroesopha-geal reflux disease, erosive gastritis	Half-lives much shorter than duration of action • low toxicity • reduction of stomach acid may reduce absorption of some drugs and increase that of others
• *H_2-receptor blockers, eg, cimetidine: Effective reduction of nocturnal acid but less effective against stimulated secretion; very safe, available over the counter (OTC). Cimetidine, but not other H_2 blockers, is a weak antiandrogenic agent and a potent CYP enzyme inhibitor*				
• *Sucralfate: Polymerizes at site of tissue damage (ulcer bed) and protects against further damage; very insoluble with no systemic effects; must be given four times daily*				
• *Antacids: Popular OTC medication for symptomatic relief of heartburn; not as useful as PPI and H_2 blockers in peptic diseases*				
DRUGS STIMULATING MOTILITY				
• Metoclopramide	D_2-receptor blocker • removes inhibition of acetylcholine neurons in enteric nervous system	Increases gastric emptying and intestinal motility	Gastric paresis (eg, in diabetes) • antiemetic (see below)	Parkinsonian symptoms due to block of central nervous system (CNS) D_2 receptors
• *Domperidone: Like metoclopramide, but less CNS effect; not available in USA*				
• *Cholinomimetics: Neostigmine often used for colonic pseudo-obstruction in hospitalized patients*				
• *Macrolides: Erythromycin useful in diabetic gastroparesis but tolerance develops*				
LAXATIVES				
• Magnesium hydrox ide, other nonabsorb able salts and sugars	Osmotic agents increase water content of stool	Usually causes evacuation within 4–6 h, sooner in large doses	Simple constipation; bowel prep for endoscopy (especially PEG solutions)	Magnesium may be absorbed and cause toxicity in renal impairment
• *Bulk-forming laxatives: Methylcellulose, psyllium, etc: increase volume of colon, stimulate evacuation*				
• *Stimulants: senna, cascara; stimulate activity; may cause cramping*				
• *Stool surfactants: Docusate, mineral oil; lubricate stool, ease passage*				
• *Chloride channel activator: Lubiprostone, prostanoic acid derivative, stimulates chloride secretion into intestine, increasing fluid content*				
• *Opioid receptor antagonists: Alvimopan, methylnaltrexone; block intestinal μ-opioid receptors but do not enter CNS, so analgesia is maintained*				
• *5-HT_4 agonists: Tegaserod; activates enteric 5-HT_4 receptors and increases intestinal motility*				
ANTIDIARRHEAL DRUGS				
• Loperamide	Activates μ-opioid receptors in enteric nervous system	Slows motility in gut with negligible CNS effects	Nonspecific, noninfectious diarrhea	Mild cramping but little or no CNS toxicity
• *Diphenoxylate: Similar to loperamide, but high doses can cause CNS opioid effects and toxicity*				
• *Colloidal bismuth compounds: Subsalicylate and citrate salts available. OTC preparations popular and have some value in travelers' diarrhea due to adsorption of toxins*				
• *Kaolin + pectin: Adsorbent compounds available OTC in some countries*				
DRUGS FOR IRRITABLE BOWEL SYNDROME (IBS)				
• Alosetron	5-HT_3 antagonist of high potency and duration of binding	Reduces smooth muscle activity in gut	Approved for severe diarrhea-predominant IBS in women	Rare but serious constipation • ischemic colitis • infarction
• *Anticholinergics: Nonselective action on gut activity, usually associated with typical antimuscarinic toxicity*				
• *Chloride channel activator: Lubiprostone (see above); useful in constipation-predominant IBS in women*				

(continued)

CVS

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 cardiac contractility (systolic failure; as seen in ischemic heart disease and dilated cardiomyopathy etc.) or in ventricular relaxation (diastolic failure; as seen in hypertension and hypertrophic cardiomyopathy etc.). Ionotropic 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 ionotropic drugs. Human body also has compensatory mechanisms to maintain 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 kidney due to β_1 stimulation. Increased renin will stimulate 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 will increase the after load and that of venules will increase the preload, thus leading to increase workload on heart. Cardiac remodeling is responsible for 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 ionotropic agents.

1. Diuretics

In heart failure there is accumulation of fluid in 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. Chronic use of these diuretics may lead to development of resistance to diuretic effect 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 morality.

2. Ionotropic Drugs

Major ionotropic drugs used in CHF are dobutamine, dopamine, inodilators and cardiac glycosides. These drugs are used for short term management of acute CHF (except digitalis that can be used orally for maintenance also).

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

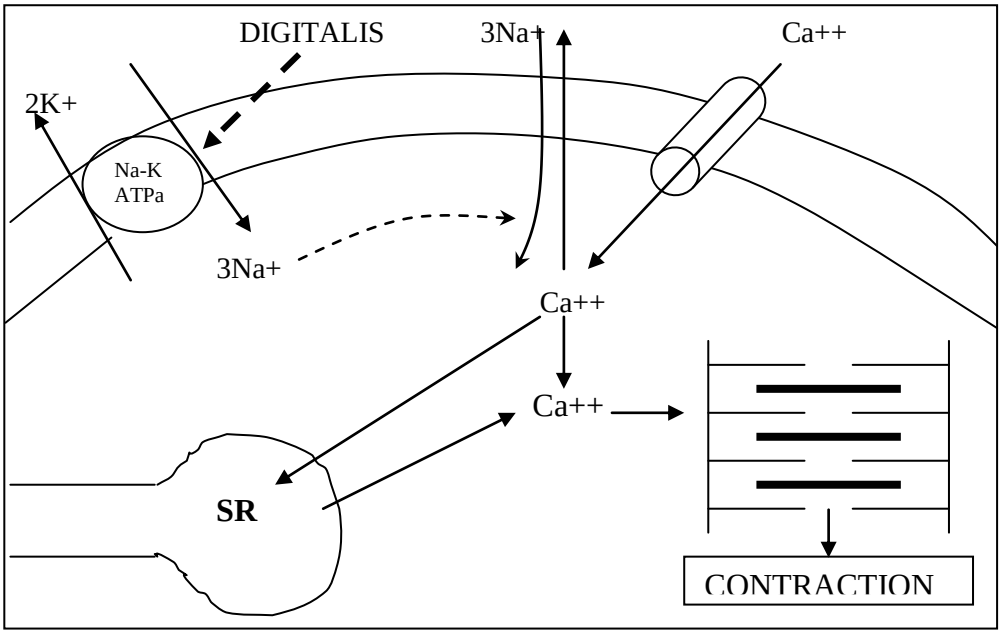
It acts on dopamine, β and α receptors depending on the concentration. At a dose of less than 2µg/kg/min., it stimulates only dopamine receptors leading to renal vasodilation. Intravenous infusion at the rate of 2-5µg/kg/min. stimulates heart by the agonistic action at β_1 receptors. At still higher dose (>5µg/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 ionotropic drugs but unlike other ionotropes, 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).

Mechanism of action

In CHF, these drugs act by inhibiting Na^+K^+ATPase of myocardial fibres by binding to its extracellular face. This result in accumulation of sodium in the cardiac cell, which in turn results in increased intracellular calcium. Normally Ca^{++} comes inside the cell in exchange with Na^+ by Na^+-Ca^{++} exchanger. When intracellular Na^+ is high, more sodium is not required in cell, so Ca^{++} is not extruded resulting in raised Ca^{++} in the cell. Increased intracellular Ca^{++} triggers release of Ca^{++} from the sarcoplasmic reticulum and finally results in increase in contractility. Binding of cardiac glycosides to Na^+K^+ATPase is slow and also after binding, intracellular Ca^{++} increases gradually. These factors are responsible for 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.



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 ventricles. But if all the contractions are passed to ventricles, cardiac output will decrease because ventricular contractions will also become ineffective due to 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 normal AV node but not through 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. Plasma t½	5 – 7 days	40 hrs
5. Elimination	Hepatic metabolism	Renal excretion (by glomerular filtration)
6. Dose adjustment in	Liver failure	Kidney failure
7. Uses	Maintenance	Routine t/t & emergency

Adverse effects and toxicity: Evaluation of adequate response to digitalis therapy is primarily by monitoring clinical symptoms; ECG is usually not valuable unless arrhythmias occur. Earliest appearing adverse effect is referable 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. Most common are pulsus bigeminus and ventricular extrasystoles. 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 drug to Na^+K^+ATPase) but in severe digitalis toxicity K^+ is rather contra-indicated because already there is excess of K^+ is extracellular fluid. For ventricular arrhythmias, lignocaine is the drug of choice (phenytoin is alternative). For atrial tachyarrhythmia, beta blockers like propanolol may be given and for bradyarrhythmias and AV block, atropine is the agent of choice. For very severe toxicity, digoxin antibody (digiband) is preferred.

Contra-indications and interactions: Hypokalemia, hypomagnesaemia and hypercalcemia increases the risk of digitalis toxicity. Diuretics like thiazides and furosemide (cause hypokalemia and hypomagnesaemia) 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 toxicity. In thyrotoxicosis and acute myocarditis, the chances of developing digitalis induced arrhthmias 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.

D. INODILATORS

Drugs in this group include inamrinone (previously known as amrinone), milrinone and vesnarinone. Name inodilators is obtained from their action as ionotropic 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 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.

3. NESIRITIDE

It is 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 kidney. It has short half life and has been used i.v. for acute CHF associated with dyspnoea at rest. The limiting factor is its breakdown by enzyme neutral endopeptidase (NEP) in the body. Inhibitors of this enzyme are being tested for use in CHF.

TREATMENT OF COMPENSATED/CHRONIC CHF

Main aim is to decrease the work of heart by decreasing preload and afterload and to decrease the mortality by reversing cardiac remodeling. Major drugs used for chronic CHF are vasodilators, beta blockers and aldosterone antagonists.

1. Vasodilators: The drugs may act by reducing preload (venodilators), afterload (arteriolar dilators) or both (combined arteriolar and venodilators). Nitrates preferentially dilate veins therefore use 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 L/min/m^2) and without markedly increased central venous pressure (<18 mm Hg). Calcium channel blockers should not be used in CHF because these drugs may result in increase in mortality in CHF (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 hypertension unless these are contraindicated. These will decrease 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 found to result in decreasing the mortality. Other vasodilators do not prolong the survival in CHF.

2. Aldosterone antagonist: Spironolactone and epleronone are aldosterone antagonists and are being used as potassium sparing diuretics. Their diuretic effect is quite feeble but in CHF these drugs reduce the mortality because of antagonism of aldosterone (reversal of remodeling). These can also be added to thiazides if tolerance develops.

3. Beta blockers: Previously beta blockers were assumed to be contra-indicated in CHF due to their negative ionotropic action but now it has been found that if used carefully, these drugs can increase the longevity of CHF patients (β_1 causes release of renin which stimulate RAAS and finally increase in aldosterone results, beta blockers antagonize this pathway resulting in 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.

4. 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.

AGENTS DECREASING MORTALITY IN CHF

- ACE inhibitors (e.g. enalapril)
- Angiotensin receptor antagonists (e.g. losartan)
- Beta blockers (e.g. carvedilol)
- Aldosterone antagonists (e.g. spironolactone)
- Isosorbide dinitrate plus hydralazine combination

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 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

renin-angiotensin aldosterone system (β_1 stimulates renin release). All these factors contribute to result in raised blood pressure. Four main group of drugs used for controlling hypertension are diuretics (decrease blood volume and sodium retention), sympathoplegics, vasodilators and agents decreasing the activity of renin-angiotensin aldosterone system (RAAS).

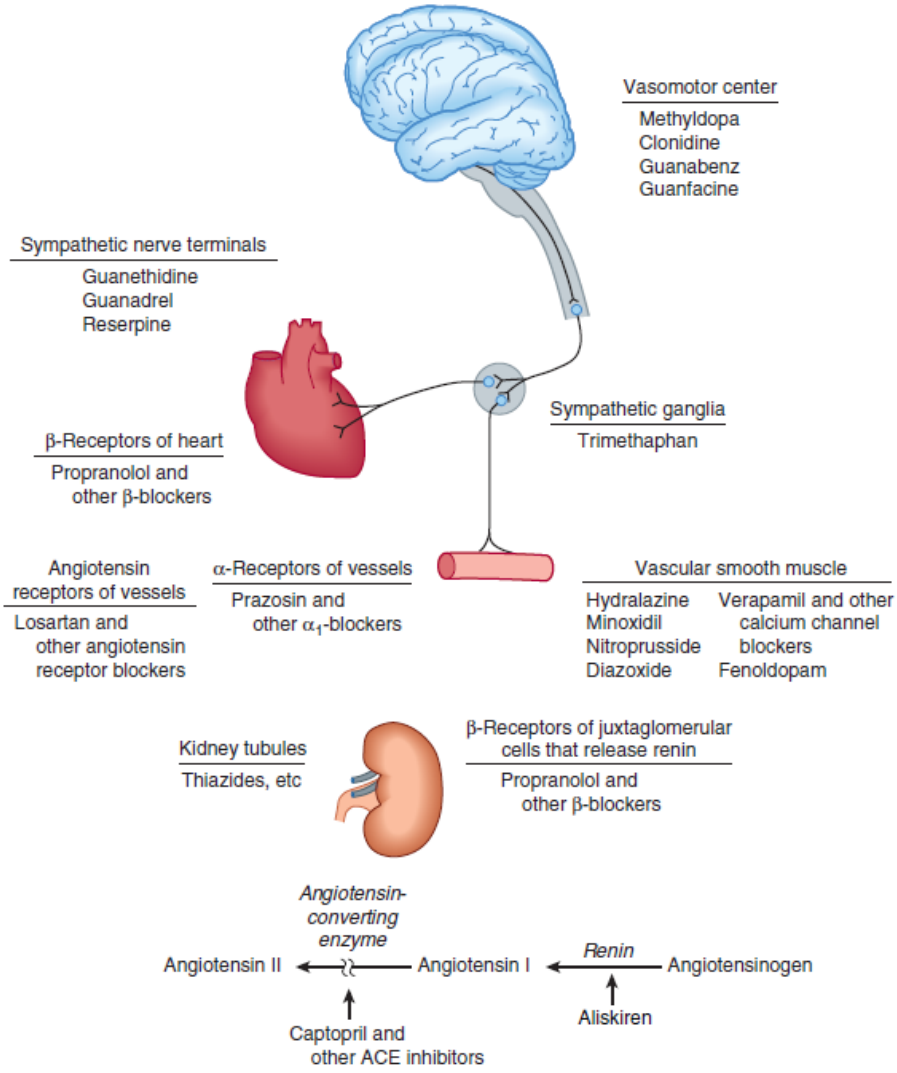


FIGURE 11–3 Sites of action of the major classes of antihypertensive drugs.

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 decrease in TPR. **Thiazides are first drugs to be used in hypertension unless contra-indicated** (according to JNC-VII guidelines). 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 hydrochlorthiazide. It is effective as an antihypertensive at lower doses than those required for diuretic effect (due to its direct vasodilatory effect). It also produces less metabolic adverse effects (hypokalemia, hyperglycemia, hyperuricemia etc.) and it can be used in case of diabetic hypertensives (whereas other thiazides are contra-indicated).

Loop diuretics (furosemide, torsemide, bumetanide, indacrinone etc.) are not indicated for mild to moderate hypertension because of 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 nephron (other loop diuretics and thiazides cause hyperuricemia).

Potassium sparing diuretics (amiloride, triamterene, spironolactone and epleronone) are used only in combination with thiazides or loop diuretics to decrease the risk of hypokalemia.

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, that block autonomic ganglia, that depletes the neurotransmitter store or the drugs that block the adrenergic receptors.

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 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 drug of choice). Clonidine, if given by i.v. route initially lead to rapid rise in blood pressure followed by prolonged fall. Initial rise is due to activation of vascular post synaptic α_2 receptors by high concentrations 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.

Beta 1 receptor antagonists like atenolol, metoprolol and propanolol etc. can also produce reduction in 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 autonomic ganglia (both sympathetic and parasympathetic). The therapeutic effect (decrease in blood pressure) is due to 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 trimethapan are the drugs in this group and are used rarely because of availability of drugs with lesser adverse effects. Trimethapan however is used along with nitroprusside as slow i.v. infusion for hypertensive emergencies in aortic dissection.

C. Adrenergic neuron blockers

Drugs of this group deplete the sympathetic neurotransmitter and thus decrease the sympathetic system activity. Reserpine 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 is taken up inside the synaptic vesicles and displaces the stored noradrenaline (which is metabolized), resulting in decreased neurotransmission. Both of these drugs can be given orally. These drugs can cause postural hypertension even if used for prolonged periods (unlike α blockers).

D. Adrenergic receptor antagonists

Two main types of adrenergic receptors are α and β receptors. Alpha 1 is present on smooth muscles of blood vessels (cause vasoconstriction) whereas β_1 is present mainly in myocardium (causing increased heart rate and cardiac output) and juxtaglomerular (JG) cells of kidney (stimulates 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 because of 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 selective α_1 blockers and cause less tachycardia. These drugs are 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 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 kidney.
- Inhibition of central and peripheral sympathetic outflow due to inhibition of presynaptic stimulatory β_1 receptors on adrenergic neurons.
- Increased vasodilatory prostacyclins 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 metoprolol, esmolol, atenolol, acebutolol, betaxolol, bisoprolol and celioprolol. 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. Celioprolol, oxprenolol, pindolol, alprenolol and acebutolol are beta blockers with intrinsic sympathomimetic activity. All beta blockers can lead to rebound hypertension on sudden withdrawal after prolonged use. These drugs can be combined with vasodilators to decrease the reflex tachycardia.

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.

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, diazoxide, fenoldopam), mainly venodilators (nitrates) or may dilate both arterioles and venules (calcium channel blockers, sodium nitroprusside). 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).

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 endothelium. Latter action requires 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 presence of slow and fast acetylators. On prolonged administration it can lead to drug induced lupus erythematosis. 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 (hirustism) 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). Latter effect has lead to its use in insulinoma.

B. **NO releasers:** Sodium nitroprusside and hydralazine act by releasing nitric oxide from 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 very short acting drug; therefore has to be given 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 accumulation of thiocyanate (antithyroid compounds).

C. **Dopamine agonist:** Fenoldopam is dopamine D_1 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. It can increase intraocular pressure and hypokalemia has also been reported with 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 heart (decrease heart rate, AV conduction and contractility). Dihydropyridine (DHP) group has little direct cardiac activity and acts mainly on blood vessels, therefore is 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 direct depressant action on heart (except DHP).

1. Effect of different CCBs on heart rate and blood pressure

	Blood vessel	**BP**	**Heart rate**		
			Direct effect	Reflex action	Net effect
Verapamil	Dilation	↓	↓↓↓	↑	↓↓
Diltiazem	Dilation	↓	↓↓	↑	↓
DHP	Dilation	↓	No effect	↑	↑

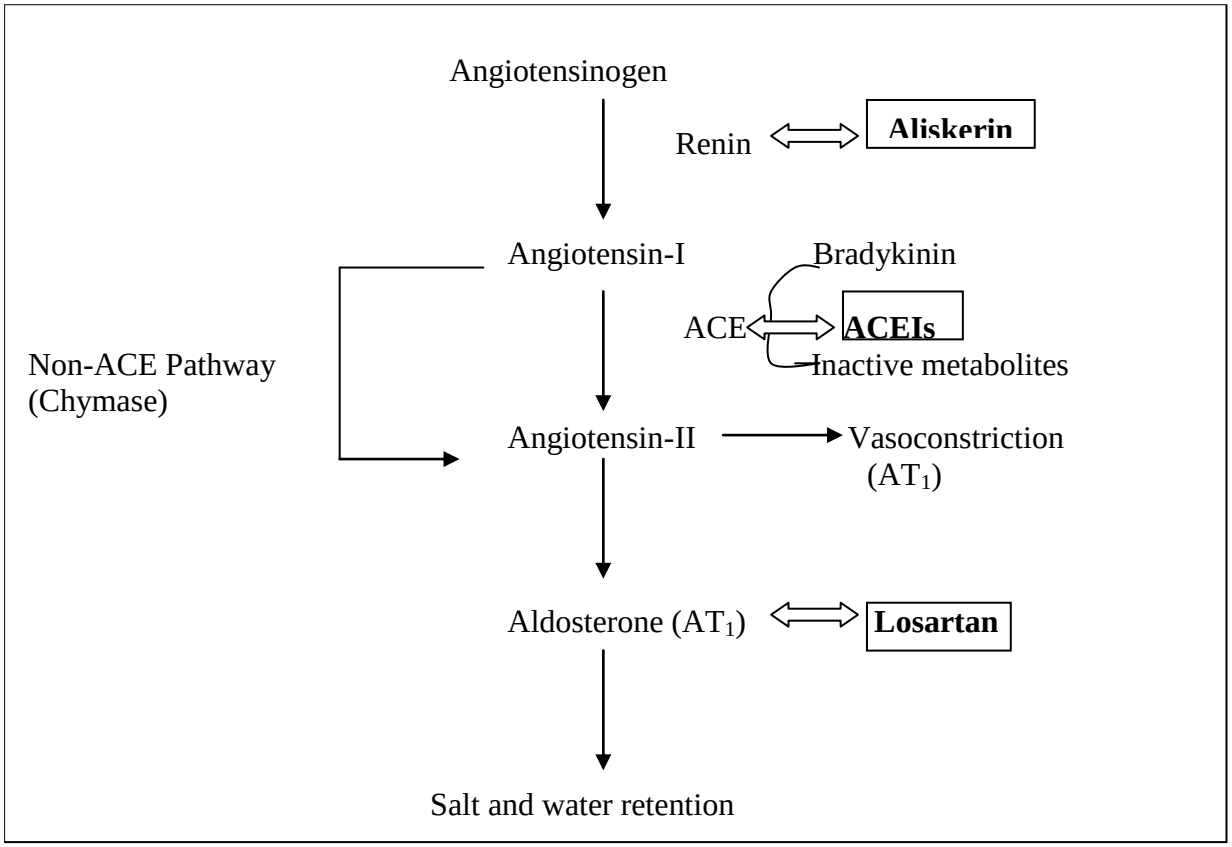
Reflex tachycardia is more marked in case of drugs with short half lives (nifedipine) whereas in long acting drugs like amlodipine (maximum half life), effects of reflex activity are hardly discernible. Due to above reason, promptly acting nifedipine can increase the risk of angina (increases cardiac work due to increase in heart rate) whereas sustained release preparation of nifedipine and amlodipine are safer in this regard. Earlier nifedipine was used sublingually for hypertensive emergencies but now this practice is banned because of reports of increased risk of MI and mortality. Nifedipine in addition also possess natriuretic property. Nimodipine is relatively cerebro-selective vasodilator, thus used to reverse the compensatory vasoconstriction after sub-arachnoid hemorrhage. Verapamil has maximum depressant action on 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 heart than verapamil and is indicated for hypertension and angina.

These drugs are especially suitable for elderly patients, patients with low renin hypertension, patient with diseases like asthma, migraine or peripheral vascular disease and in cases of isolated systolic hypertension. These drugs are safe in pregnancy. CCBs should be avoided in conditions involving decreased conductivity of heart like sick sinus syndrome, CHF and along with beta blockers (both cause myocardial depression).

4. DRUGS DECREASING THE ACTION OF RAAS

Angiotensinogen secreted from liver is converted to angiotensin I with the help of renin (secreted by JG cells of kidney). JG cells are stimulated either due to less fluid delivery to macula densa or by β_1 receptors. Angiotensin I is converted to angiotensin II mainly by angiotensin converting enzyme (also known as kininase II) and insignificant amount by chymase enzymes (non- ACE pathway). This latter pathway assumes importance when ACE is inhibited by drugs like enalapril, and can result in decreased effect of these drugs. ACE is also involved in 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 (directly, by release of adrenaline from adrenal medulla and indirectly by increasing central sympathetic outflow) and

stimulation of aldosterone release. Aldosterone is involved in salt and water retention as well as in causation of cardiac remodeling. Thus RAAS system 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 cases of sodium depleted states (like diuretic use) because activity of RAAS is more in such cases (to compensate for salt loss). Therefore, these drugs may cause postural hypotension in diuretic treated patients, which otherwise is relatively rare adverse effect. Beta blockers, renin inhibitors, ACE inhibitors, AT_1 antagonists and aldosterone antagonists can act by decreasing the activity of RAAS.



Renin angiotensin aldosterone system along with site of action of drugs

A. Renin inhibitors: Aliskerin, ramikerin and enalkerin 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.

B. 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 among 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 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. 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, dysguesia (altered taste sensation), and acute renal failure (if used in bilateral renal artery stenosis). These drugs are contra-indicated in pregnancy (teratogenic in second half of pregnancy) and when serum creatinine is more than 3.5 mg/dl.

C. Angiotensin receptor blockers (ARB): Losartan, Valsartan, irbesartan, candesartan, telmisartan and eprosartan act by antagonizing the action of angiotensin II at AT_1 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. 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**
1. Angina	β blocker, CCB	Vasodilators
2. BHP	α blocker	
3. Diabetes & 4. Hyperlipidemia	ACEI, ARB, CCB, α blocker	β blocker, diuretics
5. Elderly & 6. Isolated systolic hypertension	Diuretics, CCB	
7. Low renin hypertension	Diuretics, CCB	

8. High renin hypertension	ACEI, ARB, β blocker	
9. Asthma	CCB, diuretics, ACEI, ARB	β blocker
10. CHF	ACEI, diuretics	CCB
11. Post MI	β blocker, ACEI	
12. PVD	CCB, α blocker	β blocker
13. Thyrotoxicosis	β blocker	vasodilators

Drugs safe for the treatment of hypertension in pregnancy

Better **B**eta blockers (Cardioselective only)

Mother **M**ethyl dopa (Drug of choice)

Care **C**lonidine

During **D**ihydropyridine CCB (sustained release nifedipine, amlodipine)

Hypertensive **H**ydralazine (DOC for hypertensive emergencies in pregnancy)

Pregnancy **P**razosin (and other alpha blockers)

JOINT NATIONAL COMMITTEE GUIDELINES FOR HYPERTENSION

Earlier hypertension was classified into borderline, stage 1, 2 and 3 according to JNC 6 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 7 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.

Classification of blood pressure according to JNC 6 and JNC 7

SBP/DBP (mm Hg)	**JNC 6 category**	**JNC 7 category**
<120/80	Optimal	Normal
120-129/80-84	Normal	Prehypertension

130-139/85-89	Borderline	
≥ 140/90	**HYPERTENSION**	
140-159/90-99	Stage 1	Stage 1
160-179/100-109	Stage 2	Stage 2
≥ 180/110	Stage 3	

Classification of blood pressure according to JNC 7

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

SUMMARY Drugs Used in Hypertension

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
DIURETICS				
• Thiazides: Hydrochlorothiazide	Block Na/Cl transporter in renal distal convoluted tubule	Reduce blood volume and poorly understood vascular effects	Hypertension, mild heart failure	
• Loop diuretics: Furosemide	Block Na/K/2Cl transporter in renal loop of Henle	Like thiazides • greater efficacy	Severe hypertension, heart failure	See Chapter 15
• Spironolactone	Block aldosterone receptor in renal collecting tubule	Increase Na and decrease K excretion • poorly understood reduction in heart failure mortality	Aldosteronism, heart failure, hypertension	
• Eplerenone				
SYMPATHOPLEGICS, CENTRALLY ACTING				
• Clonidine, methyl dopa	Activate α_2 adrenoceptors	Reduce central sympathetic outflow • reduce norepinephrine release from noradrenergic nerve endings	Hypertension • clonidine also used in withdrawal from abused drugs	Oral • clonidine also patch • *Toxicity:* sedation • methyldopa hemolytic anemia
SYMPATHETIC NERVE TERMINAL BLOCKERS				
• Reserpine	Blocks vesicular amine transporter in noradrenergic nerves and depletes transmitter stores	Reduce all sympathetic effects, especially cardiovascular, and reduce blood pressure	Hypertension but rarely used	Oral • long duration (days) • *Toxicity:* Reserpine: psychiatric depression, gastrointestinal disturbances
• Guanethidine	Interferes with amine release and replaces norepinephrine in vesicles	Same as reserpine	Same as reserpine	Guanethidine: Severe orthostatic hypotension • sexual dysfunction

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
α BLOCKERS				
• Prazosin • Terazosin • Doxazosin	Selectively block α_1 adrenoceptors	Prevent sympathetic vasoconstriction • reduce prostatic smooth muscle tone	Hypertension • benign prostatic hyperplasia	Oral • *Toxicity:* Orthostatic hypotension
β BLOCKERS				
• Metoprolol, others • Carvedilol	Block β_1 receptors; carvedilol also blocks α receptors	Prevent sympathetic cardiac stimulation • reduce renin secretion	Hypertension • heart failure	See Chapter 10
• *Propranolol: Nonselective prototype β blocker* • *Atenolol: Very widely used β_1-selective blocker*				
VASODILATORS				
• Verapamil • Diltiazem	Nonselective block of L-type calcium channels	Reduce cardiac rate and output • reduce vascular resistance	Hypertension, angina, arrhythmias	See Chapter 12
• Nifedipine, amlodipine, other dihydropyridines	Block vascular calcium channels > cardiac calcium channels	Reduce vascular resistance	Hypertension, angina	See Chapter 12
• Hydralazine	Causes nitric oxide release	Vasodilation • reduce vascular resistance • arterioles more sensitive than veins • reflex tachycardia	Hypertension • minoxidil also used to treat hair loss	Oral • *Toxicity:* Angina, tachycardia • Hydralazine: Lupus-like syndrome
• Minoxidil	Metabolite opens K channels in vascular smooth muscle			Minoxidil: Hypertrichosis
PARENTERAL AGENTS				
• Nitroprusside • Fenoldopam • Diazoxide • Labetalol	Releases nitric oxide Activates D_1 receptors Opens K channels α, β blocker	Powerful vasodilation	Hypertensive emergencies	Parenteral • short duration • *Toxicity:* Excessive hypotension, shock
ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS				
• Captopril, many others	Inhibit angiotensin-converting enzyme	Reduce angiotensin II levels • reduce vasoconstriction and aldosterone secretion • increase bradykinin	Hypertension • heart failure, diabetes	Oral • *Toxicity:* Cough, angioedema • hyperkalemia • renal impairment • teratogenic
ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)				
• Losartan, many others	Block AT_1 angiotensin receptors	Same as ACE inhibitors but no increase in bradykinin	Hypertension • heart failure	Oral • *Toxicity:* Same as ACE inhibitors but less cough
RENIN INHIBITOR				
• Aliskiren	Inhibits enzyme activity of renin	Reduces angiotensin I and II and aldosterone	Hypertension	Oral • *Toxicity:* Hyperkalemia, renal impairment • potential teratogen

ANGINA

Major symptom of angina is chest pain that occurs due to imbalance between oxygen supply and demand. Coronary arteries are 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 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 treatment and prevention of angina are to decrease oxygen requirement or to increase the blood supply to the ischemic region.

Oxygen demand of 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 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 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 utilization of substrates by heart more efficient.

1. Nitrates

Glyceryl trinitrate (nitroglycerine), isosorbide dinitrate (IDN), isosorbide mononitrate (IMN), erythrityl 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 nitrates is present mainly in veins (therefore selective venodilator action). Venodilation results in peripheral pooling of 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 ischemic area (total coronary flow is not increased) by dilation of large epicardial coronary arteries. Because small vessels in 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 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 ischemic area cannot be dilated further, blood in 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 therapeutic failure of this drug.

Nitroglycerine and isosorbide dinitrate sublingually can be used for aborting 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 longest acting and amyl nitrite (by inhalation) is the shortest acting drug in this group. All drugs undergo very high first pass metabolism except IMN. 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 of cytochrome oxidase by this compound. Nitrites convert hemoglobin to methemoglobin (which possess very high affinity for cyanide ions) and forms cyanomethemoglobin. Cytochrome oxidase is freed in this process and 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 inhibition of phosphodiesterase, resulting in profound hypotension (due to excess cGMP) and risk of death.

2. 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.

3. 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.

4. Potassium channel openers

Nicorandil is the agent that causes coronary dilation by activating myocardial ATP sensitive K^+ channels (antagonized by sulfonylureas). In addition it possesses NO releasing property; to which tolerance do not develop.

5. Partial fatty oxidation inhibitors

Trimetazidine and ranolazine are the drugs which act in asthma by this new strategy. Heart normally utilizes fatty acids as fuel (not very efficient fuel). Heart starts utilizing glucose (very efficient fuel) as fuel if oxidation of fatty acids is inhibited by these drugs. Further by inhibiting lipid peroxidation, these drugs reduce generation of free radicals and protect myocardium from harmful effects of ischemia. Thus these drugs can provide beneficial effects in angina via non-hemodynamic mechanisms.

MYOCARDIAL INFARCTION

For treatment of acute 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 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 reduces 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.

CARDIAC ARRHYTHMIA

Deviation from the normal pattern of cardiac rhythm is known as arrhythmia. Knowledge of action potential of heart muscle is necessary for understanding the basic pharmacology of anti-arrhythmic drugs.

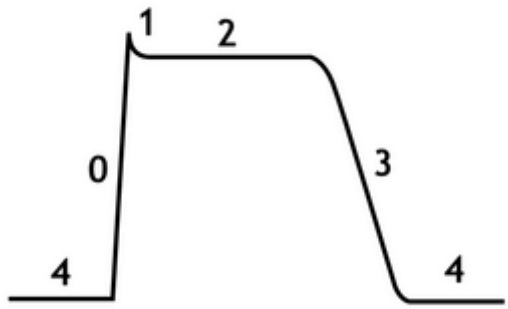
Cardiac action potential

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 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



The action potential of 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 faster in 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 Vmax. 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 arrival of 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 Vmax. 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, increasing 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 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.

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)

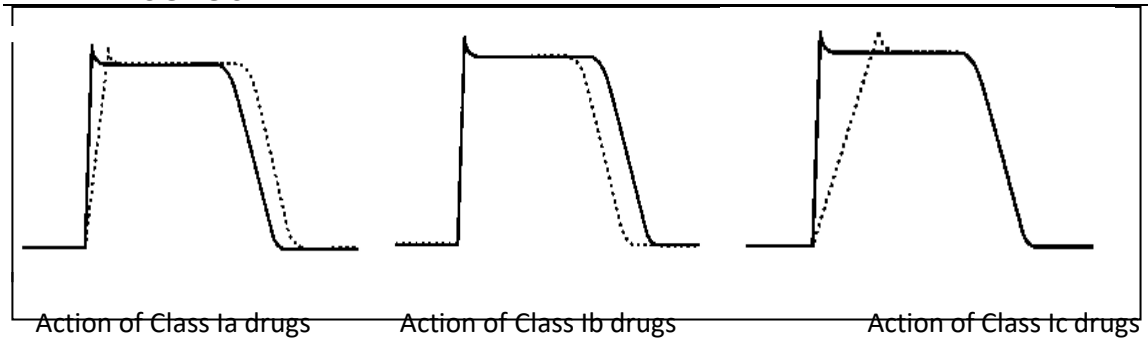
Vaughan William's classification of antiarrhythmic drugs

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

Class I agents

The class I antiarrhythmic agents interfere with the activity of Na^+ channels. Thus all of these drugs will result in decrease in the slope of phase 0 (Vmax). More frequently the sodium channels open, greater will be the blockade by these drugs (use dependent blockade). These are further classified according to action of these drugs on K^+ channels.



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. Quinidine, procainamide, and disopyramide are the important members of Class Ia.

- **Quinidine** is 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 erythematosis (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 and possess K^+ channel opening property. Class Ib agents have fast onset and offset kinetics, 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 opening of K^+ channels). These agents will decrease Vmax in partially depolarized cells with fast response action potentials. 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.

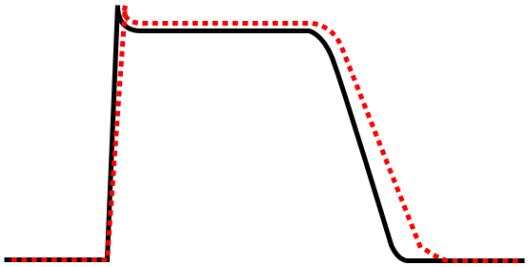
Class Ic agents: These agents have the most potent sodium channel blocking effects with negligible effect on K^+ channels (therefore no effect on APD). Drugs in this group include encainide, moricizine, flecainide and propafenone. These drugs have maximum pro-arrhythmic property, therefore indicated only for resistant and life-threatening ventricular tachycardia or ventricular fibrillation and for the treatment of refractory supraventricular tachycardia. Flecainide is the drug of choice for acute treatment of Wolf Parkinson White (WPW) syndrome.

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 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 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.



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 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 and can result in hyperthyroidism. It can also cause hypothyroidism by inhibiting peripheral conversion of T_3 to T_4. Other adverse effects include peripheral neuropathy, myocardial depression, pulmonary fibrosis, corneal microdeposits and photosensitivity. These adverse effects can be remembered by the mnemonic:

The	**T**hyroid (both hypo and hyperthyroidism)
Periphery of	**P**eripheral neuropathy
My	**M**yocardial depression
Lung and	**L**ung fibrosis
Cornea is	**C**orneal microdeposits
Photosensitive	**P**hotosensitivity

- 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.
- 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 treatment of atrial fibrillation or atrial flutter by i.v. use only. **Ibutilide is the only antiarrhythmic agent currently approved by FDA for acute conversion of atrial fibrillation to sinus rhythm**.

Class IV agents

Class IV agents are 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.

Class V agents

Class V agents include digoxin, adenosine, magnesium 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 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.

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 treatment of choice
WPW syndrome	Flecainide	Propanolol Amiodarone	**Laser ablation** of aberrant pathway is definitive treatment
Torsades-de pointes	Magnesium	**Propanolol**	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 liver to blood. TG content of chylomicrons is more than cholesterol content. In the wall of blood vessels, TGs contained in the chylomicrons are metabolized by lipoprotein lipase (LPL) and 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 metabolism of remaining TGs by HL (LDL contains only CE) or it is taken up in 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 transport of this cholesterol to liver (reverse cholesterol transport). Thus HDL is good cholesterol and LDL, IDL and VLDL are bad cholesterols. 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

Anti-

Type of disorder	LP increased	Lipids elevated		Risk of atherosclerosis	Treatment
		TG	CH		
I	CM	+++	N	No	None
IIa	LDL	N	++	+++	Statins
IIb	VLDL & LDL	++	++	+++	Statins, fibrates, nicotinic acid
III	IDL & CMR	++	++	++	Fibrates
IV	VLDL	++	N	++	Fibrates, nicotinic acid
V	VLDL & CM	++	N	No	None

dyslipidemic drugs

First line drugs include statins, bile acid binding resins and intestinal cholesterol absorption inhibitors whereas second line drugs include fibrates and niacin.

1. **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 rosuvastatin followed by atorvastatin 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 pleotropic effects of statins and are responsible, in part for lowering the risk of stroke and MI. Pravastatin also cause decrease in plasma fibrinogen levels.

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.

Major adverse effect of these drugs is myopathy and hepatotoxicity. Chances of myopathy increases if these are co-administered with fibrates or niacin. Myopathy can proceed to rhabdomyolysis with resultant renal shutdown. Pravastatin remains confined to liver and is safer in this regard.

These drugs are the first line drugs for type IIa, type IIb and secondary hyperlipoproteinemia (in these conditions, cholesterol level is raised more than TG).

2. **Intestinal cholesterol absorption inhibitor:** Ezetimibe is the drug in this group. Due to decreased absorption, cholesterol content of 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.

3. **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 plasma by increasing LDL receptors. Bile acids inhibit TG production in 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 cholesevelam. Cholestyramine and colestipol are available as sachets. These are mixed with water, kept for some time (to increase palatability) and then taken with meals. Cholesevelam is available as a tablet and has better patient compliance. Major adverse effect of these drugs is constipation.

4. **Fibric acid derivatives:** This group of drugs acts by inhibiting LPL by activating a nuclear receptor PPARα (peroxisome proliferators activated receptor alpha). Major effect of 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 effect of fibric acid derivatives. Risk of myopathy is increased if these are used with statins except bezafibrate.

5. **Nicotinic acid:** Niacin (not nicotinamide) is an inexpensive drug (vitamin B_3) that produces decrease in LDL cholesterol and VLDL triglycerides along with increase in HDL cholesterol. It acts by inhibiting lipolysis in 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 side effects, it 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.

6. **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.

7. **New Drugs:**

    - Avasimibe is an inhibitor of enzyme ACAT-1 (acyl coenzyme A: cholesterol acyl transferase-1) which forms cholesterol ester from cholesterol.
    - Torcetrapib increases HDL cholesterol by inhibiting the enzyme CETP (cholesterol ester triglyceride transport protein).

Plasma levels of lipids for drug treatment (National Cholesterol Education Program 2001)

Plasma Lipids	Desirable Plasma Concentration (mg/dl)
Total Cholesterol	< 200
LDL-C	< 130
HDL-C	> 40 for male > 50 for female
TG	< 150

CHEMOTHERAPY

Antibiotics are the substances produced by microorganisms, which suppress the growth of or kill other microorganisms at very low concentrations

CLASSIFICATION: Antimicrobials can be classified according to several characteristics.

1. BASED ON MECHANISM OF ACTION

A. DRUGS INHIBITING CELL WALL SYNTHESIS

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 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 cytoplasm. The resulting molecule formed is transported across the plasma membrane by bactoprenol. Elongation of 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 1 below. All these drugs are bactericidal drugs.

Table 1. Mechanism of action of cell wall synthesis inhibiting antimicrobial drugs

Drug	**Step in cell wall synthesis inhibited**
Fosfomycin	Enolpyruvate transferase
Cycloserine	Alanine racemase & alanine ligase
Vancomycin	Transpeptidase
Bacitracin	Dephosphorylation of bactoprenol
Beta lactam antibiotics	inhibit transpeptidase

B. DRUGS INHIBITING TRANSLATION (PROTEIN SYNTHESIS)

Protein synthesis in bacteria is accomplished with the use of 70S ribosome, mRNA and tRNA. 70S ribosome contains two subunits 30S and 50S. 50S subunits contain 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 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 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 termination codon on mRNA (at this point protein synthesis stops). All drugs inhibiting protein synthesis are bacteriostatic except aminoglycosides and Streptogramins.

Table 2. Mechanism of action of protein synthesis inhibiting antimicrobial drugs

Drug	**Binds to**	**Mechanism of action**
Tetracyclines	30S ribosome	Inhibit aminoacyl-tRNA attachment to A Site
Chloramphenicol	50S ribosome	Inhibits peptidyl transferase which results in inhibition of peptide bond formation and transfer of peptide chain from P to A site
Macrolides Lincosamides Streptogramins	50S ribosome	Inhibit translocation of peptide chain from A site to P site
Aminoglycosides	Several site at 30 S and 50 S subunits as well as to their interface	Freezing of initiation Interference with polysome formation Misreading of mRNA code
Linezolide	23S fraction of 50S ribosome	Inhibits initiation

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: Polymixin B, colistin and tyrothricin (bacitracin is also polypeptide but act by inhibiting protein synthesis).
- Polyene antibiotics: Amphotericin B, nystatin, hamycin, natamycin
- Azoles: ketoconazole, Fluconazole, itraconazole.

D. DRUGS AFFECTING NUCLEIC ACIDS (DNA & RNA)

These drugs include

- **DNA gyrase inhibitors:** DNA replication occurs on 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 position bacteria, same function is carried out by a similar enzyme topoisomerase IV. The drugs inhibiting DNA gyrase or topoisomerase are quinolones (nalidixic acids and flouroquinolones) 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 strands breakage. Nitrofurantoin is also considered to be acting by 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 DNA or RNA. This results in 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 drug action is folic acid synthesis.

- **Drugs inhibiting folic acids synthesis:** Folic acid synthase (dihydropteroate synthase) results in formation of folic acid by incorporation of PABA. Sulfonamides, dapsone and paraaminosalicylic acid (PAS) are structural analogues of paraaminobenzoic acid (PABA). There drugs act as competitive inhibitors of folic acid synthase.
- **Dihydrofolate reductase (DHFRase) inhibitors:** DHFRase is the enzyme responsible 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 and methotrexate.
- **Arabinogalactan synthesis inhibitors:** Ethambutol inhibits arabinogalactan synthesis and thus incorporation of mycolic acid in the cell wall of mycobacteria.

2. BASED ON TYPE OF ACTION

According to this classification, drugs may be bacteriostatic or bactericidal (see Table 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 bacterium in culture plates using serial dilutions. A small difference between MIC and MBC indicates that the antibiotics is primary bactericidal whereas a larger difference indicates bacteriostatic action. In immunocompromised patients (patients with HIV, on steroid therapy etc.) only bactericidal drugs should be used.

3. BASED ON THERAPEUTIC INDEX

High TI	**Low TI**	**Very low TI**
Penicillins	Aminoglycosides	Polymixin B
Cephalosporins	Tetracyclines	Vancomycin
Macrolides	Chloramphenicol	Amphotericin B

Table 3. Classification of antibiotics according to type of action

Bacteriostatic	**Bactericidal**
Protein synthesis inhibitors • Tetracyclines • Chloramphenicol • Macrolides • Lincosamides • Linezolide	**Protein synthesis inhibitors** • Aminoglycosides • Streptogramins
Drugs affecting DNA • Nitrofurantoin • Novobiocin	**Drugs affecting DNA** • Quinolones • Metronidazole
Drugs affecting metabolism • Sulfonamides • 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 • Isoniazide • Pyrazinamide • Streptomycin (aminoglycoside)

DRUGS RESISTANCE

Drugs resistance in the 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 physical contact between bacteria and is responsible for multidrug resistance. This is very important mechanism for development of resistance against chloramphenicol and streptomycin.
- Transduction: It is transfer of resistance gene through bacteriophage e.g. penicillin erythromycin and chloramphenicol.
- Transformation: It is transfer of resistance gene through environment and is not significant clinically e.g. penicillin G.

Resistance once acquired become prevalent due to selection pressure of a widely used antimicrobial agent i.e. antimicrobials allow resistant organism to grow preferentially.

Mechanism of resistance: Microorganism may develop resistance due to

a) Decreased affinity of the target e.g. pneumococci develop altered penicillin binding proteins

b) Development of alternative metabolic pathway e.g. sulfonamide resistant organisms starts utilizing preformed folic in place of synthesizing it from PABA.

c) Elaboration of enzymes which inactivate the drug e.g. β- lactamases (penicillins and cephalosporins), chloramphenicol acetyl transferase (chloramphenicol) and aminoglycoside inactivating enzymes (aminoglycosides).

d) Decreased drug permeability due to loss of specific channels e.g. aminoglycosides and tetracyclines have much lower drug concentration in the resistant organisms than in sensitive organisms.

e) Development of efflux pumps (by tetracyclines, erythromycin and flouroquinolones) results in active extrusion of drug from the resistant microorganism.

SUPERINFECTION

If refers to 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 development of new infection. Super infection is more commonly seen in immunocompromised person. 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 super infection may result in pseudomembranous colitis for which metronidazole is drugs of choice (alternative drug is vancomycin). Further, due to loss of commensal flora, there may be decreased formation of vitamin K leading to enhanced anticoagulant effects of warfarin.

CONCENIRATION DEPENDENT KILLING (CDK) AND TIME DEPENDEDT KILLING (TDK):-

- CDK means that killing effect of the drug is high when ratio of peak concentration to MIC is more. This type of killing behaviour is exhibited by aminoglycosides and flouroquinolones. These drugs produces 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 MIC. This is exhibited by β-lactams and macrolides. For these drugs multiple daily doses is preferred over single dose.

- Post antibiotic effect (PAE): After exposure of an organism to 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 its concentration is below MIC. This period is known as PAE. Long PAE has been noted with flouroquinolones, aminoglycosides and β-lactam antibiotics. 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)

COMBINDED 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 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 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 cause grey baby syndrome

- Sulfonamide in new born cause kernicterus

- Half life of aminoglycosides is prolonged in elderly

- Tetracyclines are contra indicated in children below 6 years because it accumulate in developing teeth and bone

2. Pregnancy – All antibiotics pose risk to the fetus when used in pregnancy. Penicillins, most cephalosporins and erythromycin appear safe.

3. Impaired host defenses – Bactericidal drugs are must in immunocompromised patient

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	Chloramphenicol
Tetracyclines	Isoniazid
Pyrazinamide	Rifampicin
Pefloxacin	Clindamycin

6. Genetics Factors – Antimicrobials producing hemolysis in glucose 6 phosphate dehydrogenase (G-6PD) deficient patients are primaquine, chloramphenicol, nitrofurantoin, flouroquinolones and sulfonamides etc.

BETA – LACTAM ANTIBIOTICS

Beta lactam antibiotics are those drugs that contain β-lactam ring in their structure. These drug act by inhibiting cell wall synthesis and include

1. Penicillins
2. Cephalosporins
3. Monobactams e.g. aztreonam
4. Carbapenems e.g. imipenem
5. Beta lactamase inhibitors e.g. clavulanic acid

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 cross linking of peptidoglycan chains. Bacteria formed in presence of these drugs are without cell wall and die due to imbibition of water (cell wall provides turgidity).

PENICILLINS:-

Penicillin is commercially obtained from Penicillium chrysogenum. Penicillinase is beta lactamase developed by most staphylococci and many gram negative organisms that is responsible for breakdown of beta lactam ring (thus resistance to penicillins). Based on susceptibility to penicillinases and spectrum of action, penicillins are classified as

a) Narrow Spectrum penicillinase susceptible agents e.g. penicillin G and penicillin V

b) Narrow spectrum penicillinase resistant e.g. methicillin, nafcillin, oxacillin, cloxacillin

c) Wide spectrum penicillinase susceptible:

- Aminopenicillins – Amoxicillin, ampicillin, bacampicillin
- Carboxypenicillins – Carbenicillin, ticarcillin
- Ureidopenicillins – Piperacillin, azlocillin, mezlocillin
- Mecillinam

Pharmacokinetics

One gram of penicillin is equivalent to 1.6 million units. Gastric acid breaks down penicillins and result in decreased oral bioavailability. Penicillin V (phenoxymethyl penicillin), amoxicillin and ampicillin are acid resistant and thus can be given orally. These are usually excreted in the urine by glomerular filtration and tubular secretion. Tubular secretion is inhibited by probenecid thus resulting in increased plasma concentration. Ampicillin and nafcillin are excreted partly in bile. Benzyl penicillin (Penicillin G) is given by i.m. injection. It is has small t1/2 so given 6-12 hourly whereas procaine penicillin (12-24 hourly) and

benzathine penicillin are long acting due to slow release. Procaine helps to prolong the duration of action.

Clinical uses

Penicillin G – It is drug of choice for syphilis. Benzathine or Procaine penicillin is used. It can also be used for gram positive bacteria like streptococci and meningococci. Most staphylococci and gonococci are now resistant.

Methicillin, Nafcillin, oxacillin and cloxacillin – Main use of these drugs is for treatment of Staphylococcus aureus infections although organisms resistant to these drugs also have been isolated. Methicillin resistance is developed due to 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 and 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.

Piperacillin, ticarcillin, carbenicillin, azlocillin and mezlocillin – These have activity against gram negative rods including pseudomonas. These are used with beta lactamase inhibitors and with aminoglycosides.

Note – MRSA is not susceptible to β-lactam antibiotics.

Toxicity

- Main toxicity is hypersensitivity including serum sickness. Anaphylaxis is most commonly associated these drugs therefore sensitivity testing is must before administration of penicillins. If a patient develops severe hypersensitivity reaction to penicillin, all other beta lactams antibiotics are contra-indicated except aztreonam (cross sensitivity is not present).
- Ampicillin is involved in causing maculopapular skin rash in patient with viral diseases like infections mononucleosis.
- Methicillin is 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 cause 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 doses can result in bleeding.

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	Ceftobiprole
Cephalexin	Cephalothin	Cefaclor	Cefuroxime	Cefixime		Cefotaxime	Cefepime	Ceftaroline
Cefadroxil	Cefazolin	Cefuroxime axetil	Cefotetan	Cefopodoxime proxetil		Ceftizoxime	Cefpirome	
Cephradine			Cefoxitin	Cefdinir		Ceftriaxone		
			Cefamandole	ceftibuten		Ceftazidime		
						Cefoperazone		
						Moxalactam		

Pharmacokinetics: - Most cephalosporins are excreted via kidney through tubular secretion. Ceftriaxone and cefoperazone are excreted mainly in the bile. Nephrotoxicity of these drugs is increased with loop diuretics

Clinical Uses:

First generation: These are active against gram positive cocci including staphylococci. MRSA is resistant to cephalosporins also. Cefazolin is drug of choice for surgical prophylaxis.

Second generation: This group of drugs is less active against gram positive organisms than first generation but has extended gram negative coverage. Cefotetan 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 also are able to penetrate blood brain barriers (except cefoperazone and cefixime). Ceftazidime (maximum) and cefoperazone are active against pseudomonas. Ceftizoxime has maximum activity against bacteroides. Ceftriaxone and cefixime are first choice drugs for gonorrhoea. 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 and have similar efficacy against gram positive cocci as with 3rd generation compounds. However, these are not active against anaerobes.

Note:

- Cefotaxime and ceftriaxone are most active cephalosporins against penicillin resistant pneumococci.
- No cephalosporin is active against Enterococcus fecalis, MRSA and Listeria monocytogenes.
- Ceftazidime plus aminoglycoside is 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. These may increase the nephrotoxicity of aminoglycosides (except cefoperazone). Drugs containing a methylthiotetrazole group like cefamandole, cefoperazone and cefotetan may cause hypoprothrombinemia (bleeding) and disulfiram like reaction with alcohol.

OTHER BETA LACTAM ANTIBIOTICS

Monobactams: This group includes aztreonam. This is active against β- lactamase producing gram negative rods including pseudomonas but have no activity against gram positive organisms or anaerobes. It is administered i.v. and its half life is prolonged in renal failure.

Carbapenems: These include imipenem, meropenem and ertapenem. These have wide spectrum of activity including gram positive cocci, gram negative rods as well as anaerobes. For treatment of pseudomonas infections these drugs should be combined with aminoglycosides. Carbapenems are β-lactamase resistant and are drug of choice for Enterobacter species. Imipenem is rapidly inactivated by renal dehydropeptidase I, so 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 effect of imipenem-cilastatin combination includes seizures and gastrointestinal distress. Meropenem and ertapenem are not metabolized by renal dehydropeptidase and are less likely to cause seizure.

Loracarbef: It is chemically similar to Cefaclor. It can be given orally and its uses and spectrum resembles second generation cephalosporins. In overdose it can cause seizures.

Beta lactamase inhibitors: These include clavulanic acid, sulbactam and tazobactam. These are more active against plasmid encoded beta lactamases (produced by gonococci and E. coli) than against inducible chromosomal beta lactamases (by pseudomonas and enterobacter)

- Amoxicillin is combined with clavulanic acid (Co-amoxy-clav)
- Ampicillin is combined with sulbactam (Sultamicin)
- Piperacillin is combined with tazobactam

OTHER CELL WALL SYNTHESIS INHIBITORS

VANCOMYCIN: 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. Teicoplanin is another glycopeptide with similar characteristics. These are given parenterally and are excreted unchanged in urine. Rapid i.v. infusion of vancomycin can cause RED MAN SYNDROME (diffuse flushing due to histamine release). Other toxic effects include chills, ototoxicity and nephrotoxicity. Dose should be decreased in renal failure. Teicoplanin do not cause redman syndrome or nephrotoxicity. Vancomycin is used ORALLY to treat pseudomembranous colitis by clostridium diffcide because it is not absorbed from gastrointestinal tract and higher concentration reaches the colon.

FOSFOMYCIN: It inhibits cell wall synthesis by inhibiting enolpyruvate transferase. It can be used for urinary tract infections but is used less often because resistance emerges rapidly and diarrhea is quite common.

BACITRACIN: It also inhibits cell wall synthesis but because of marked nephrotoxicity, it is applied only for topical use.

CYCLOSERINE: It also inhibits cell wall synthesis. It has potential neurotoxic effects (tremors and seizures). It also causes neuropsychiatric symptoms. It is a second line drug for treatment of tuberculosis.

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 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 formation of inactivating enzyme acetyl transferase. Because of rapid development of resistance and high toxicity, this drug has very few systemic uses. Earlier it was drug of choice for typhoid fever (enteric fever) but due to development of resistance, ceftriaxone or ciprofloxacin are now drug of choice. 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. Neonates and premature infants are deficient in hepatic glucoronyl transferase and because it is excreted in 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 inhibits 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 given to pregnant female. All tetracyclines undergo enterohepatic circulation. All tetracyclines are excreted primarily in the urine except doxycycline. Doxycycline is excreted in feces and thus can be used in renal failure. Half life of doxycycline and minocycline is longer than other tetracyclines.

Clinical uses: Tetracyclines are broad spectrum bacteriostatic drugs. Development of resistance to tetracyclines is mainly due to development of efflux pumps. Tetracyclines are first choice drugs for

- Lymphogranuloma venereum (LGV)

- Granuloma inguinale
- Atypical pneumonia due to mycoplasma
- Cholera
- Brucellosis
- Plague
- Relapsing Fever
- Rickettsial Infections

Uses of individual tetracyclines include

- Peptic ulcer by H. pylori (tetracycline)
- Lyme's disease (Doxycycline)
- Meningococcal carrier state (Minocycline)
- Malaria prophylaxis (Doxycycline)
- Amoebiasis (Doxycycline)
- Syndrome of inappropriate ADH secretion (Demeclocycline)

These can also be used as secondary drugs for gonorrhoea, syphilis and chlamydial infections. Another use of tetracyclines is for pleurodesmosis in malignant pleural effusion.

Toxicity: Tetracyclines may cause super infection diarrhea and pseudomembranous colitis. These are contra indicated in pregnancy because of risk of fetal tooth enamel dysplasia and irregularities in fetal bone growth. Treatment of young children may cause dentition abnormalities. High dose of tetracyclines may lead to hepatic necrosis especially in pregnant females. Out dated 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. Diabetes insipidus may be precipitated by ADH antagonistic action of demeclocycline. Tetracycline also possess anti anabolic effects.

MACROLIDES

These antibiotics have large cyclic lactone ring structure with attached sugars. The drugs included in this group are erythromycin, azithromycin, roxithromycin and clarithromycin. 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 route. Excretion of azithromycin is quite slow (longest half life)

and mainly in the urine. Erythromycin is given four times a day where as azithromycin as a single daily dose.

Clinical uses: Erythromycin is drugs of choice for (remembered as CLAW)

- **C**hancroid by Haemophilus ducreyi
- **L**egionella infections
- **A**typical pneumonia caused by mycoplasma
- **W**hooping cough by Bordetella pertussis

It can also be used for diphtheria and infections caused by chlamydia and gram positive organisms.

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 treatment of urogenital infections caused by chlamydia. Roxithromycin has similar spectrum to azithromycin.

Clarithromycin is approved for prophylaxis and treatment of mycobacterium avium complex and in treatment of peptic ulcer caused by H. pylori.

Spiramycin is another macrolide antibiotic that is drug of choice for treatment of toxoplasmosis in pregnancy.

Toxicity: - Erythromycin can cause diarrhea by stimulation of motilin receptors. Erythromycin estolate is implicated in causation of acute cholestatic hepatitis especially in pregnant female. Erythromycin, roxithromycin and clarithromycin inhibit CYP 3A4. If given to patients receiving astemizole/ astemizole/cisapride (substrates of CYP 3A4) 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. Erythromycin also increases plasma concentration of theophylline by inhibiting CYP 1A2.

KETOLIDES

This group includes telithromycin. It has same mechanism of action and indications as macrolides. It is excreted in bile and urine and is a potent inhibitor of CYP3A4.

LINCOSAMDES

This group includes clindamycin and lincomycin. These have same mechanism of action as macrolides. Main use of clindamycin is against anaerobes like bacteroides. It is also active against Pneumocystis jirvoci (previously called P. carnii) and Toxoplasma gondii. It is the most common antibiotic implicated in causing pseudomembranous colitis. 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, MRSA as well as VRSA. These drugs are potent inhibitors of CYP3A4, therefore drugs interactions are possible. Other adverse effects include arthralgia myalgia syndrome.

OXAZOLIDINONES

This group includes the drug linezolid. It acts by binding to 23S part of 50S ribosomal subunit and inhibits initiation of protein synthesis. There is no cross resistance with other protein synthesis inhibiting drugs. It is active against MRSA, VRSA and vancomycin resistant Enterococcus faecalis. Major adverse effect of linezolid is thrombocytopenia and neutropenia.

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. Penetration across the cell wall is dependent on oxygen dependent transport; therefore these drugs are inactive against anaerobes. Further, transport is enhanced if used along with cell wall synthesis inhibitors like penicillins. These bind to 30S and 50S ribosomes and freeze initiation, inhibit translocation 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 formation of inactivating enzymes which acetylate, phosphorylate or adenylate the aminoglycosides. All aminoglycoside 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. However these are not reliable for gram positive organisms if used alone. Streptomycin is first line drug for treatment of tuberculosis, plague and tularemia. Amikacin is a second line drugs in tuberculosis and is 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 related drug to aminoglycosides, which is used as a single dose treatment for penicillinase producing Neisseria gonorrhoea (PPNG).

Note: - Tobramycin is much less active against enterococcal endocarditis than gentamicin or streptomycin.

Toxicity: - Auditory impairment is more likely with amikacin and kanamycin whereas gentamicin and tobramycin causes vestibular dysfunction. Ototoxicity is increased by loop diuretics. Nephrotoxicity can occur in elderly patients, in setting of hypokalemia, in pre-existing renal disease and in those taking concomitant nephrotoxic medications (like AMB, vancomycin etc.) Gentamicin and tobramycin have

most nephrotoxic potential. Aminoglycosides may also cause neuromuscular blockade (decrease the release of acetylcholine at neuromuscular junction i.e. pre-synaptic action) and thus respiratory paralysis. Therefore these are contraindicated in patients with myasthenia gravis. Skin reactions are more likely with neomycin.

Note:

- Maximum nephrotoxic aminoglycoside is gentamicin.
- Maximum auditory toxic aminoglycoside is amikacin.
- Maximum vestibulotoxic aminoglycoside is streptomycin.
- Maximum neuromuscular blocking aminoglycoside is streptomycin.
- Netilmicin is not ototoxic.

ANTIMETABOLITES

The drugs that are able to interfere with the role of an endogenous compound in cellular metabolism are called antimetabolites e.g. sulfonamides, trimethoprim, pyrimethamine and methotrexate.

SULFONAMIDES

These drugs are bacteriostatic agents and act by inhibiting folate synthase competitively. The selective toxicity for the bacteria is due to the reason that mammalian cells do not synthesize folic acid and utilize preformed folic acid in diet. Sulfonamides are not effective in the presence of pus because it contains large amount of PABA. These drugs undergo hepatic metabolism by ACETYLATION. The solubility of sulfonamides decreases in acidic urine, which may result in precipitation of the drug causing crystalluria. These are classified as

1. **For systemic use as oral agents**

- Short acting: Sulfadiazine, sulfisoxazole, sulfamethizole
- Intermediate acting: Sulfamethoxazole
- Long acting: Sulfadoxine

2. **For use in GIT:** Sulfasalazine, olsalazine
3. **For topical use:** Sulfacetamide, silver sulfadiazine, mafenide

Clinical uses:

- Sulfacetamide in 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 treatment of ulcerative colitis

- Sulfadoxine plus pyrimethamine is used for malaria.
- Sulfadiazine and pyrimethamine combination can be used for treatment of toxoplasmosis and prophylaxis of pneumocystis jirvoci pneumonia in AIDS patients.

Toxicity:

- Skin rash due to hypersensitivity is most common adverse effect.
- It can also cause granulocytopenia, thrombocytopenia and aplastic anemia.
- Sulfonamides can cause acute hemolysis in persons with G-6 PD deficiency.
- These can precipitate in urine at acidic pH and result in crystalluria and hematuria.
- These can displace bilirubin from plasma protein binding sites and may result in kernicterus in new born (if given in third trimester of pregnancy).

TRIMETHOPRIM

It is a bacteriostatic antimetabolite that inhibits dihydrofolate reductase. It attains high concentrations in 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, leucopenia and pancytopenia (can be ameliorated by folinic acid).

Note:

- Other DHFRase inhibitors are pyrimethamine, methotrexate 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, plasma concentration of the two drugs attained is 20:1. The bactericidal activity is due to sequential blockade at two steps in DNA synthesis (sulfamethoxazole inhibits folate synthase and trimethoprim inhibits DHFRase). Cotrimoxazole is effective in UTI, respiratory tract infections, middle ear and sinus infections caused by hemophilus and moraxella. It is drug of choice for pneumocystosis and nocardiosis. Adverse effects are similar to sulfonamides and trimethoprim.

FLOUROQUINOLONES

These drugs act by inhibiting DNA gyrase (topoisomerase II) and topoisomerase IV resulting in inhibition of DNA replication. These drugs have long PAE. On the basis of 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, sparfloxacin (more against gram positive)
- **Fourth generation:** Moxifloxacin and trovafloxacin (BROADEST SPECTRUM)

Pharmacokinetics: - These have good oral bioavailability but like tetracycline multivalent cations interfere with absorption. Excretion of moxifloxacin and trovafloxacin is by hepatic metabolism and biliary excretion. Sparfloxacin is 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 flouroquinolones except moxifloxacin and trovafloxacin. These two drugs, levofloxacin and sparfloxacin (maximum $t_{1/2}$) can be given once daily.

Clinical use: First generation drugs like norfloxacin has 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. Levofloxacin is l-isomer of ofloxacin and is effective against infections caused by atypical micro organisms like mycoplasma. Sparfloxacin has greater activity against gram positive organisms but is not effective against pseudomonas. Moxifloxacin and trovafloxacin has widest including gram negative, gram positive as well as anaerobes. Flouroquinolones are also effective in tuberculosis and can be used for prophylactic management of neutropenic patients.

Toxicity: GI distress is most common side effect. These may also cause cartilage problems thus are not advocated in children less than 18 year old. Tendinitis resulting in tendon rupture can be seen rarely in adults. These drugs can also cause phototoxicity, the incidence of which maximum with lomefloxacin and sparfloxacin. Sparfloxacin and gatifloxacin prolong QTc interval (grepafloxacin was withdrawn because of arrhythmias caused due to prolongation of QT interval). Trovafloxacin has hepatotoxic potential.

Flouroquinolones increase the plasma concentration of methylxanthines like theophylline and thus enhance their toxicity. NSAIDs increases CNS toxicity of these drugs.

Note: Other drugs causing prolonged QT interval are Amiodarone, bretylium, disopyramide, procainamide, quinidine, sotalol, mefloquine, pentamidine, thioridazine and ziprasidone

URINARY ANTISEPTICS

These are oral drugs that are rapidly excreted in the urine and suppress 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

It is active against most urinary pathogens except pseudomonas and proteus. Resistance develops to it 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 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.

OTHER ANTIBACTERIAL DRUGS

These include daptomycin, mupirocin, polypeptide antibiotics, fusidic, acid, teicoplanin and glycylcyclines.

DAPTOMYCIN

It is a new bactericidal drug that acts by causing depolarization of bacterial membranes and subsequently inhibiting protein and nucleic acid synthesis. It is used for serious gram positive infections including penicillin resistance pneumococci, MRSA and VRSA. It is also effective against organism's resistance to linezolid and streptogramins. Myopathy is dose limiting toxicity of this drug.

MUPIROCIN

It acts on gram positive organisms by inhibiting protein synthesis due to binding with isoleucyl-tRNA. It is used topically or nasally for staphylococcus infections.

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, polymyxin B is used only topically.

FUSIDIC ACID

It acts by blocking protein synthesis and is used topically for staphylococcal infections.

TEICOPLANIN

It is a glycopeptide antibiotic like vancomycin and is used for treatment of MRSA and VRSA.

GLYCYLCYCLINES

This new drugs group of antibiotics includes tigecycline, which acts by inhibiting protein synthesis via a mechanism similar to tetracycline. But these are more resistant than tetracyclines to efflux pumps developed by microorganisms. Their main indication is serious complicated skin and soft tissue infections.

MAJOR ROUTES OF DRUG ELIMINATION

Renal	**Hepatic/ Biliary**
Aminoglycosides	Ampicillin
Amphotericin B	Nafcillin
Beta lactams	Chloramphenicol
Quinolones	Erythromycin
Sulfonamides	Rifampicin
Tetracyclines	Isoniazid
	Novobiocin
	Cefoperazone
	Doxycycline

DRUGS EFFECTIVE AGAINST ANAEROBIC ORGANISMS

- Clindamycin
- Moxifloxacin
- Trovafloxacin
- Metronidazole
- Vancomycin
- Chloramphenicol

Note: Aminoglycosides are not effective against anaerobic micro-organisms.

DRUGS EFFECTIVE AGAINST PSEUDOMONAS

1. **Beta lactam antibiotics**

- Carboxypenicillins (Carbenicillin, Ticarcillin)
- Ureidopenicillin (Piperacillin, azlocillin and mezlocillin)
- Carbapenems (Imipenem)
- Monobactams (Aztreonam)
- Cephalosporins (Ceftazidime, Cefoperazone, Moxalactam, Cefepime)

2. **Flouroquinolones**

- Ciprofloxacin
- Pefloxacin

3. **Polypeptide antibiotics**

- Colistin
- Polymixin B

4. **Aminoglycosides**

Note:

- ✓ Vancomycin is not active against pseudomonas
- ✓ Ceftazidime plus aminoglycoside is treatment of choice for pseudomonas infections

PROPHYLACTIC USE OF ANTIBIOTICS

Cholera – Doxycycline

Rheumatic fever- Benzathine penicillin (or long acting penicillin G)

Tuberculosis – Isoniazid alone or with rifampicin

Meningococcal meningitis – Rifampicin / Ciprofloxacin

Gonorrhoea / Syphilis – Procaine Penicillin

Rickettsial infections – Tetracyclines

Malaria – Chloroquine / mefloquine

Influenza A – Amantadine

Surgical prophylaxis – Cefazolin

MOST IMPORTANT MECHANISM OF DRUG RESISTANCE

Beta lactams Inactivating enzyme (beta lactamase)

Tetracyclines Efflux pump (decreased concentration in 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

Flouroquinolones Altered DNA gyrase with reduced affinity

Note: Transfer of resistance against all antibiotics is plasmid mediated except flouroquinolones (due to chromosomal mutation)

ANTI-MYCOBACTERIAL ANTIBIOTICS

TUBERCULOSIS

It is caused by mycobacterium tuberculosis. The drugs used for tuberculosis are

First line	**Second line**	
Isoniazide (H)	Thiacetazone	Ciprofloxacin
Rifampicin (R)	Paraaminosalicylic acid	Ofloxacin
Pyrazinamide (Z)	Ethionamide	Azithromycin
Ethambutol (E)	Cycloserine	Clarithromycin
Streptomycin (S)	Kanamycin	Rifabutin
	Capreomycin	

ISONIAZID (INH)

This is bactericidal drug and inhibits the enzymes required for mycolic acid, an essential component of mycobacterial cell wall. It is the single most important drugs used in tuberculosis. Mycobacterial strains are assumed to be susceptible to isoniazid, if resistance is less than 4%. It is effective orally and metabolized by ACETYLATION which is genetically controlled. Fast acetylators require high dose and slow acetylators are predisposed to toxicity. It is an essential component of multi drug therapy of tuberculosis and can be used solely for prophylaxis of tuberculosis. 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. Hepatotoxicity is age dependent which affects less than 0.3% of adults 21-35 year old but the incidence in elderly is more than 2%. Isoniazide also inhibits MAO-A and can result in cheese reaction. Lupus like syndrome has also been reported with this drug.

RIFAMPICIN (R)

It is a derivative of rifamycin (another derivatives are rifabutin and rifapentine). It is bactericidal to mycobacterium and acts by inhibiting DNA dependent RNA polymerase. It undergoes enterohepatic circulation and is partly metabolized in liver. Metabolites are coloured and can cause orange discolouration of urine and secretions. It is eliminated mainly in feces and can be used safely in renal dysfunction. Apart from tuberculosis, it can be 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 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, flue like syndrome and anemia. Rifampicin is an inducer of drugs metabolizing enzyme 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 treatment of tuberculosis in AIDS patient (getting antiretroviral drugs). The female on oral contraceptives should either increase the dose of the pill or use alternative method of contraception, when using rifampicin as a component of ant tubercular treatment.

Notes: It is least toxic drugs for TB and also is safest in pregnancy.

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 causes dose dependent and reversible visual disturbances like optic neuritis, red-green colour blindness (blue vision) and retinal damage. Because children are unable to report early visual impairment, this drugs is contra indicated in children. It also cause hyperuricemia, peripheral neuritis and hepatotoxicity.

PYRAZINAMIDE (Z)

This is a weakly bactericidal drug but is more active in acidic media (intracellular sites and at sites of inflammation). It mechanism seems to be similar to isoniazid but exact site is not known. Half life of this drug increase in hepatic as well as renal impairment. In 40% of patients it causes non gouty arthralgia. Hyperuricemia also occurs commonly but is usually asymptomatic and it should not be stopped if hyperuricemia develops. It also can cause hepatic dysfunction, porphyria and photosensitivity.

STREPTOMYCIN (S)

This is a tuberculocidal aminoglycoside. It is not absorbed orally and must be given by i.m injection. It is poorly plasma protein bound. Its half life is prolonged in renal failure. It is NOT HEPATOTOXIC. Other features are similar to aminoglycosides. Other aminoglycosides used for treatment of tuberculosis are amikacin, kanamycin and capreomycin. Streptomycin is contraindicated in PREGNANCY.

OTHER DRUGS

Thiacetazone is a tuberculostatic drug. Major adverse effects include hepatitis, bone marrow depression and Steven Johnson syndrome (not used in HIV positive patients). Paraaminosalicylic acid is related to sulfonamides, acts by similar mechanism and is bacteriostatic. It can cause kidney, liver and thyroid dysfunction. Ethionamide is another tuberculostatic drugs which can cause hepatitis, optic neuritis and impotence. Ethionamide can also be used in leprosy. Cycloserine is a cell wall synthesis inhibiting drug and can cause neuropsychiatric adverse effects. Kanamycin, capreomycin and amikacin are injectable aminoglycosides which can be used in treatment of MDR tuberculosis. Flouroquinolones used for this indication include ciprofloxacin, ofloxacin, moxifloxacin and sparfloxacin. These are also effective against mycobacterium avium complex in AIDS patients. Newer macrolides like azithromycin and clarithromycin are effective against non-tubercular atypical mycobacteria.

TREATMENT OF TUBERCULOSIS

Combination chemotherapy (short course chemotherapy) is used to prevent emergence of resistance to any one drug. All the contacts should be treated with INH especially young children. According to RNTCP guidelines:

Category I: New smear positive pulmonary TB or smear negative TB with extensive pulmonary tuberculosis or severe forms of extra pulmonary TB cases are treated by two months of therapy with HRZE (S) followed by four months therapy with HR in continuation phase (2HRZE+4HR).

Category III: Limited parenchymal involvement or less severe extra pulmonary TB patients (lymph node, skin TB) are treated by 2 HRE+ 4HR

Category II: These include treatment failure, relapse and defaulters. These are treated vigorously because these have maximum changes of being drug resistant. The treatment for these is 2HRZES+IHRZE +5 HRE.

Category IV: Chronic cases are drug resistant cases and are treated as

INH resistant- RZE for 12 months

H+R resistant – ZE + S/ Ethionamide + Ciprofloxacin/ Ofloxacin

ATYPICAL MYCOBACTERIAL INFECTIONS

Clarithromycin or azithromycin is recommended for prophylaxis of Mycobacterium avium complex (MAC) in patients with CD4 counts less than 50 / µl. 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.

Note:

- Ethambutol and streptomycin do not cross blood brain barrier.
- Ethambutol and streptomycin are not hepatotoxic among first line drugs.
- Ethambutol and pyrazinamide can cause hyperuricemia.

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. 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 treatment of pneumocystis jirvoci 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 template function of DNA. It can cause gastrointestinal irritation, icthyosis 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 drug used in leprosy and is most effective. It is used to prevent resistance to dapsone.

OTHER DRUGS

Ethionamide has antileprotic activity but causes hepatotoxicity in 10% patients. Ofloxacin, pefloxacin and sparfloxacin 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.

Mutli bacillary leprosy: It includes leprosy with more than five skin lesions or smear positive cases even if 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 2 years.

Another regime called single lesion single dose therapy utilizes 600mg rifampicin + 400mg ofloxacin + 100mg minocycline (**ROM therapy**) as a single dose.

ANTI-FUNGAL AGENTS

According to mechanism of action these can be classified as

1) **Drugs altering membrane permeability**
    - Azoles
        - ✓ Triazoles e.g. Fluconazole, itraconazole, voriconazole
        - ✓ Imidazoles e.g. Ketoconazole, miconazole, clotrimazole
    - Terbinafine
    - Polyenes e.g. Amphotericin B, nystatin, hamycin
2) **Drugs blocking nucleic acid synthesis** e.g. Flucytosine
3) **Drugs disrupting microtubule function** e.g. Griesofulvin
4) **Drugs inhibiting cell wall synthesis** e.g. caspofungin, nikkomycin

DRUGS USED FOR TREATMENT OF SYSTEMIC FUNGAL INFECTIONS

These include amphotericin B, flucytosine, triazoles, ketoconazole and echinocandins.

1. Amphotericin B

It is polyene antibiotic similar to nystatin. It is not absorbed orally so given by slow i.v. infusion. It is widely distributed except in CNS. It binds to ergosterol and causes the formation of artificial pores in fungal cell membrane. Amphotericin B has the widest antifungal spectrum and is 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. It may also result in anemia. Intrathecal administration may cause seizures and neurological damage. Liposomal formulations, colloidal dispersion (ABCD) and lipid complex (ABLC) are lipid preparations of amphotericin B (costly 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.

2. Flucytosine

This is a pyrimidine analogue and given 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.

3. Azoles

Ketoconazole, fluconazole, voriconazole, itraconazole, posaconazole and rabuconazole are azoles used for systemic fungal infections. These drugs act by inhibiting 14α demethylase, which is responsible for conversion of lanosterol to ergosterol.

- Ketoconazole has narrow antifungal spectrum and due to severe and frequent adverse reactions, is now rarely used.
- 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 drug of choice for candidiasis and cryptococcal meningitis (co-drug of choice with AMB).

- Itraconazole is drug of choice for blastomycosis (non-meningeal), histoplasmosis, coccidioidomycosis, paracoccidioidomycosis and sporotrichosis infections. Its entry into CNS is limited, therefore not used for CNS fungal infections.

- Voriconazole has widest spectrum and is drug of choice for invasive aspergillosis. Adverse reactions of azoles include diarrhea, rash and hepatotoxicity in preexisting liver dysfunction. Ketoconazole inhibits cytochrome P450 enzymes 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. Voriconazole causes visual disturbances like blurred vision, altered colour perception and photophobia.

4. Echinocandins

This is a new group of antifungal drugs that include caspofungin. It is used intravenously and acts by inhibiting synthesis of β1,2 glycan, a component of fungal cell walls. It is approved only for invasive aspergillosis. It is quite nontoxic and causes only mild infusion related reactions.

5. 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 also can 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 and resulting in decreased ergosterol synthesis. Inhibition of this enzyme can lead to accumulation of squalene that is toxic to fungus. Main adverse effect of terbinafine is rash and gastrointestinal upset.

3. **Azoles:** Ketoconazole, fluconazole and itraconazole can be used orally for superficial fungal infections but voriconazole is not used for this purpose.

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, ketoconazole
- Allylamines e.g. terbinafine, butenafine, naftifine
- Ciclopirox
- Benzoic acid
- Tolnaftate
- Undecylenic acid

ANTI VIRAL AGENTS

Antiviral drugs can act at any step of viral replication. Viral replication involves first 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.

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 & 2) and varicella zoster virus (VZV). Acyclovir is not active against CMV infections. It is activated first by virus specific kinase to form acyclovir monophosphate and then by host kinases to form acyclovir triphosphate. This product competitively inhibits action of DNA polymerase 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 treatment of mucocutaneous and gential herpes and also for prophylaxis of herpes infections in AIDS and immunocompromised patients. Parenteral administration for serious herpes infections can cause seizures, hypotension and nephrotoxicity but it does not cause bone marrow suppression. 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 penciclovir (also developed as separate drug) and acts via similar mechanism.

Ganciclovir

It is active against CMV & HSV and acts by inhibiting DNA polymerase. First phosphorylation step again is virus specific. Ganciclovir is used only intravenously whereas valganoiclovir has good oral absorption.

Ganciclovir is 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.

Cidofovir

It is activated exclusively by host cell kinases and is active against HSV, CMV, adenovirus and papilloma virus. Dose limiting toxicity is nephrotoxicity

Foscarnet

It is not an antimetabolite and do not require phosphorylation for activity. It is used i.v for CMV infections. Nephrotoxicity (30% incidence), hypocalcemia and CNS effects are major adverse effects.

Other drugs

- Vidarabine, idoxuridine, trifluridine, fomivirsen and docosanol 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. It can cause iritis, vitreitis 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 cream) for herpes labialis. It prevents the entry of virus in cell by inhibiting the fusion of virus envelope with 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 duration of symptoms of influenza if used prophylactically. Rimantadine is longer acting than amantadine. Amantadine can cause adverse effects like livedo reticularis and ankle edema. Amantadine is also effective for treatment of Parkinsonism.

Oseltamivir and zanamavir

These drugs act as neuraminidase inhibitors and prevent 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 zanamivir is administered intranasally

(bronchospasm is important adverse effect). These can be used prophylactically to prevent influenza during epidemics.

ANTI HEPATITIS DRUGS

Drugs active against hepatitis B (HBV) and hepatitis C virus (HCV) are interferon α (IFN-α), lamivudine, ribavirin and adefovir.

IFN-α

It acts by JAK-STAT pathway to increase antiviral proteins and also promotes formation of natural killer (NK) cells. It can be used alone or with lamivudine in chronic HBV infections. It can be used with ribavirin in acute HCV infections and prevent its progression to chronic disease.

Lamivudine

It is a nucleoside reverse transcriptase inhibitor used in 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 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.

Adefovir:

It acts as antimetabolite for HBV but nephrotoxicity is dose limiting. It can also cause lactic acidosis with hepatomegaly and steatosis.

Note:

- Acute HBV and HCV infections require only symptomatic treatment.
- IFN-α can be used alone for treatment of chronic HBV or HCV infections.
- Lamivudine can be combined in HBV and ribavirin in HCV infections with IFN-α.

ANTI HIV DRUGS

There are three major classes of drugs for treatment of HIV infection. These are reverse transcriptase inhibitors, protease inhibitors and fusion inhibitors.

NRTIs	Fusion inhibitor	PIs	NNRTIs
Zidovudine	Enfuvirtide	Saquinavir	Efavirenz
Stavudine		Ritonavir	Delavirdine
Lamivudine		Indinavir	Nevirapine
Zalcitabine		Nelfinavir	
Didanosine		Amprenavir	
Abacavir		Fosamprenavir	
Emtricitabine		Lopinavir	
Tenofovir (Nucleotide)		Atazanavir	

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 inhibitor (e.g. tenofovir). The non- competitive inhibitors are also known as non-nucleoside/non-nucleotide reverse transcriptase inhibitors (NNRTIs).

a. NRTIs: Most of these are prodrugs and are activated by host cell kinases to form triphosphates. These drugs competitively inhibit reverse transcriptase and also acts as chain terminators by incorporation into 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 as single agents.

- Zidovudine is frequently used NRTI in treatment of HIV infections. It can also be used for prophylaxis of needle stick injury patients and for prevention of vertical transmission of HIV form mother to fetus. Major adverse effect of zidovudine is bone marrow suppression leading to megaloblastic anemia and thrombocytopenia. It can also cause myopathy. Rifampicin increases the clearance of this drug.

- 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 peripheral neuropathy.

- Stavudine causes dose limiting peripheral neuropathy. It has maximum chances of causing lactic acidosis. It can also result in pancreatitis.

- Lamivudine and emtricitabine are best tolerated NRTIs. These are not associated with peripheral neuropathy or pancreatitis.

- All NRTIs are excreted by kidney (require dose adjustment in renal failure) except abacavir which gets metabolized by alcohol dehydrogenase. Hypersensitivity is major adverse reaction of abavacir. 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 kidney.

c. NNRTIs: These drugs inhibit reverse transcriptase by acting at a site (allosteric site) different from that of NRTIs. Resistance to these drugs develops very rapidly. Drugs in this group are efavirenz, nevirapine and delavirdine. Skin rash is adverse effect of all these drugs and nevirapine can cause Steven Johnson syndrome and toxic epidermal necrolysis. Delavirdine and efavirenz should be avoided in pregnancy. Nevirapine is used in pregnancy to prevent vertical transmission (single oral dose to mother during labour and single oral dose to neonate within 3 days after birth).

Protease inhibitors

Protease helps in maturation of infectious virions and inhibitors of this enzyme can be used in treatment of HIV infections.

- Oral bioavailability of indinavir is decreased by food. It can cause thrombocytopenia and kidney stones. To prevent renal damage, good hydration must be maintained.

- This group of drugs inhibit the metabolism of several drugs by inhibiting CYP 3A4. Ritonavir in low doses can be used with other protease inhibitors to increase their plasma concentration. Lopinavir is used only in combination with ritonavir.

- Amprenavir can cause Steven Johnson syndrome.

- All protease inhibitors are metabolized by liver and all can cause lipodystrophy characterized by hyperglycemia, hyperlipidemia, insulin resistance and altered fat distribution.

Fusion inhibitor

Enfuvirtide is a drug that binds to gp 41 subunit of HIV envelope protein and inhibits fusion of viral and host cell membranes. This prevents entry of virus to host cells. It is used subcutaneously and can cause injection site reactions, hypersensitivity and pneumonia.

Highly active anti-retroviral therapy (HAART): Treatment of HIV under HAART includes use of 3 or more drugs, of which one or two are NRTIs. The combinations may be 2NRTIs + 1PI (protease inhibitor) or 1NRTI + 1NNRTI + 1 PI or 3NRTI. for prophylaxis zidovudine alone or along with other anti HIV drugs like lamivudine may be used.

ANTIMALARIAL DRUGS

Malarial parasite (plasmodium) undergoes a primary developmental stage in liver (pre erythrocytic stage) and then it enters the RBCs (erythrocytic stage). Symptoms of malaria (fever, chills and rigors) correspond to erythrocytic stage. Plasmodium may give rise to gametes in blood or the schizonts can again go back to liver and remain dormant there. These dormant hepatic stages (exo erythrocytic) are responsible for relapse of malaria. Exo-erythrocytic stage is absent in P. falciparum, so relapses do not occur. The drugs used for treatment or prevention of malaria may be classified on the basis of stage in the life cycle of parasite at which these act as

a. **Primary tissue schizonticides:** These are the drugs that kill schizonts in the liver (pre-erythrocytic) e.g. proguanil, primaquine and tetracyclines. These drugs are used for causal prophylaxis.

b. **Erythrocytic schizonticides:** These drugs kill schizonts in blood and are used for treatment of acute attacks as well as suppressive prophylaxis of malaria. These may be fast acting or slow acting:

    - Fast acting: Chloroquine, mepacrine, quinine, mefloquine, halofantrine, atovaquone and artemisinin derivatives
    - Slow acting: Proguanil, pyrimethamine, sulfonamides, tetracyclines

c. **Exo-erythrocytic schizonticides:** These drugs kill the exo-erythrocytic forms and are thus used for radical cure e.g. primaquine.

d. **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.

Chloroquine

It is the drug possessing largest volume of distribution (>1300L). It accumulates in the food vacuole of 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 erythrocytic schizonticides and has no effect on exo-erythrocytic stages. It is also used for other indications that are

- **R**heumatoid arthritis
- **E**xtra intestinal amoebiasis

- **D**iscoid lupus erythematosis
- **L**epra reaction
- **I**nfectious mononucleosis
- **P**hotogenic reactions
- **M**alaria
- **G**iardiasis

Note: it can be remembered from the pneumonic: **RED LIP M**ahatma **G**andhi

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. 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. It is often used with doxycycline or clindamycin to decrease 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 α1 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.

Mefloquine

It can be used for chloroquine resistant P. falciparum infections, both for treatment as well as prophylaxis. It is drug of choice for treatment of chloroquine resistant malaria in pregnancy (quinine should not be used). It can cause cardiac conduction disturbances, psychosis and seizures. Administration with halofantrine or quinine is contraindicated because it can cause prolongation of QT interval.

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 schizonticide 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 in P. falciparum malaria because this organism has no exo-erythrocytic stage.

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 with 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 rapidly acting blood schizonticide and act by collapsing the parasite's membrane. Proguanil potentiates its antimalarial action. It can also be used for Pneumocystis jirvoci pneumonia and Toxoplasma gondii infections.

Artemisinin derivatives

Artemisinin, dihydroartemisinin, artesunate, artemether and arteether are compounds obtained from 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 fastest acting drugs against malaria. Artesunate has very short half life. These can be used for 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 new drug similar to halofantrine and is always used along with artemether.

Other drugs

Other antimalarial drugs include doxycycline, amodiaquine, mepacrine and pyronaridine etc. Mepacrine is most concentrated in collagen.

Type of Malaria	Drug of choice	
	Treatment	**Prophylaxis**
P. vivax malaria and Chloroquine sensitive P. falciparum malaria	Chloroquine (in pregnancy also)	Chloroquine
Chloroquine resistant malaria	Quinine	Mefloquine
Quinine resistant malaria	Mefloquine	Mefloquine
Mefloquine resistant malaria	Quinine + Doxycycline/ Sulfadoxine-Pyrimethamine	Proguanil + Atovaquone

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 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 proximal intestine and very little reaches the colon. Metronidazole is also drug of choice for treatment of trichomoniasis, giardiasis, bacterial vaginosis and pseudomembranous colitis by C. difficile. It is also used for treatment of infections caused by anaerobic bacteria like bacteroides and clostridium, and in combination therapy for H. pylori. Nausea, metallic taste and abdominal cramps are most common adverse effects. It can also cause discolouration of urine, leucopenia and dizziness. Seizures can occur with high use of high dose. Opportunistic fungal infections can occur in a patient on metronidazole. It can cause disulfiram like reaction if used in patient 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.

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.

Iodoquinol and quinidochlor: Iodoquinol is 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 treatment of kala-azar.

Nitazoxanide: It has some activity against Entamoeba histolytica but is approved only for 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 haemo lymphatic 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 haemo lymphatic stage of sleeping sickness. It do not cross blood brain barrier, therefore is not effective against late CNS stages. It is also used for prophylaxis (aerosol) and treatment (i.v) of Pneumocystis jirvoci pneumonia and in treatment of kala-azar. It can cause respiratory abnormalities, hypotension, hyperglycemia, neutropenia and pancreatitis.

Melarsoprol: it is organic arsenical and is drug of choice for late stages of African trypanosomiasis.

Other drugs: Nifurtimox is drug of choice for Chagas disease. Suramin is drug of choice for early haemo lymphatic stages of African trypanosomiasis. It is also used as an alternative to ivermectin in onchocerciasis. Eflornithine is also effective in some cases of trypanosomiasis.

Trypanosomiasis	**Drug of Choice**	
African sleeping sickness	Early haemo lymphatic stage	Suramin

	Late CNS stage	Melarsoprol
South-american (Chagas disease)		Nifurtimox

DRUGS FOR LEISHMANIASIS

Leishmaniasis can be visceral (kala-azar), mucocutaneous or cutaneous. Sodium stibogluconate (pentavalent antimonial compound) is primary 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, miltifosine and sitamaquine. Paromomycin has been recently approved for treatment of kala-azar. Fluconazole or metronidazole can be used for cutaneous lesions and amphotericin B can be used for mucocutaneous lesions. 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	Paromomycin
Cyclospora	Cotrimoxazole
Isospora	
Pneumocystis jirvoci	
Leishmania sp.	Sodium stibogluconate
Giardia lamblia	Metronidazole
Trichomonas vaginalis	
Toxoplasma gondii	Pyrimethamine + Clindamycin
T. gondii in pregnancy	Spiramycin
Early African trypanosomiasis	Suramin
Late (CNS) African trypanosomiasis	Melasoprol
Chagas disease	Nifurtimox

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 of antihelminthic drugs: 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 (N_N receptor agonist): Pyrantel pamoate, levamisol
- Drugs causing flaccid paralysis ($GABA_A$ 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 about antihelminthic drugs:

- Albendazole, mebendazole and pyrantel pamoate has wide antihelminthic spectrum.
- Albendazole is drug of choice for 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).
- Praziquantal is drug of choice for all trematodes and cestode infestations except Fasciola hepatica (Bithionol) and hydatid disease (albendazole).
- High dose albendazole if used for greater than 3 months (as for hydatid disease) may cause hepatotoxicity.
- DEC act 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.

ENDOCRINOLOGY:

Hormones are the substances 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 & Somatostatin CRH TRH GnRH (FSHRH/LHRH) PRIH (**same as dopamine**)
	Intermediate	Melanocyte stimulating hormone (MSH)	

	Lobe		
	Posterior Lobe	Oxytocin Vasopressin (ADH)	
Thyroid	Follicular Cells	T_3, T_4	
	Parafollicular Cells	Calcitonin	
Parathyroid		Parathyroid hormone (PTH)	
Pancreas	α Cells	Glucagon	
	β Cells	Insulin	
	δ Cells	Somatostatin	
Adrenal	Cortex	Glucocorticoids	
		Mineralocorticoids	
		Sex Corticoids	
	Medulla	Adrenaline (Epinephrine)	
		Nor-adrenaline (Nor-epinephrine)	
Gonads	Testes	Androgens (Testosterone and Dihydrotestosterone)	
	Ovary	Progestins	
		Estrogens	

MECHANISM OF ACTION OF HORMONES

NUCLEAR RECEPTORS		T3, T4, Estrogen
CYTOPLASMIC RECEPTORS		All Steroid Hormones i.e. Glucocorticoids Mineralocorticoids Progesterone Testosterone
MEMBRANE RECEPTORS		Insulin Growth Hormone Prolactin

1. Tyrosine Kinase		Oxytocin Vasopressin (V1)
2. GPCRs	**a) IP3/DAG/Ca^{2+}**	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

1. 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).

1. Growth Hormones (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 (1GF-1 & 1GF-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.
- Excess of GH causes acromegaly and its deficiency results in dwarfism.
- Recombinant growth hormones (**somatrem & somatropin**) are approved for pituitary dwarfism and AIDS related wasting.
- **Sermorelin & hexarelin** are recombinant GHRH analogs that are used for pituitary dwarfism.
- **Pegvisomant** is a GH receptor antagonist indicated for the treatment of acromegaly.

2. Somatostatin

It is secreted by hypothalamus 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, bleeding due to esophageal varices and secretory diarrhea but has disadvantage of short duration of action.
- **Octreotide** is somatostatin analogue having high potency and *long duration of action*. It is preferred over somatostatin for all the indications.
- **Lanreotide** is another somatostatin analog that can be given i.m. in slow release formulation.

3. 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 D_2 blockers like antipsychotics and metoclopramide can cause hyperprolactinemia.

- **Bromocriptine** is dopamine agonist useful in the treatment of hyperprolactinemia (amenorrhoea, 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.

- Nausea, vomiting & postural hypertension 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 longer acting dopamine agonist that is better tolerated than bromocriptine.
- **Quinagolide** is non-ergot dopamine agonist having less adverse effects.

4. Gonadotropins and gonadotropin releasing hormone (GnRH)

Follicle stimulating hormone (FSH) and lutenising 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 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).
- **GnRH analogues** like *busurelin, goserelin, leuprolide, nafarelin and histrelin* are more potent and longer acting than natural GnRH. These drugs stimulate gonadotropin secretion when given in 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 carcinomas, PCOD and uterine fibroids. Most of these drugs are used by s.c. route whereas nafarelin 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 condition like prostatic carcinoma and endometriosis.
- *Cetrorelix, ganirelix and abarelix* are **GnRH antagonists**. GnRH antagonists 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.

2. THYROID HORMONES

Thyroid gland contains follicular cells and parafollicular (C) cells. Former secretes thyroid hormones (T_3 and T_4) whereas 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 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 follicles where these remain stored as colloid. On stimulation via TSH, these hormones are released in the circulation.
- 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 & 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 (T3)	l-Thyroxine (T4)

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 hyperthyroidism.

Actions of thyroid hormones

1. These are required for normal growth and development. Deficiency of thyroid hormones leads to cretinism in children and myxedema in adults.
2. These are catabolic hormones and increase the breakdown of fats (to FFA), carbohydrates (cause hyperglycemia) and proteins (cause weight loss).
3. These are calorigenic and increase basal metabolic rate (BMR). Heat intolerance occurs in hyperthyroidism whereas hypothyroidism causes cold intolerance.
4. Thyroid hormones stimulate the heart (increase rate, contractility and cardiac output). In hyperthyroidism, atrial fibrillation can occur.
5. Hypothyroidism results in mental retardation whereas hyperthyroidism can result in anxiety, tremors, nervousness and excitability.

Indications of use of thyroid hormones

Main indication of these 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 cautiously used in patients with heart disease like AF).

DRUGS USEFUL FOR HYPERTHYROIDISM

Drugs can inhibit various steps in thyroid hormone synthesis and release.

1. Inhibitors of NIS

Iodine is trapped in follicular cells with Na^+:I^- symporter. Thiocyanate, perchlorate, pertechtenate and nitrates inhibit this transporter and thus thyroid hormone synthesis. These drugs are very toxic and are obsolete now.

2. Thyroid Peroxidase inhibitors

Thyroid peroxidase enzyme catalyzes three reactions (oxidation, organification and coupling) in the process of thyroid hormone synthesis. **Carbimazole, methimazol and propylthiouracil** act by inhibiting this enzyme. Carbimazole is a prodrug and acts after conversion to methimazole. Major differences between carbimazole and **propylthiouracil** are that latter is:

- Has high **P**lasma protein binding
- Can be used in **p**regnancy (because less transfer across placenta due to high PPB)
- Less **p**otent
- Less half-life so require multiple daily dosing
- Also inhibits **p**eripheral conversion of T_4 to T_3

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.

- Thyroid peroxidase inhibitors are used for the control of thyrotoxicosis in patients with Graves' disease and toxic nodular goiter.
- 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.

3. Inhibitors of thyroid hormones 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.

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 gastro intestinal distress. These drugs may also cause flaring up of acne in adolescents.

4. Drugs causing destruction of thyroid gland

I^{131} is most commonly used radioactive iodine with half-life of 8 DAYS (stable isotope of iodine is I^{127}). When administered (as sodium salts, orally), these are actively taken up by 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. I^{131} can be used for the treatment of hyperthyroidism but response is slow (maximum response may take 3 months). Thyroid peroxidase inhibitors are given 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** age [and in the presence of other contra-indications of surgery). These drugs **are not suitable for young children and in pregnancy**. Another disadvantage of radioactive iodine is that if **hypothyroidism** develops, it is **permanent** (requiring life long T_4 therapy).

3. INSULIN AND ORAL HYPOGLYCEMIC AGENTS

Diabetes mellitus (DM) is diagnosed when fasting blood glucose exceeds 126mg/dl. Type I DM (IDDM) is treated only by insulin whereas in treatment of type II DM (NIDDM), orally active drugs are tried first in uncomplicated cases. Insulin is used in all patients of type I diabetes mellitus and in patients of type II diabetes who are not controlled with oral hypoglycemic agents (OHA).

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**. Glucose is the main stimulus for the release of insulin from the β cells of pancreas. Glucose stimulates GLUT 2 and inhibits ATPase sensitive K^+ channels; factors that are responsible for the depolarization of β cells and release of insulin. 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)

- Increasing glycolysis (by stimulation of glucokinase) and glycogenesis (by stimulating glycogen synthase)
- Inhibiting glycogenolysis (by inhibiting phosphorylase) and gluconeogenesis (by inhibiting phosphoenol pyruvate carboxykinase)

2. It inhibits lipolysis and thus favors triglyceride deposition
3. It increases the synthesis and inhibits the breakdown of proteins.

Preparations

Conventional preparations are obtained from pork and beef. Addition of zinc makes it long acting. Insulin may be

- Short acting (regular insulin and semilente)
- Intermediate acting (lente insulin and neutral protamine hagedron) or
- Long acting (ultralente and protamine zinc insulin).

These preparations contain impurities (that impart antigenicity) and can result in allergic reactions. Highly purified preparations include single peak insulin and monocompetent insulin. These are less immunogenic than conventional preparations and the incidence of allergic reactions with pork monocompetent insulin is similar to that with human insulin. 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 and aspart**) and ultralong acting (**insulin detemir and glargine**) preparations have also been developed.

Route of administration

- All preparations can be given by s.c. routes
- Only regular (crystalline zinc) insulin can be given i.v.
- Inhalational route (exubera) is currently being investigated.

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 injection site can occur with conventional preparations and the chances are less with highly purified and recombinant forms of insulin.
- Allergic reactions can occur with conventional preparations.

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.

ORAL HYPOGLYCEMIC AGENTS

These drugs may be classified into two groups based on the mechanism of action.

1. ***Drugs acting by release of insulin***

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.

a) *Sulfonylureas*: These may be first generation (chlorpropamide) or second generation (glibenclamide, glipizide, gliclazide and glimepride) compounds. *Tolbutamide is shortest acting whereas chlorpropamide is longest acting sulfonylurea.* Second generation drugs are more potent than first generation agents. Sulfonylureas can cause weight gain (less chance with glipizide and gliclazide). All these drugs can cause hypoglycemia and **chlorpropamide** has additional actions as well. It can cause **dilutional hyponatremia** (ADH like action), **cholestatic jaundice and disulfiram like action** (intolerance to alcohol). Gliclazide has additional anti platelet action also.

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.

2 ***Drugs acting by other mechanisms without affecting insulin***

These drugs do not cause hypoglycemia because these are not increasing serum insulin concentrations.

a) *Biguanides: Metformin and phenformin* are biguanides and are preferred agents for obese patients (as these cause weight loss). These drugs decrease blood glucose by decreasing the production (inhibit gluconeogenesis and glycogenolysis) and increasing the utilization (stimulation of glycolysis and tissue uptake of glucose). 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 presence of hepatic and renal impairment or alcohol ingestion ^{Q}.

Metformin is also useful for polycystic ovarian disease (PCOD).

NOTE **:** *MOST – Metformin for Obese and Sulfonylureas for Thin*

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 (PPARγ). These drugs are used to reverse insulin resistance in type II DM. Troglitazone was withdrawn due to serious hepatotoxicity and monitoring of hepatic function is recommended for other glitazones also.

c) *α- glucosidase inhibitors:* 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 GIT. Major adverse effect of these drugs is flatulence due to fermentation of unabsorbed carbohydrates. If high doses are taken, simple carbohydrates like glucose (not sucrose or other complex carbohydrates) can be used.

NEW DRUGS

A) *EXENATIDE:* It is recombinant glucagon like peptide (GLP) analogue. GLP is normally secreted (in GIT) when food enters stomach and it stimulates release of insulin. GLP is normally metabolized by dehydropeptidylpeptidase 4 (DPP-4). Exenatide is GLP analogue resistant to DPP-4 and can be used for the treatment of DM.
B) *SITAGLIPTIN:* It is DPP-4 inhibitor and thus decreases the metabolism of endogenous GLP.
C) *PRAMLINTIDE:* It delays gastric emptying and suppresses glucagon secretion.

4. CORTICOSTEROIDS

Adrenal cortex consists of three layers; zona glomerulosa, zona fasciculate 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. Glucocorticoids secretion is maximum in early morning.

ACTIONS

Mineralocorticoids: Major endogenous mineralocorticoid is aldosterone. It acts in DCT of 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 drugs decreasing this effect (spironolactone, ACE inhibitors, angiotensin receptor antagonists (ARB) and β blockers) decrease mortality in patients with CHF.

Glucocorticoids: Major endogenous glucocorticoid is hydrocortisone (cortisol).

1. **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 extremities is seen. Glucocorticoids cause negative Ca^{2+} balance (by inhibiting intestinal absorption, enhancing renal excretion and causing loss of Ca^{2+} from the bones) and can predispose to osteoporosis.

2. **Effect on CVS and CNS:** Glucocorticoids prevent increase in permeability of capillaries. These have mild euphoric effect and high doses can lower seizure threshold.

3. **Effect on GIT**: These hormones may aggravate peptic ulcer by increasing the secretion of HCl and pepsin in stomach.

4. **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 and basophils in tissues.

5. **Effect on inflammatory response:** Glucocorticoids are powerful anti-inflammatory agents. Most important mechanism is *inhibition of chemotaxis* (recruitment of the cells at the site of inflammation). These hormones also induce production of lipocortins that are responsible for inhibition of phospholipase A_2 (involved in the production of prostaglandins and leukotrienes). They also delay healing of wounds and scar formation.

6. **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

	DURATION OF ACTION	**GLUCOCORTICOID ACTIVITY**	**MINERALOCORTICOID ACTIVITY**	**POTENCY**
GLUCOCORTICOIDS				

1. HYDROCORTISONE (CORTISOL)	Short acting	1	1	
2. CORTISONE	Short acting	Minimum (0.8)	(0.8)	**Least potent Glucocorticoid**
3. PREDNISONE	Intermediate acting	4	0.5	
4. PREDNISOLONE	Intermediate acting	5	0.5	
5. METHYL- PREDNISOLONE	Intermediate acting	5	0	
6. TRIAMCINOLONE	Intermediate acting	5	0	
7. PARAMETHASONE	Long acting	10	0	
8. BETAMETHASONE	Long acting	25	0	**Most potent Glucocorticoid**
9. DEXAMETHASONE	Long acting	**Maximum (30)**	0	
MINERALOCORTICOIDS				
1. DOCA		0	100	
2. FLUDROCORTISONE		10	200	**Most potent mineralocorticoid**
3. ALDOSTERONE		0.3	**3000 (max.)**	Not used clinically

IMPORTANT POINTS

- Max glucocorticoid activity *:* *Dexamethasone*
- Max. mineralocorticoid activity: *Aldosterone*
- Glucocorticoid with max. mineralocorticoid activity *:* *Hydrocortisone*
- Least potent glucocorticoid *:* *Cortisone*
- Most potent glucocorticoid: *Betamethasone*
- Selective mineralocorticoid action (with zero glucocorticoid activity) : *DOCA*
- Selective glucocorticoid action (with zero mineralocorticoid activity): *Methylprednisolone, triamcinolone,*

paramethasone, dexamethasone, betamethasone

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.

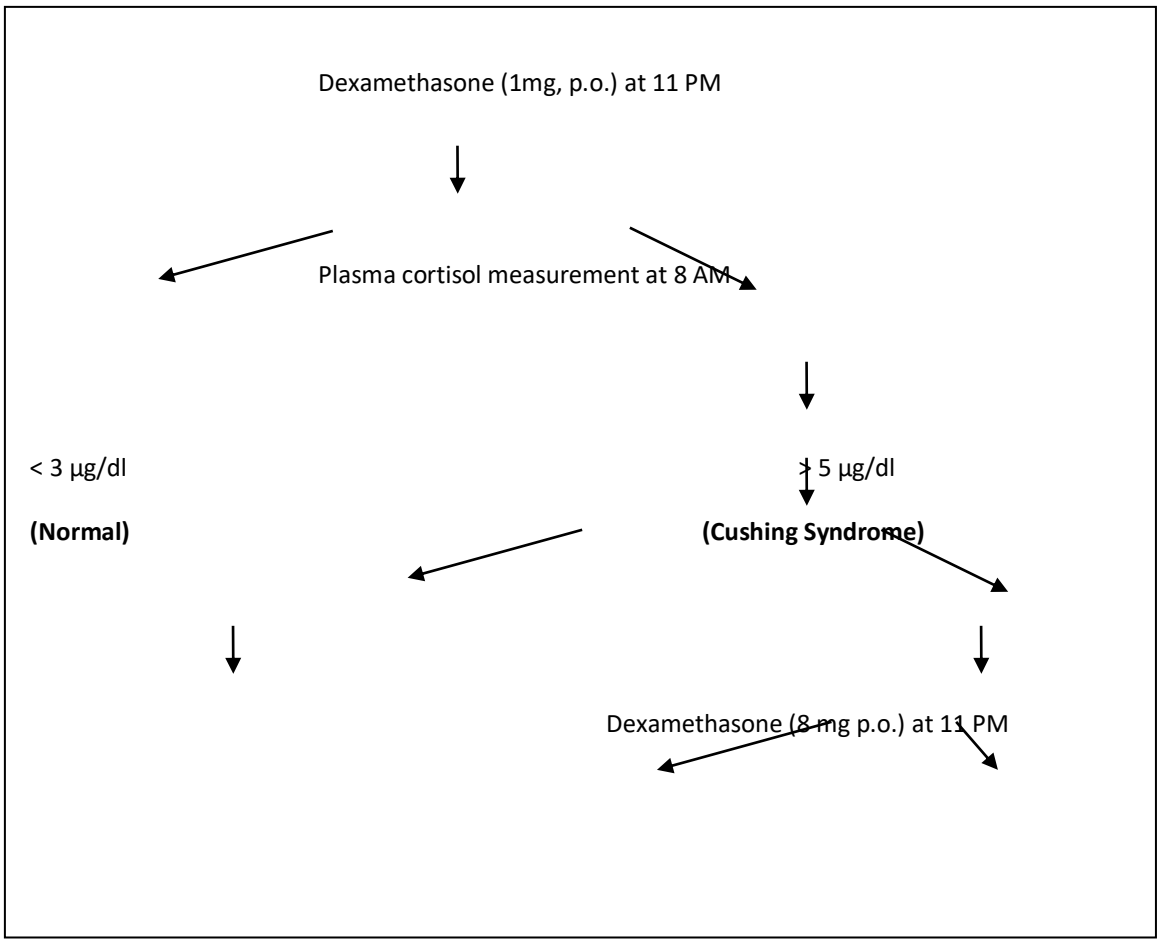
B) *Chronic adrenal insufficiency (Addison's disease):* It is treated with oral doses of hydrocortisone. Mineralocorticoid like fludrocortisone may also be required.

C) *Congenital adrenal hyperplasia:* This disorder is a result of congenital deficiency of 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 amelioration of symptoms.

2. Diagnostic use

Dexamethasone suppression test is used to test 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 there is excess 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 given at night and plasma cortisol level is measured in the morning. If Cushing disease is present, cortisol levels will be less than 50% of 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.



Plasma cortisol measurement at 8 AM

> 50% reduction in cortisol levels

< 50% reduction in cortisol levels

Cushing disease

(due to pituitary tumor)

Plasma ACTH measurement

Low

(Adrenal tumor)

High

(Ectopic ACTH production)

Dexamethasone suppression test

3. Use of antenatal steroids

Betamethasone can be given to accelerate the **fetal lung maturat**ion if delivery is anticipated before 32 weeks of gestation. In selected patients, antenatal steroid therapy decreases the incidence, severity and complications of RDS, 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

a) *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.**

b) *Anti allergic uses:* Corticosteroids are useful in 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.

c) *Immunosuppressive uses:* High dose corticosteroid therapy is required in 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.

d) *Anti cancer uses:* Due to prominent lympholytic action in malignant cells, steroids are essential components of combination therapy of ALL and lymphomas (both Hodgkin as well as non Hodgkin). These are also useful in breast carcinoma.

e) *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 acute crisis. However these are contra-indicated in intestinal TB due to risk of perforation.
- These can be used as desperate measure in septicemic shock.

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.
- 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. *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 contraindicated in psychosis (due to CNS stimulatory action) and epilepsy (due to lowering of seizure threshold).

GLUCOCORTICOID SYNTHESIS INHIBITORS

These drugs are useful in the diagnosis of adrenal diseases and in the treatment of Cushing's syndrome.

- **Metyrapone** inhibits *11β hydroxylase* enzyme (involved in the synthesis of cortisol and cortisone) and results in 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 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.
- **Trilostane** inhibits *3β hydroxysteroid dehydrogenase* enzyme, which is involved in production of adrenal and gonadal hormones. It is *also an aromatase inhibitor*.
- **Ketoconazole** is an antifungal agent that can be used for treatment of Cushing's syndrome due to inhibitory actions on *17 α hydroxylase and 3β hydroxysteroid dehydrogenase* enzymes.

CORTICOSTEROID RECEPTOR ANTAGONISTS

- **Mifepristone** is *antagonist at 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.

5. DRUGS AFFECTING CALCIUM BALANCE

Calcium and phosphate levels are maintained in blood by vitamin D (active form is **calcitriol**), parathyroid hormone (PTH) and calcitonin.

	Serum PO_4^{3-}	Serum Ca^{2+}	Mechanism
VITAMIN D	↑	↑	• Increases intestinal absorption of calcium and phosphate • Decreases renal excretion of both
PTH	↓	↑	• Decreases renal excretion of calcium and increases that of phosphate • Increases resorption of calcium from bone
CALCITONIN	↓	↓	• Increases excretion of both calcium and phosphate • Decreases resorption of calcium from bone

Thus **vitamin D and calcitonin can be used tom treat osteoporosis whereas PTH excess can result in osteoporosis**.

DRUGS USEFUL FOR TREATMENT OF OSTEOPOROSIS

1. Calcium
2. Vitamin D
3. Bisphosphonates
4. Estrogen and SERMs
5. Thiazides
6. Calcitonin
7. Teriparatide
8. Fluorides
9. Gallium nitrate
10. Donesumab
11. Cinacalcet

BISPHOSPHONATES

These agents are used for the treatment of osteoporosis by 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). Drugs in this group include **alendronate, risedronate, pamidronate and zolindronate**. These are used for the treatment of steroid induced osteoporosis, Paget's disease and hypercalcemia of malignancy (pamidronate and zolindronate by i.v route are preferred). 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.

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Estrogen increases bone formation and its deficiency in old age may result in post menopausal osteoporosis. Use of hormone replacement therapy for this condition predisposes the patients to adverse effect of estrogens on breast and endometrium (increased incidence of breast and endometrial carcinoma). **Raloxifen** is a selective estrogen receptor modulator with estrogen agonistic action on bone and antagonistic action on breast and endometrium. It is therefore preferred drug for the treatment and prevention of post menopausal osteoporosis. Major adverse effect of this agent is increased risk of **thromboembolism.**

TERIPARATIDE

It is **recombinant PTH $_{1\text{-}34}$**. It has been noted that PTH in low doses stimulates bone formation whereas in excess it causes resorption of bones. Teriparatide is available for the treatment of osteoporosis by intermittent s.c. administration.

DONESUMAB

Osteoclast 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. **Donesumab is a monoclonal antibody against this ligand** and is useful for the treatment of osteoporosis.

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.

OTHER DRUGS

- **Calcium and calcitriol** (vitamin D) can be used in osteoporosis.
- **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 use for treatment of osteoporosis (apart from its 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.

6. 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 & most potent estrogen)**, estrogen and estriol (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.*
- 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 & thromboembolism).

ACTIONS

1. Growth & development of female reproductive system.
2. *Increased risk of breast, endometrial and cervical carcinoma.*
3. Feedback inhibition of gonadotropin (LH/FSH) secretion.
4. Stimulation of CTZ to cause nausea & vomiting.
5. *Increased predisposition to deep vein thrombosis and pulmonary embolism* due to increased synthesis of factor II, VII, IX and X and decreased production of antithrombin III by liver.
6. *Favourable effect of lipid profile* by decreasing LDC-C and increasing HDL-C.
7. Glucose intolerance and sodium and water retention.
8. *Maintain bone mass by decreasing bone resorption*.
9. Increased risk of gall bladder stones and cholestatic jaundice.
10. Can result in hepatic adenoma on prolonged use.

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 *due to estrogen withdrawal*.
- Estrogens reduce testosterone production due to feed back inhibition of LH secretion. This property had been utilized for 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 & breast) in females*.
- Diabetes, fluid retention, hepatic adenomas, cholelithiasis and predisposition to thromboembolism can be seen in both sexes.
- 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 reabsorption) and blood (better lipid profile) whereas it is deleterious in endometrium, breast (increased risk of carcinoma) and liver (predisposition to thromboembolism).*

SERMs are targeted to provide beneficial effect of estrogens as well as to antagonize its adverse effects. **Clomiphene, tamoxifen, doloxifen, toremifen, fulvestrant, raloxifen and ormeloxifen** are now classified as SERMs.

- In humans **clomiphene** has estrogen antagonists action in hypothalamus (inhibits 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, doloxifen and toremifen** possess estrogen antagonistic activity in breast and blood vessels whereas agonistic activity in bone, uterus and liver. Their major indication is in treatment of **breast carcinoma**. *These have beneficial effect on bone and lipid profile but increase the risk of endometrial carcinoma and thromboembolism.*
- **Fulvestrant** has antagonistic activity only and is useful in **tamoxifen resistant breast cancer**.
- **Raloxifen** is used for **osteoporosis**. It also possesses beneficial effects on lipid profile, breast and endometrium. *Major adverse effect is increased predisposition to thromboembolism*.
- **Centchroman (ormeloxifen)** is used as **non hormonal oral contraceptive (Saheli)** and is also approved for the treatment of DUB.

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 and exemestane**. These are useful for 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 21-C or 19-C compounds. The *21-C* compounds (*hydroxyprogesterone, medroxyprogesterone, megestrol and dimethisterone*) are closely related to progesterone whereas third generation progestins containing 19-C (19 nor-testosterone derivatives) have lower androgenic activity than older compounds. *Desogestrel, norgestimate and gestedone are examples of 19-nor compounds.*

Actions:

- Progesterone increases basal insulin levels and the insulin response to glucose.
- These can act as competitors of aldosterone causing decrease in Na^+ reabsorption.
- 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 **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.**

HORMONAL CONTRACEPTIVES

Hormonal contraceptives can be used *orally or by implants*.

- **Oral contraceptives** mostly contain combination of estrogen and progestin. However progestin only pills are also available. Combined oral contraceptives (**OCPs**) may be given continuously (**monophasic pills**) or in **biphasic** (dose of progestin is changed once in cycle) or **triphasic** (dose of progestin is changed twice in cycle). *Biphasic and triphasic pills decrease breakthrough bleeding without increasing the total hormone content*.
- **Parenteral contraceptives** include subcutaneous implant of norgestrel (*Norplant*) and depot medroxyprogesterone acetate (*DMPA)*.

Mechanism of action: 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 *change in cervical mucus and endometrium and decreased motility and secretions of fallopian tube.*

Adverse effects

- *Nausea,* mastalgia, *breakthrough bleeding* and edema are related to amount of estrogen in the preparation.
- *Migraine* is made worse with the use of OCPs.
- *Failure of withdrawal bleeding* to occur.
- **Breakthrough bleeding is most common problem with 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 (*21-C compounds*). **Desogestrel and norgestimate cause less weight gain.**
- **Acne and hirsutism may worsen by 21-C progestins.**
- **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*.

Contraindications: Thromboembolism, liver disease, migraine,

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: Most of the actions of androgens are mediated by DHT whereas testosterone is itself active at few sites.

Actions of DHT

- Development and maturation of external genitalia (scrotum, penis, urethra etc.) in male.
- Male behaviour and changes of puberty.
- **Growth and hypertrophy of prostate in elderly**.
- Growth of hair follicles (pubic, axillary and beard) during puberty.
- Loss of scalp hair in adults.
- Activation of sebaceous glands.

Actions of testosterone

- *Feedback inhibition of LH secretion* from pituitary.
- *Spermatogenesis* in testes.
- Development of *internal genitalia* in male fetus.
- Stimulation of **erythropoiesis.**

Actions of both testosterone and DHT

- *Increase in mass and strength of skeletal muscle and bone*

- *Epiphysial fusion*

Pharmacokinetics

Testosterone is inactive orally due to high first pass metabolism. **17-alkylated derivatives like methyltestosterone and fluoxymestrane are effective per orally.**

USES

- Long acting derivatives like testosterone enanthate (i.m.) are indicated for *hypogonadal men* to compensate for 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 *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 masculinising of the female fetus and under masculinising 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, male carcinoma of the breast and prostate and patients with cardiac and renal disease.

DANAZOL:

It is a compound with **weak androgenic, progestational and glucocorticoid activities**. It decreases the secretion of gonadotropins from pituitary by causing feedback inhibition. Its major use is in **treatment of endometriosis**. *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.*

ANTI-ANDROGENS

Drugs in this group can act **by inhibiting the synthesis, activation or action of androgens**.

1) **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
2) **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,** a 5-α reductase inhibitor, is useful in the *treatment of BHP, male pattern baldness and hirsutism* by reducing the production of DHT.

3) **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 **contraceptive** pill. **Flutamide, bicalutamide and nilutamide** are other anti androgens that act by same mechanism. These are useful for the treatment of *prostatic carcinoma*. *Flutamide can cause gynaecomastia and reversible liver damage*. These drugs *can also be combined with GnRH agonists (like leuprolide) to reduce the initial flare up reaction.*
4) **Spironolactone**: It is 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 contraction of upper segment* (fundus and body) of uterus *whereas lower segment is relaxed* facilitating the expulsion of 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 doses and can result in fluid retention.

Uses: It is used for *induction of labor* in post maturity and uterine inertia. It can 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.

ERGOT DERIVATIVES

Ergometrine is derived from *Claviceps purpura* and is used as oxytocic agent. It produces uterine *contractions in 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 and isoxsuprine are *selective β_2 agonists* useful as tocolytic agents. These drugs should not be used in mother having heart disease or diabetes mellitus. Salbutamol and terbutaline can also be used.

MAGNESIUM SULPHATE

It is mainly used *to control convulsions in eclampsia*. It also possesses tocolytic activity and can be used when β_2 agonists are contraindicated.

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 efficacious tocolytic agent and is *anaesthetic of choice for version (external or internal*).

NEW DRUGS APPROVED IN 2010 AND 2011

Cardiology/ Vascular Diseases

Ticagrelor; for the reduction of thrombotic events in patients with acute coronary syndrome

Azilsartan medocomil; for the treatment of hypertension

Rivaroxaban ; for the prophylaxis of deep vein thrombosis during knee or hip replacement surgery.

Dabigatran etexilate mesylate ; for the risk reduction of stroke and embolism due to artial fibrillation

Dermatology/ plastic Surgery

Ceftaroline fosamil; for the treatment of bacterial skin infections and bacterial pneumonia

Icatibant- for the treatment of acute attacks of hereditary angioedema,

Azficel – T; for the improvement of nasolabial fold wrinkles in adults

Peginterferon alfa – 2b; For the treatment of melanoma

Ipilimumab; For the treatment of metastatic melanoma,

Vemurafenibe; For the Treatment of BRAF + melanoma,

Endocrinology
Ulipristal acetate; For the emergency prevention of contraception
Denosumab; for the treatment of postmenopausal women with osteoporosis at high risk for fracture,
Liraglutide; for the treatment of type 2 diabetes mellitus,
Everolimus; for the treatment of advanced pancreatic neuroendocrine tumors,
Sunitinib malate; for the treatment of pancreatic neuroendocrine tumors,
Linagliptin; for the treatment of type II diabetes,

Gastroenterology
Trastuzumab; for the treatment of gastric cancer
Everolimus; for the treatment of advanced pancreatic neuroendocrine tumors,
Fidaxomicin; for the treatment of Clostridium difficile-associated diarrhea,
Telaprevir; for the treatment of genotype 1chronic hepatitis C,
Sunitinib malate; for the treatment of pancreatic neuroendocrine tumors,
Boceprevir; for the treatment of chronic hepatitis C genotype 1,

Hematology
Velaglucerase alfa; for the treatment of type 1 Gaucher disease,
Brentuximab vedotin; for the treatment of Hodgkin lymphoma and anaplastic large cell lymphoma,
Deferiprone; for the treatment of transfusional iron overload due to thalassemia
Eculizumab; for the treatment of atypical hemolytic uremic syndrome,
Rivaroxaban; for the prophylaxis of deep vein thrombosis during knee or hip replacement surgery.

Immunology/Infectious Diseases
Aztreonam for inhalation solution; for the treatment of cystic fibrosis patients with pseudomonas aeruginosa,
Tesamorelin for injection; for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy,
Fingolimod; for the treatment of relapsing multiple sclerosis,
Pegloticase; for the treatment of chronic gout (hyperuricemia)
Denosumab; for the treatment of postmenopausal women with osteoporosis at high risk for fracture,
Indacaterol maleate; for the treatment of airflow obstruction resulting from chronic obstructive pulmonary disease,
Belimumab; for the treatment of systemic lupus erythematosus,
Roflumilast; for the treatment of chronic obstructive pulmonary disease,
Fidaxomicin; for the treatment of Clostridium difficile-associated diarrhea,
Rilpivirine; for the treatment of HIV- 1,
Icatibant – for the treatment of acute attack of hereditary angioedama,
Telaprevir; for the treatment of genotype 1chronic hepatitis C,
Belatacept; for the prevention of organ rejection following kidney transplant,
Boceprevir; for the treatment of chronic hepatitis C genotype 1,
Tocilizumab; for the treatment of systemic juvenile idiopathic arthritis,

Nephrology/Urology
Carglumic acid; for the treatment of hyperammonemia,
Cabazitaxel; for the treatment of prostate cancer,
Sipuleucel-T; for the treatment of hormone refractory prostate cancer,
Rifaximin; for the treatment of hepatic encephalopathy
Everolimus; for the prevention of organ rejection following kidney transplant,
Belatacept; for the prevention of organ rejection following kidney transplant,
Eculizumab; for the treatment of atypical hemolytic uremic syndrome,

Neurology
Doxepin; for the treatment of insomnia,
Dalfampridine; for the improvement of walking in patients with multiple sclerosis,
Ezogabine; for the treatment of partial-onset seizures,
Vilazodone hydrochloride; for the treatment of major depressive disorder,

Oncology
Eribulin mesylate; for the treatment of metastatic breast cancer,
Trastuzumab; for the treatment of gastric cancer
Cabazitaxel; for the treatment of prostate cancer,
Brentuximab vedotin; for the treatment of Hodgkin lymphoma and anaplastic large cell lymphoma,

Everolimus; for the treatment of advanced pancreatic neuroendocrine tumors,
Sunitinib malate; for the treatment of pancreatic neuroendocrine tumors,
Peginterferon alfa-2b; for the treatment of melanoma
Vandetanib; for the treatment of thyroid cancer,
Crizotinib; for the treatment of ALK+ non small cell lung cancer,
Ipilimumab; for the treatment of metastatic melanoma,
Vemurafenibe; for the treatment of BRAF + melanoma,
Abiraterone acetate; for the treatment of prostate cancer,
Aflibercept is a VEGF inhibitor for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD)

Otolaryngology
Vandetanib; for the treatment of thyroid cancer,

Pediatrics/Neonatology
Tocilizumab; for the treatment of systemic juvenile idiopathic arthritis,
Roflumilast; for the treatment of chronic obstructive pulmonary disease,
Psychiatry/Psychology
Lurasidone; for the treatment of schizophrenia,
Trazodone hydrochloride; for the treatment of major depressive disorder,
Vilazodone hydrochloride; for the treatment of major depressive disorder,

Pulmonary/Respiratory Diseases
Indacaterol maleate inhalation powder; for the treatment of airflow obstruction resulting from chronic obstructive pulmonary disease,
Roflumilast; for the treatment of chronic obstructive pulmonary disease,
Crizotinib; for the treatment of ALK+ non small cell lung cancer

S.NO	DRUG (Mechanism of action)	USE/S
1	**Bevacizumab** (anti – VEGF antibody	Metastatic carcinoma of the colon or rectum
2	**Pemetrexed** (folate enzyme antagonist)	Malignant pleural mesothelioma
3	**Erlotinib** (tyrosine kinase inhibitor)	Non- Small – cell lung cancer
4	**Geftinib** (tyrosine kinase inhibitor)	Non – small cell lung cancer
5	**Varenicline** (Nicotinic receptor agonist)	Smoking cessation
6	**Acamprosate** (NMDA antagonist)	Maintenance of abstinence from alcohol
7	**Duloxetine** (SNRI/SSRI)	Major depressive disorder (MDD)
8	**Tiotropium bromide** (anticholinergic)	Bronchospasm

		(COPD\ Acute severe asthma)
9	**Cinacalcet (calcimimetics)**	Secondary Hyper parathyroidism in CRF
10	**Eplerenone** (selective aldosterone antagonist)	Heart failure
11	**Treprostinil** (Prostaglandin analogue)	Pulmonary arterial hypertension (PAH) in patients with NYHA Class II-IV symptoms
12	**Botulinum toxin type A** (Inhibits Ach release)	Glabellar lines (cosmetic use) in adult men and women. Also used in Strabismus, (Blepharospasm, Cervical dystonia, hemifacial spasms)
13	**Urofollitropin** (human FSH)	Ovulation induction
14	**Imatinib mesylate** (Anti- tyrosine kinase) CML - (DOC)	Chronic myeloid leukemia, Inoperable and/or metastatic malignant gastrointestinal stomal tumors (GISTs)
15	**Nitazoxanide** (antiprotozal agent)	Giardia lamblia, Cryptosporidium parvum
16	**Nitisinone** (inhibits -homogentisate production	Alcaptonuria
17	**Pegylated interferon alfa-2a**	Chronic hepatitis C (With Ribavirin), Chronic hepatitis B
18	**Tegaserod** (5- HT_4 partial agonist)	Irritate bowel syndrome with predominant constipation, chronic constipation
19	**Voriconazole** (azole Antifungal)	Excellent activity against *Candida* species, & the dimorphic fungi, & T.O.C for invasive aspergillosis
20	**Adefovir** (anti – HBV)	Active HBV infection
21	**Fulvestrant** (ER antagonist)	Tamoxifen resistant breast cancer
22	**Aripiprazole** (D_2 , 5-HT_{1A} partial agonist & 5-HT_{2A} antagonism)	Schizophrenia (also has anti-anxiety properties)
23	**Escitalopram** (SSRI)	Major depressive disorder

24	**Interferon beta -1a**	Relapsing multiple sclerosis (RRMS)
25	**Atomoxetine** (SNRI)	Attention deficit hyperkinetic disorder
26	**Sodium oxybate** (neurotransmitter)	Cataplexy associated with narcolepsy
27	**Ziprasidone** (D1 & 5- HT2A partial agonist)	Acute exacerbations of schizophrenia
28	**Adalimumab** (TNF Alpha blocker))	Approved for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis, plaque psoriasis & crohn's disease. It decreases the rate of formation of new erosions
29	**Omalizumab** (IgE antibody)	Asthma (inhibits mast cell activation & release)
30	**Etanercept** (Soluble TNF-α receptor)	Rheumatoid arthritis, psoriatic arthropathy
31	**Rosuvastatin** (statin – HMG CoA reductase inhibitor)	Hypercholesterolemia
32	**Memantine** (NMDA blocker)	Alzheimer's disease
33	**Laronidase** (Recombinant enzyme)	Mucopolysaccharidosis I (MPS-1)
34	**Agalsidase beta** (Recombinant human α-galactosidase A enzyme)	Fabry's Disease
35	**Pegvisomant** (GH receptor antagonist)	Acromegaly
36	**Tocilizumab** (Inhibition of IL-6 mediated signaling)	Adult patients with moderate-severe active rheumatoid arthritis inadequately responding to one or more TNF antagonists
37	**Vardenafil** (PDE-5 inhibitor)	Erectile dysfunction
38	**Tadalafil** (PDE-5 inhibitor)	Erectile dysfunction
39	**Enfuvirtide(**fusion inhibitor) (Blocks viral entry in CD4 cells)	Anti – HIV drug
40	**Bortezomib** (proteosome inhibitor)	Multiple myeloma
41	**Memantine** (NMDA antagonist)	Moderate to severe dementia in Alzhemer's disease

42	**Galantamine** (anti acetylcholinesterase)	Mild to moderate dementia of the Alzheimer's type
43	**Donepezil** (anti- acetylcholinesterase)	Mild to moderate dementia of the Alzheimer's type
44	**Letrozole** (aromatase inhibitor); others are: Anastrazole, Exemestane (a steroid molecule) & Fadrozole	Advanced ovarian and breast cancer
45	**Somatropin** (recombinant GH)	Growth failure associated with GH deficiency, SGA with failure to catch up by age 2 yrs
46	**Nesiritide** (ANP analogue)	Congestive cardiac failure
47	**Trovaprost** (PG analogue)	Open – angle glaucoma or ocular hypertension
48	**Mesalamine** (anti-inflammatory)	Active ulcerative proctitis
49	**Zoledronic acid** (Bisphosphonate)	Paget's disease, prevention of osteoporosis in prostate and breast cancer patients receiving hormonal therapy, hypercalcemia of malignancies, and for preventing fractures and skeletal complications in cancer patients with bone metastases
50	**Sultroban** (TxA2 antagonist)	Thromboembolic disorders/pulmonary hypertension
51	**Montelukast\Zafirlukast\pranlukast** (LTD_4 ,or cys-LT_1 receptor antagonist)	Asthma
52	**Terbinafine** (Allylamine – Antifungal (DOC)	Onychomycosis
53	**Amifostine** (SH donating agent)	Cytoprotective agent that reduces renal toxicity associated with repeated administration of cisplatin
54	**Miltefosine** (SH donating agent)	Leishmaniasis
55	**Nicorandil** (K+ channel opener)	Angina
56	**Ibutilide \dofetilide** (K+ channel blockers)	Atrial arrhythmias
57	**Vemurafenib (**Highly selective small molecule inhibitor of BRAFV600E)	Metastatic malignant melanoma

58	**Licofelone** (Dual inhibitor of the COX and 5-LOX pathways)	New NSAID for arthritis (free from ulcer)
59	**Levobupivacaine** (local anesthetic)	Obstetrical anesthesia (no cardio- toxicity
60	**Escitalopram** (SSRI)	Depression (most specific antidepressant)
61	**Lumefantrine** (antimalarial)	MDR\severe malaria
62	**Fluticasone** (inhalational corticosteroid)	Bronchial asthma
63	**Zolpidem, zaleplon, zopiclone**, **eszopiclone {Z compounds}**-Selective agonist at the benzodiazepine binding site of the $GABA_A$ receptors containing the α_1 subunit	Hypnosis, are effective in relieving sleep-onset insomnia
64	**Bambuterol** (beta -2 agonist)	Asthma
65	**Topiramate** (reduces voltage-gated Na^+ currents in cerebellar granule cells, activates a hyperpolarizing K^+ current, enhances postsynaptic $GABA_A$-receptor currents, and limits activation of the AMPA-kainate-subtype(s) of glutamate receptor. Topiramate is a weak carbonic anhydrase inhibitor	FDA-approved as initial monotherapy (in patients at least 10 years old) and as adjunctive therapy (for patients as young as 2 years of age) for partial-onset or primary generalized tonic-clonic seizures, for Lennox-Gastaut syndrome in patients 2 years of age and older, and for migraine headache prophylaxis in adults
66	**Zonisamide (**inhibits the T-type Ca^{2+} currents, inhibits the sustained, repetitive firing of spinal cord neurons by prolonging the inactivated state of voltage-gated Na^+ channels)	FDA approved as adjunctive therapy of partial seizures in adults
67	**Levosimendan** is a calcium sensitizer and ATP-dependent potassium channel opener that has positive inotropic and vasodilatory effect	Acute Heart Failure Syndrome
68	**Indacaterol** (LABA)	COPD
69	**Febuxostat** (Xanthine oxidase inhibitor)	Chronic gout

70	**Exenatide** (GLP-1 analogue)	Diabetes
71	**Clenbuterol (**β_2 Agonist)	'Anabolic' action to increase muscle strength
72	**Cilnidipine (**dual L/N-type Ca2+ channel-blocking action)	Hypertension
73	**Rifaximin** (binds the beta subunit of the DNA-dependent RNA polymerase, and inhibits RNA synthesis)	Traveler's diarrhea caused by noninvasive strains of E coli, Patients with Irritable Bowel Syndrome without Constipation
74	**Pegaptanib** (VEGF antagonist)	Neovascular -Age related macular degeneration
75	**Anagrelide** (Antiplatelet)	Essential thrombocytosis
76	**Pramlintide** (Amylin analogue)	Diabetes
77	**Metrifonate** (Organophosphate)	Alzheimer's disease , in the treatment of *S. haematobium* infections
78	**Retigabine (**activates potassium currents)	Being examined in patients with partial refractory seizures and patients with postherpetic neuralgia
79	**Talampanel** (blocks AMPA receptors in a stereoselective)and non-competitive fashion	Currently being examined in patients with amyotrophic lateral sclerosis, adults with partial seizures, patients with recurrent glioma or advanced Parkinson's disease
80	**Prasugrel** (ADP antagonist)	Anti-platelet; prevention of thrombotic events
81	**Fingolimod** (a sphingosine-1-phosphate–receptor modulator)	Relapsing–Remitting Multiple Sclerosis
82	**Fidaxomicin**(a macrocyclic antibiotic)	*C. difficile* infection
83	**Efonidipine** (CCB)	Prevention of LVH, IHD or Arrhythmias
84	**Efoproxiral** (is a radiation sensitizer)	Brain cancer or metastatic brain cancer
85	**Laromustine** (A Novel Alkylating Agent)	Used in elderly patients with poor-risk AML
86	**Cevimeline** (Cholinergic- M_3 agonist)	Dry mouth, dry eyes (Sjogren syndrome)
87	**Vilazodone**	Major depressive disorder (MDD).
88	**Spinosad** (is a pediculicide)	Prescribed for head lice infestation

89	**Retapamulin** is a semisynthetic pleromutilin derivative, selectively inhibits bacterial protein synthesis by interacting at a site on the 50S subunit of bacterial ribosomes.	Treatments of uncomplicated superficial skin infection caused by group A β hemolytic streptococci and *S aureus*, excluding MRSA. Topical Retapamulin 1% ointment is indicated for use in adult and pediatric patients, 9 months or older, for the treatment of impetigo
90	**Azilsartan medoxomil** (an angiotensin II receptor antagonist)	Hypertension
91	**Ruxolitinib** is a kinase inhibitor	High-risk myelofibrosis.
92	**Ticagrelor (**reversible inhibitor of $P2Y_{12}$)	As an antiplatelet drug in acute coronary syndromes.
93	**Belatacept(**is a selective T-cell costimulation blocker)	Indicated for prophylaxis of organ rejection in adult patients receiving a kidney transplant.
94	**Romidepsin** is a histone deacetylase (HDAC) inhibitor	Cutaneous T-cell lymphoma, peripheral T-cell lymphoma
95	**Aflibercept** is a dimeric glycoprotein	Neovascular (Wet) age-related macular degeneration (AMD).
96	**Belimumab(**Inhibits the biological activity of B-lymphocyte stimulator)	SLE
97	**Axitinib** (inhibit receptor tyrosine kinases including vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2, and VEGFR-3 at therapeutic plasma concentrations	Indicated for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy.
98	**Vismodegib** (small-molecule inhibitor of Hedgehog signaling)	For the treatment of basal cell carcinoma that is either metastatic or locally advanced in patients who are not candidates for surgical resection or radiation.
99	**Emtricitabine &Tenofovir** (Anti-HIV drugs)	Pre-Exposure Prophylaxis
100	**Phentermine & topiramate**	Obesity
101	**Rufinamide (**reduces the capacity of sodium	It is approved as add-on therapy for Lennox-Gastaut syndrome (LGS) in patients of ≥ 4 yrs

	channels to recover from inactivation)	
102	**Lacosamide** is a sodium channel modulator	As add-on therapy in partial-onset seizures with and without secondary generalization in adult patients with epilepsy.
103	**Daptomycin** (It binds to bacterial membranes resulting in depolarization, loss of membrane potential, and cell death)- bactericidal	For treatment of complicated skin and soft tissue infections, and complicated bacteremia and right-sided endocarditis
104	Ceftaroline fosamil(4th generation cephalosporin)	MRSA
105	Telavancin (Lipoglycopeptide antibiotic-Cell wall synthesis inhibitor)	MRSA
106	Dalbavancin (Lipoglycopeptide)	MRSA, VISA

1. The common side effect with fluoxetine therapy is:
a. Seizure.
b. Anxiety
c. Hypotension.
d. Loose stools.

2. All of the following drugs are protease inhibitors except:
a. Nelfinavir.
b. Saquinavir.
c. Abacavir.
d. Ritonavir.

3. All of the following antibacterial agents act by inhibiting cell wall synthesis, except:
a. Carbapenems.
b. Monobactams.
c. Cephamycins.
d. Nitrofurantoin.

4. A diabetic patient developed cellutitis due to Staphylococcus aureus, which was found to be Methicillin resistant on the antibiotic sensitivity testing. All the following antibiotics will be appropriate except:
a. Vancomycin.
b. Imipenem.
c. Teichoplanin.
d. Linezolid

5. Emergency contraception prevents pregnancy by all of the following mechanisms, except:
a. Delaying / inhibiting ovulation.
b. Inhibiting fertilization.
c. Preventing implantation of the fertilized egg.
d. Interrupting an early pregnancy.

6. Misoprostol is a:
a. Prostaglandin E_1 analogue.
b. Prostaglandin E_2 analogue.
c. Prostaglandin antagonist.
d. Antiprogestin.

7. Bisphosphonates act by:
a. Increasing the osteoid formation.
b. Increasing the mineralisation of osteoid.

c. Decreasing the osteoclast mediated resorption of bone.
d. Decreasing the parathyroid hormone secretion

8. Which one of the following antibacterials should not be used with d-tubocurarine?
a. Norfloxacin
b. Streptomycin.
c. Doxycycline
d. Cefotaxime

9. The following statements regarding benzodiazepines are true except:
a. Binds to both $GABA_A$ and $GABA_B$ receptors.
b. They have active metabolites.
c. Decreases nocturnal gastric secretion in human being.
d. Extensively metabolized by CYP enzymes.

10. One of the following statements regarding mycophenolate mofetil is incorrect:
a. It is a prodrug.
b. It is a selective uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase.
c. It also inhibits calcineurin.
c. Selectively inhibits lymphocyte proliferation.
d. All are true

11. All of the following mechanisms of action of oral contraceptive pills are true, except:
a. Inhibition of ovulation.
b. Prevention of fertilization.
c. Interference with implantation of fertilized ovum.
d. Interference with placental functioning

12. Which one of the following drugs does not interfere with folic acid metabolism?
a. Phenytoin.
b. Gabapentin.
c. Phenobarbitone.
d. Primidone.

13. Which one of the following drugs is LEAST LIKELY to cause constipation?
a. Propranolol.
b. Verapamil.
c. Nitroglycerin.
d. Pentazocine

14. Which of the following drugs is not used topically for treatment of open angle glaucoma:
a. Latanoprost.
b. Brimonidine.
c. Acetazolamide.
d. Dorzolamide.

15. Which one of the following agents has been associated with hemorrhagic stroke?
a. Phenylpropanolamine.
b. Terfenadine.
c. Quinidine.
d. Fenfluramine-

16. Which enzyme is inhibited by aminophylline?
a. Monoamine Oxidase.
b. Alcohol dehydrogenase,
c. Phosphodiesterase.
d. Cytochrome P-450.

17. Which of the following is the muscle relaxant of choice in renal failure?
a. Rapacurium.
b. Pancuronium.
c. Atracurium.
d. Rocuronium.

18. All of the following are part of the treatment of Lithium toxicity, except:
a. Treating dehydration.
b. Ingestion of polystyrene sulfonate.
c. Hemodialysis.
d. Using an antagonist.

19. All are side effects of clozapine except:
a. Granulocytopenia.
b. Seizures.
c. Sedation.
d. Extrapyramidal side effects.

20. Which of the following is the drug of choice for treatment of corneal ulcers caused by filamentous fungi?
a. Itraconazole.
b. Natamycin.
c. Nystatin
d. Fluconazole

21. Which of the following drugs is not a part of the 'Triple Therapy' immunosuppression for post renal transplant patients?
a. Cyclosporine.
b. Azathioprine.
c. FK506.
d. Prednisolone.

22. All of the following cause hypertension except

a. NSAID

b. Erythropoietin

c. Cyclosporine

d. L-dopa

23. All cause interstitial nephritis except

a. Diuretics

b. □ lactam antibiotics

c. Allopurinol

d. INH

24. All are antiemetic except

a. Domperidone

b. Cyclizine

c. Phentazocine

d. Ondansetron

25. Which of the following in Imatinib mode of action

a. Competitive inhibitor of bcr abl gene product

b. P glycoprotein inhibitor

c. P glycoprotein stimulator

d. Competitively antagonizes the ATP binding site

26. Maternal carbimazole intake causes all except

a. Choanal atresia

b. Cleft lip and cleft palate

c. Fetal goitre

d. Scalp defects

27. Drug used to prevent renal toxicity in case of alcoholic hepatitis

a. Silymarin

b. S adenosyll methionine

c. Thalidomide

d. Pentoxyphylline

28. Aplasia of the bone marrow not seen with

a. Methicillin

b. Chloramphenicol

c. Methyl hydantoin

d. Chlorpromazine

29. Impotence is caused by which of the following drugs

a. Angiotensin antagonists

b. CCB

c. □ blockers

d. ACE inhibitors

30. Which antitumor drug is not an alkylating agent?

a. Cyclophosphamide

b. 5-FU

c. Busulfan

d. Melphalan

31. True about Octreotide:

a. Is active orally

b. Is not a somatostatin analogue

c. Used in secretory diarrhea

d. Is a growth hormone agonist

32. Filgrastrim is used for:

a. Neutropenia

b. anemia

c. Polycythemia

d. Neutrophilia

33. Which of the following is not an anticonvulsant?

a. Phenytoin

b. Flunarizine

c. T opiramate

d. Phenobarbitone

34. Which antiepileptic does not act via sodium channel blockade?

a. Vigabatrin

b. Carbamazepine

c. Lamotrigine

d. Phenytoin

35. All are true for immunosuppressants except:

a. Sirolimus acts by T cell modification

b. Tacrolimus inhibits calcineurin pathway

c. Mycofenolate acts by inhibiting GMP dehydrogenase

d. Cyc1osporin is integral in transplant rejection regimen.

36. Which anticancer drug causes hypercoagulable syndrome?

a. 5-FU

b. L-asparaginase

c. Melphalan

d. Carmustine

37. Which of the following chemotherapy agent can cause syndrome of Inappropriate ADH secretion (SIADH)?

a. Vincristine

b. Vinblastine

c. Dacarbazine

d. Cyclophosphamide

38. Which of the following is an anti – pseudomonal antibiotic?

a. Ciprofloxacin

b. Vancomycin

c. Cefaclor

d. Tetracycline

39. A child is on beta-agonist for treatment of asthma. He may have all of the following except:

a. Tremor

b. Hypoglycemia

c. Hypokalemia

d. Bronchodilatation

40. Which of the following anticancer drug acts by hypomethylation?

a. Gemcitabine

b. 5-Fu

c. Decitabine

d. Homoharringotonine

41. True about heparin is all except:

a. Prolongs aPTT

b. Hyperkalemia is not seen

c. Alopecia is seen

d. Thrombocytopenia is seen

42. Drug causing maximal peripheral neuropathy is:

a. Zidovudine

b. Lamivudine

c. Stavudine

d. Didanosine

43. Which drug is not used for erectile dysfunction?

a. Phenylephrine

b. Apomorphine,

c. Yohimbine

d. Vardenafil

44. High dose methotrexate is given in:

a. Osteosarcoma

b. Rhabdomyosarcoma

c. Retinoblastoma

d. Ewing's sarcoma

45. Which of the following is longest acting insulin?

a. Lispro

b. Insulin aspartate

c. Glargine

d. NPH

46. Naltrexone is used in a case of opioid dependence:

a. To treat withdrawl symptoms

b. To prevent relapse

c. To treat overdose

d. Addiction potential

47. A patient with active tuberculosis is being treated with INH and ethambutol as part of the overall regimen. Which of the following is the main reason for including the ethambutol?
a. To facilitate entry of the INH into the mycobacteria
b. To facilitate penetration of the blood-brain barrier
c. To retard the development of organism resistance
d. To slow renal excretion of INH to help maintain effective blood levels

48. Many therapeutic insulins are often modifications of "regular" insulin. The modifications include substituting some amino acids in the protein using recombinant DNA technology, conjugating insulin with NPH or combining it with zinc. For all these insulin, which of the following is the one common result of such changes?
a. Elimination of allergic responses

b. Enabling administration by either subcutaneous or intravenous routes

c. Modification of onsets, durations of action

d. Prevention of cellular K^+ uptake as glucose enters cells

49. All are fibrinolytic, except:
a. Streptokinase
b. Urokinase
c. Alteplase
d. Epsilon aminocaproic acid

50. Best indication for use of abciximab is:

a. Stroke

b. Acute coronary syndromes

c. Following angioplasty

d. Deep vein thrombosis

51. Acamprosate is:

a. Detoxifying agent for alcoholism

b. Used for decreasing alcohol craving

c. NMDA agonist

d. Used in opioid poisoning

52. Adalimumab is:

a. TNF-alpha antagonist

b. Ant-IgG antibody

c. EGF antagonist

d. VEGF antagonist

53. Aliskiren is:

a. Renin antagonist

b. Renin synthesis inhibitor

c. Renin modulator

d. Renin releaser

54. Anagrelide is:

a. Antiplatelet drug

b. Platelet maturation inhibitor

c. Anticancer drug

d. Antibiotic

55. Aprepitant is:

a. Antibiotic

b. Anticancer drug

c. Immunosuppressive

d. Antiemetic

56. Capecitabine is mainly used for:

a. Breast and colorectal cancer

b. Lung cancer

c. Skin cancer

d. Testicular cancer

57. Cetrorelix is:

a. GnRH analog

b. GnRH antagonist

c. Both

d. None

58. Cinacalcet is:

a. Calcimimetics agent used in CRF (chronic renal failure)

b. Newer calcium lowering agent

c. Used in osteoporosis

d. Antipyretic

59. Dalbavancin is:

a. Short acting

b. Long acting

c. Ineffective against Gram-positive infections

d. Non glycopeptide

60. Viral entry blocker is:

a. Enfuvirtide

b. Anagrelide

c. Atomoxetine

d. Daclizumab

61. Exenatide and pramlintide are:

a. Antidiabetic agents

b. Antipyretics

c. NSAIDs

d. Newer corticosteroids

62. Ezetimibe is:

a. Bile acid binding drug

b. Cholesterol absorption inhibitor

c. Newer statin

d. Fibrate

63. Febuxostat is:

a. Newer xanthine oxidase inhibitor

b. Uricosuric drug

c. Inhibits mitotic spindle

d. NSAID

64. Flavopiridol is:

a. Newer D2 blocker

b. NSAID

c. Anti proliferative drug

d. Antiemetic

65. Linezolid is not useful in:

a. Gram-positive infections

b. VRE

c. VRSA

d. Pseudomonas

66. MALARONE is used for:

a. Prophylaxis of malaria among travelers

b. Treatment of malaria

c. Malaria in pregnancy

d. Treatment of malaria among travelers

67. Muromonab is:

a. OKT3

b. Antiepileptic

c. Antidepressant

d. NSAID

68. Pemetrexed is used in:

a. Malignant mesothelioma

b. Small cell lung cancer

c. Non-small cell lung cancer

d. Superficial cancer of urinary bladder

69. Not prolonging QT interval:

a. Quetiapine

b. Sertindole

c. Lumefentrine

d. Artemisinins

70. Drug used for "secondarily infected dermatitis" (SID):

a. Retapamulin

b. Rimonabant

c. Ramelteon

d. Ropinirole

71. Not true about rituximab:

a. Used in B-cell lymphomas

b. Anti-CD20

c. Infusion-related side effects occur

d. Used in asthma

72. Not used in Alzheimer's disease:

a. Memantine

b. Galantamine

c. Donepezil

d. Cevimeline

73. Rotigotine is:

a. Dopamine agonist

b. Dopamine antagonist

c. Both

d. None

74. Ruboxistaurin is:

a. Protein kinase inhibitor used in diabetic complications

b. NSAID

c. Antibiotic

d. Anticancer

75. Untrue about streptogramins:

a. Synergistic combination; arthralgia is a side effect

b. Enzyme inhibitors

c. Eliminated by bile

d. Bactericidal

76. Drug used in constipation:

a. Rifaximin

b. Rifabutin

c. Riluzole

d. Tegaserod

77. Teriparatide is used in

a. Osteoporosis

b. CRF

c. ARF

d. Osteomalacia

78. Diuretic with uricosuric action:

a. Ticrynafen

b. Bumetanide

c. Mannitol

d. Spironolactone

79. Antiepileptic drug that could produce weight loss and is used in migraine as well:

a. Tiagabine

b. Topiramate

c. Felbamate

d. Vigabatrin

80. LEAST COMMONLY used in pulmonary arterial hypertension:

a. Epoprostenol

b. Treprostinil

c. Nitric oxide

d. Nifepdine

81. Not an antiplatelet agent:

a. Triflusal

b. Ticlopidine

c. Cilostazol

d. Trientine

82. Antismoking drugs are:

a. Nicotine

b. Varenicline

c. Bupropion

d. All of them

83. Oral substitute of warfarin is:

a. Ximelagatran

b. Argatroban

c. Enoxaparin

d. Dalteparin

84. Longest acting bisphosphonate is:

a. Zoledronic acid

b. Alendronate

c. Pamidronate

d. Risedronate

85. Anti-malarial used for resistant P. falciparum malaria in children is

a. Doxycycline

b. Chloroquine

c. Lummfantrine

d. Tetracycline

86. Antifungal drugs are all of the following EXCEPT

a. Ketoconazole

b. Undecylenic acid

c. Ciclopirox

d. Cyclofazimine

87. Drug of choice for Diphtheria chemoprophylaxis is

a. Doxycycline

b. Erythromycin

c. Tetracycline

d. Ampicillin

88. Treatment of choice for Neurosyphilis is

a. Procaine penicillin

b. Benzathine penicillin

c. Penicillin G

d. Ampicillin

89. Drug not effective in treatment of typhoid is

a. Amikacin

b. Cotrimoxazole

c. Ciprofloxacin

d. Ceftriaxone

90. Which of the following antibiotics inhibit protein synthesis?

a. Doxycycline

b. Nitrofurantoin

b. Cephalosporin

d. Penicillin

91. TRUE about the Side-effects of Tetracycline include all of

the following EXCEPT

a. Can cause Pseudotumor cerebri

b. NOT teratogenic if used during pregnancy

c. Discoloration of teeth may occur

d. Superinfection can occur

92. Ipratropium bromide is absolutely contraindicated in

a. Asthma

b. Hypertension

c. Peptic ulcer

d. Urinary retention

93. Heparin in pregnant female if given, should be supplemented

with

a. Zinc
b. Calcium
c. Copper
d. Folic acid

94. Paclitaxel acts by

a. Topoisomerase inhibitor
b. Inhibition of Microtubule formation

c. Mitotic cell inhibitor

d. Exaggerates polymerization and causes the stabilization of the microtubules

95. Which one of the following anti-cancerous drug is a

Peptide?

a. Doxorubicin

b. Valinomycin

c. Bleomycin

d. Aspartame

96.Leucovorin is used as Rescue therapy for patients who are

on one of the following drug therapies

a. Asparagine

b. Methotrexate

c. 6-mercaptopurine

d. Cyclophosphamide

97. Adverse effects of Tacrolimus include all of the following

EXCEPT

a. Nephrotoxicity

b. Diabetes mellitus

c. Neurotoxicity

d. Hirsutism

98. Which one of the following is the correct mechanism of

action of clomiphene citrate?

a. Binds to estrogen receptors only

b. Blocking estrogenic inhibition of pituitary
c. Inhibit progesterone receptors

d. Progesterone agonist

99. Tiotropium is used for the treatment of which of the following?

a. Ptyalism

b. Asthma

c. Urinary retention
d. Ileus

100. All of the following are useful in relieving Post-op urinary spasm EXPECT

a. Darifenacin
b. Ipratropium
c. Tolterodine

d. Bethanechol

ANSWER KEY

1. B
2. C

3. D
4. D
5. A
6. A
7. C
8. B
9. D
10. D
11. D
12. B
13. A
14. C
15. A
16. C
17. C
18. D
19. D
20. B
21. C
22. D
23. D
24. C
25. D
26. B
27. A
28. A
29. C
30. B
31. C
32. A
33. B
34. A
35. C
36. B
37. A
38. A
39. B
40. C
41. B
42. C
43. A
44. A
45. C
46. C
47. C
48. C
49. D
50. C
51. B
52. A
53. A
54. B
55. A
56. C
57. D
58. A
59. A
60. A
61. D
62. A
63. D
64. D
65. A
66. A
67. D
68. D
69. A
70. A
71. B
72. D
73. D
74. A
75. A
76. C
77. C
78. D
79. B
80. B
81. A
82. A
83. B
84. D
85. B
86. D
87. C
88. B
89. D
90. B
91. B
92. *

1. Which antiarrhythmic in not class IC agent
   a. Propafenone
   b. Tocainide
   c. Flecainide
   d. Encainide

2. Which NSAID undergoes enterohepatic circulation
   a. Phenylbutazone
   b. Aspirin
   c. Ibuprofen
   d. Piroxicam

3. 200 mg of a drug given I.V has a peak plasma value of 40 micrograms/ml. What is the volume of distribution:
   a. 0.5 litre
   b. 1 litre
   c. 5 litre
   d. None

4. Which of the following is not true about benzodiazepines:
   a. Acts on GABA receptor complex
   b. Midazolam is shortest acting
   c. Nitrazepam decreases REM sleep
   d. Flumazenil is a specific antagonist

5. True about Rotigotine is
   a. Ergot alkaloid
   b. Non ergot alkaloid
   c. MAO – B inhibitor
   d. COMT inhibitor

6. GpIIb / IIIa antagonist all except:
   a. Abciximab
   b. Clopidogrel
   c. Tirofiban
   d. Eptifibatide

7. Memantine Act by?
   a. Inhibiting cholinesterase
   b. NMDA blocker
   c. MAO – B inhibitor
   d. COMT inhibitor

8. Morphine causes all, EXCEPT:
   a. Peripheral vasodilatation
   b. Decrease intracranial tension
   c. Nausea and vomiting
   d. Decrease in gastrointestinal secretion

9. Beta agonist used in preterm labour causes all except:
   a. Hyperkalemia
   b. Hyperglycemia
   c. Tachycardia
   d. Relaxation of uterine muscles

10. Intrinsic activity is present in:
   a. Labetalol
   b. Propranolol
   c. Sotalol
   d. Atenolol

11. Pharmacogenetics is important in metabolism of
   a. Rifampicin
   b. Isoniazid
   c. Digitalis
   d. Propranolol

12. True statement about clonidine all except:
   a. Increases parasympathetic outflow
   b. Decreases sympathetic outflow by blocking central alpha receptor
   c. Used in HT
   d. Prazosin is used to antagonize side effects of clonidine

13. False statement about selegiline is:
   a. It is a MAO-A inhibitor
   b. Does not cause cheese reaction
   c. May be used in on-off phenomenon
   d. It is used in parkinsonism

14. Which of the following is not true about Nesiritide?
   a. It is BNP analogue
   b. Used in decompensated CHF
   c. Given orally

d. Causes loss of Na+ in urine

15. Which of the following drugs would be removed by dialysis?
    a. Digoxin
    b. Salicylates
    c. Benzodiazepines
    d. Organophosphates

16. Which of the following have receptors which are transcription factors all except:
    a. Insulin
    b. Estrogen
    c. Glucocorticoids
    d. Vitamin D

17. All of the following statements about ticlopidine are true except:
    a. Directly interacts with platelet membrane, Gpllb/IIIa receptors
    b. Onset of action is delayed
    c. Duration of action is long
    d. It is used as an alternative to aspirin in patients with cerebrovascular disease.

18. Used for the treatment of migraine, the triptans act through:
    a. 5HT-1A
    b. 5HT-1B
    c. 5HT-1F
    d. 5HT-3

19. All but one acts via GABA except:
    a. Thiopentone
    b. Midazolam
    c. Zolpidem
    d. Promethazine

20. Regarding Phenytoin, false is:
    a. Induces microsomal enzymes
    b. At very low doses, zero order kinetics occurs
    c. Higher the dose, higher is the half life
    d. Highly protein bound

21. Good Laboratory Practices are not a part of:
    a. Preclinical studies
    b. Phase I studies
    c. Phase II studies
    d. Phase IV studies

22. Which of the following is not used as a sedative, but causes sedation as a side effect:
    a. Antipsychotics
    b. Antihistaminics
    c. Antidepressant
    d. Lithium

23. A drug X with high affinity to albumin is given I.V. binds with albumin, but not enough to saturate it. Another drug Y. also having affinity to albumin is given I.V. in concentration 150 times enough to saturate albumin. Which of the following happens:
    a. Tissue concentration of X increases
    b. $t^{l}/_{2}$ of X decreases
    c. Volume of distribution of X increases
    d. Tissue concentration of X decreases

24. Mechanism of action of Nitric oxide is,
    a. Increase CAMP
    b. Increase cGMP
    c. Increase IP3/ DAG
    d. Non- adrenergic/non-non-cholinergic

25. All of the following utilize NO except
    a. Hydralazine
    b. Sildenafil
    c. Glycery1 nitrate
    d. Minoxidil

26. True about Benzodiazepines as compared to other hypnotics
    a. They alter sleep pattern more than other hypnotics
    b. More sedative than other hypnotics
    c. Overdose is better tolerated compared to other hypnotics
    d. All of above

27. All are pharmacogenetics conditions, except:
    a. Adenosine deaminase deficiency
    b. Malignant hyper-pyrexia
    c. Coumarin insensitivity
    d. G6PD deficiency

28. Which of the following is true?
    a. As the concentration of a drug increases over the therapeutic range, the bound form of the drug increases.
    b. The bound form is not available for metabolism but is available for excretion.

c. Acidic drug binds to albumin; and basic drug binds to □□□□□□□1 glycoprotein

d. Binding sites are non-specific and one drug can displace the other.

29. □ blocker with peripheral vasodilator action is:
a. Carvedilol
b. Propranolol
c. Atenolol
d. Acebutolol

30. 'Coronary steal phenomenon' is caused by:
a. Dipyridamole
b. Diltiazem
c. Propranolol
d. Verapamil

31. The Nitrate which does not undergo first pass metabolism is:
a. Isosorbide mononitrate
b. Nitroglycerine
c. Pentaerythritol tetranitrate
d. Isosorbide dinitrate

32. Enalapril is contraindicated in all of the following except:
a. Diabetic nephropathy with albuminuria
b. Single kidney
c. Bilateral renal artery stenosis
d. Hyperkalemia

33. A 6 yr old child presents with malignant hypertension The Drug of choice is:
a. Na Nitroprusside
b. Sublingual Nifedipine
c. Frusemide
d. Enalapril

34. Which of the following is not given in a patient with pheochromocytoma:
a. Atenolol
b. Prazosin
c. Nitroprusside
d. Metyrosine

35. Eplerenone has action similian to?
a. Frusemide
b. Thiazide
c. Spironolactone
d. Mannitol

36. Neostigmine is a:
a. Primary ammonium compound
b. Secondary ammonium compound
c. Tertiary ammonium compound
d. Quaternary ammonium compound

37. Drug of choice in Acute central anticholinergic syndrome is
a. Neostigmine
b. Physostigmine
c. Tacrine
d. 4-amino pyridine

38. Selective α_1-A blocker is:
a. Prazosin
b. Terazosin
c. Tamsulosin
d. Indolamine

39. All of the following are non-selective blockers with no pharmacological action on any other receptor except?
a. Propranolol
b. Timolol
c. Sotalol
d. Carvedilol

40. 'Vigabatrin' a new antiepileptic agent acts by:
a. GABA-antagonism
b. GABA- T inhibition
c. NMDA antagonism
d. Carbonic anhydrase inhibition

41. All of the following statements are true about nitrates except:
a. It releases NO
b. It causes vasodilatation
c. It decreases A.V. conduction
d. It has high first pass metabolism

42. All of the following are true about competitive inhibitor except:
a. Resembles chemically with the agonist
b. Bind the same receptors
c. Reduces potency
d. Maximum level is not reached by increasing the concentration of the drug

43. On higher doses zero order kinetics is seen:
a. Phenytoin
b. Propranolol

c. Lithium
d. Probenecid

44. Dulox tine is indicated in all except
a. Painful diabetic neuropathy
b. Fibromyalgia
c. Mild to moderate depression
d. Anxiety with insomnia

45. All are classified as reversible anticholinesterases except
a. Ambenonium
b. Physostigmine
c. Pyridostigmine
d. Echothiophate

46. In treatment of cardiac failure, dobutamine acts by all of the following mechanisms except:
a. α receptors agonist
b. β adrenergic receptors agonist
c. Dopamine receptor agonist
d. Increasing force of contraction

47. Which of the following antiarrhythmics drugs causes prolonged repolarization of ventricles & ERP:
a. Amiodarone
b. Propranolol
c. Verapamil
d. Quinidine

48. . All of the following are side effects of Amiodarone except:
a. Pulmonary fibrosis
b. Corneal micro deposits
c. Thyroid dysfunction
d. Osteoporosis

49. Which of the following statements regarding adenosine is not true:
a. Used in PSVT
b. Administered as rapid I.V. infection
c. Has short lived side effects
d. Disopyramide increases its therapeutic effect

50. Most commonly postural hypotension is seen with:
a. Prazosin
b. Nifedipine
c. Atenolol
d. ACE inhibitors

51. Which of the following is not a part of phase I reaction?
a. Oxidation
b. Reduction
c. Conjugation
d. Hydrolyses

52. The most common side effect associated with chronic use of Phenothiazines is:
a. Akathisia
b. Parkinsonism
c. Tardive dyskinesia
d. Muscular dystonia

53. All of the following may be seen with Neuroleptic malignant syndrome except:
a. Hypothermia
b. Altered consciousness
c. Muscle rigidity
d. Involuntary movements

54. Tetrahydrocannabinol is the active component of:
a. Marijuana
b. LSD
c. Hashish
d. Heroin

55. Pralidoxime acts by:
a. Reactivating cholinesterase enzyme
b. Promoting synthesis of cholinesterase
c. Promoting synthesis of acetylcholine
d. Direct action on cholinergic receptors

56. Clonidine is a:
a. $\acute{\alpha}_1$selective agonist
b. ά2 selective agonist
c. $\acute{\alpha}_1$ selective antagonist
d. ά2 selective antagonist

57. Propranolol is indicated in all of the following conditions except:
a. Thyrotoxicosis
b. Variant angina
c. Migraine
d. Hypertension

58. Anti-Adrenergic drug which crosses the blood-brain barrier minimally is:
a. Propranolol
b. Atenolol
c. Oxprenolol
d. Alprenolol

59. All of the following drugs may be used for motion sickness except:
    a. Hyoscine
    b. Dicyclomine
    c. Domperidone
    d. Scopolamine

60. Which of the following drug is not used in Detrusor instability:
    a. Flavoxate
    b. Solifenacin
    c. Tolterodine
    d. Tropspium

61. ACE inhibitors which of the following is true?
    a. (-) Angiotensinogen conversion to angiotension-I
    b. Omit diuretics to prevent 1st dose hypotension
    c. Enalapril is more long acting than lisinopril
    d. Can't given till systolic dysfunction resolve

62. Drug of choice in PSVT is :
    a. Verapamil
    b. Propranolol
    c. D.C. shock
    d. Digoxin

63. Predominant arteriolar dilators include all of the following except:
    a. Sodium Nitroprusside
    b. Diazoxide
    c. Hydralazine
    d. Minoxidil

64. Which of the following antihypertensive drugs is devoid of any central action:
    a. Clonidine
    b. ά methyl dopa
    c. Propranolol
    d. Indapamide

65. First drug to be used in anaphylactic shock is:
    a. Subcutaneous adrenaline
    b. I.V. corticosteroid
    c. Theophylline
    d. Antihistamine

66. Absorption of a drug depends on all, EXCEPT:
    a. Half life
    b. Concentration of drug
    c. *Route of absorption*
    d. Vascularity of absorbing surfaces

67. The metabolism of a drug proceeding at a fixed rate regardless of any further increase in substrate concentration is:
    a. Zero order kinetics
    b. First order kinetics
    c. Second order kinetics
    d. Third order kinetics

68. All of the following drugs reduce afterload, EXCEPT:
    a. Nitroglycerine
    b. Dopamine
    c. Hydralazine
    d. Sodium nitroprusside

69. Loading dose of a drug is given:
    a. When half-life of a drug is long
    b. When therapeutic index is low
    c. When drug follows first order kinetics
    d. When serum concentration is to be achieved rapidly

70. Which of the following feature differentiates pethidine from morphine:
    a. Local anaesthetic action
    b. More analgesic action
    c. More respiratory depression
    d. Suppresses cough effectively

71. Exogenous adrenaline is metabolized by:
    a. AchE
    b. COMT
    c. Decarboxylase
    d. Acetyl transferase

72. Fluoxetine causes all, EXCEPT:
    a. Diarrhea
    b. Insomnia
    c. Sedation
    d. Anxiety

73. Loading dose depends on
    a. Half life
    b. Plasma volume
    c. Volume of distribution
    d. Rate of clearance

74. Buprenorphine is
    a. Partial opioid agonist
    b. Pure opioid agonist
    c. Pure opioid antagonist
    d. Opioid with strong analgesic property

75. Steady state plasma level is achieved after:
    a. 2-3 plasma half lives

b. 3-4 plasma half lives
c. 4-5 plasma half lives
d. 10 plasma half lives

76. Katanserin:
a. $5HT_{1B}$ antagonist
b. $5HT_2$ antagonist
c. $5HT_{1A}$ agonist
d. $5HT_{1D}$ antagonist

77. Bioavailability of drug depends on:
a. Disintegration of drug
b. Dissolution of drug
c. Particle size
d. All of the above

78. All are true about digoxin except:
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

79. Which of the following is not used in treatment of pulmonary hypertension?
a. Beta blocker
b. Amlodipine
c. Frusemide
d. Digoxin

80. Prostaglandin inhibiting action of aspirin is useful in treatment of all of the following conditions, EXCEPT:
a. Analgesia and antipyretic
b. Closure of ductus arteriosus
c. Uricosuria
d. Antiinflammatory and anti platelet aggregation

81. Which of the following statement about drug action is not true:
a. Competitive antagonist has no intrinsic activity but affinity
b. Competitive antagonist has intrinsic activity and affinity
c. Partial agonist has submaximal intrinsic activity and affinity
d. Inverse agonists have affinity but minus intrinsic activity

82. Inter dose interval depends on:
a. Half life of drug
b. Dose of drug
c. Age of patient
d. Bioavailability of drug

83. Digibind is used to:
a. Potentiate the action of digoxin
b. Decrease the metabolism of digoxin
c. Treat digoxin toxicity
d. Rapidly digitalize the patient

84. Which of the following benzodiazepine is used as anxiolytic:
a. Temazepam
b. Diazepam
c. Midazolam
d. Clonazepam

85. All are 2nd generation antihistaminic except
a. Atavastin
b. Cyclizine
c. Fexofenadine
d. Loratidine

86. Which of the following is not an indication for oxytocin:
a. Spontaneous premature labour
b. Post partum haemorrhage
c. Uterine inertia
d. Breast engorgement due to inefficient milk ejection reflex

87. Calcium channel blockers are useful in all, EXCEPT:
a. Angina
b. Supraventricular arrhythmia
c. Sick sinus syndrome
d. Hypertension

88. The drug causing curare like effect is all, EXCEPT:
a. Chloramphenicol
b. Polymyxin
c. Tetracycline
d. Streptomycin

89. Clofibrate, a lipid lowering agent inhibits both cholesterol and triglyceride synthesis by:
a. Inhibiting HMG CoA reductase
b. Bile acid binding, preventing its reabsorption
c. Inhibiting VLDL production

d. Activating lipoprotein lipase, resulting in VLDL degradation

90. Rimonabent is used in
    a. Obesity
    b. Hypertension
    c. Renal failure
    d. Diabetes

91. True about teratogenicity of a drug is all except
    a. It is genetically predetermined
    b. Environment influences it
    c. Related to then dose of the teratogenic drug
    d. Affects specifically at a particular phase of development of fetus

92. Both barbiturates and salicylates are maximally absorbed in stomach because:
    a. They are weakly basic and so highly ionized in stomach
    b. They are highly basic and so less ionized in stomach
    c. They are weakly acidic and do not ionized in stomach
    d. They are highly acidic and are highly ionized in stomach

93. Which of the following has least extrapyramidal side effect:
    a. Haloperidol
    b. Fluphenazine
    c. Clozapine
    d. Flupenthixol

94. Buspirone as compared to benzodiazepines:
    a. Is more potent anticonvulsant
    b. Does not interfere with GAB Anergic transmission
    c. COPD
    d. Aphakia

95. Therapeutic index is indicator of
    a. Safety
    b. Efficacy
    c. Potency
    d. Toxicity

96. Which one of the following is TRUE about Phase II clinical trial?
    a. Large number of patients are included
    b. Efficacy
    c. Toxicity
    d. Safety

97. Xenobiotics involves all of the following enzymes except?
    a. Hydroxylation
    b. Cytochrome oxidase
    c. Cytochrome P450
    d. Methylation

98. Regarding efficacy and potency of a drug, all are true, EXCEPT:
    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 efficacy
    d. Drugs that produce a similar pharmacological effect can have different levels of efficacy

99. All are reasons for reducing drug dosage in elderly except:
    a. They are lean and their body mass is less
    b. Have decreasing renal function with age
    c. Have increased baroceptor sensitivity
    d. Body water is decreased

100. Untrue about fenoldopam
    a. Dopamine agonist
    b. Dopamine antagonist
    c. Sympathomimetic drug
    d. Used in hypertensive emergencies

ANSWER KEY

1. B
2. D
3. C
4. C
5. B
6. B
7. B
8. B
9. A

10. A
11. B
12. D
13. A
14. C
15. B
16. A
17. A
18. B
19. D
20. B
21. A
22. B
23. A
24. B
25. D
26. C
27. A
28. A
29. A
30. A
31. A
32. A
33. A
34. A
35. C
36. D
37. B
38. A
39. D
40. B
41. C
42. D
43. A
44. D
45. D
46. C
47. A
48. D
49. D
50. A
51. C
52. A
53. A
54. A
55. A

56. B
57. B
58. B
59. C
60. A
61. B
62. A
63. A
64. D
65. A
66. C
67. A
68. B
69. D
70. A
71. B
72. C
73. C
74. A
75. C
76. B
77. D
78. C
79. A
80. C
81. B
82. A
83. C
84. B
85. B
86. A
87. C
88. A
89. D
90. A
91. A
92. C
93. C
94. B
95. A
96. D
97. D
98. C
99. C
100. B

Cardiovascular drugs, Hypolipidemic agents, & Diuretics

1.The beneficial effect of nitrates in angina is primarily due to

a. Increase coronary blood flow

b. Reduction of cardiac preload
c. Reduced force of contraction
d. Reduced afterload

2. Nitrates act by

a. Increasing cAMP
b. Activating adenyl cyclase
c. Activating guanylyl cyclase
d. Increasing cytoplasmic Calcium

3.The drug you will avoid in a patient with prinzmetals variant angina is

a. Prazosin
b. Calcium channel blockers
c. Nitroglycerine
d. Propranolol

4. Drug used to treat cyanide poisoning

a. Na nitroprusside
b. Na nitrite
c. GTN
d. Isosorbide dinitrate

5.Coronary steal phenomenon is shown by

a. Verapamil
b. Disopyramide
c. Amiodarone
d. None of the above

6.Gall bladder stones are seen with use of

a. Clofibrate
b. Niacin
c. Statins
d. Colestipol

7. Choose the statin which is a prodrug

a. Atorvastatin
b. Rosuvastatin
c. Lovastatin
d. Pravastatin

8. Which of the statins need not be given in the night

a. Simvastatin
b. Lovastatin
c. Fluvastatin
d. Rosuvastatin

9.The drugs that is least useful in heart failure

a. Digoxin
b. Amlodipine
c. Beta agonists
d. Beta blockers

10.When Digoxin therapy is initiated serious cardiac arrhythmias may be caused due to

a. Hyper kalemia
b. Hypercalcemia
c. Hypermagnesemia
d. All the above

11. Digoxin causes all except

a. Inhibition of Na K ATPase
b. Hyperkalemia
c. Hypokalemia
d. Positive inotropy

12. Digitalis produces the following changes in ECG except

a. Inverted T wave
b. Prolonged QT interval
c. ST depression
d. Prolonged PR interval

13. If a patient on digoxin develops ventricular arrhythmias, best management is ,use

a. Quinidine
b. Phenytoin
c. Lidocaine
d. Cardioversion

14.Digoxin is contraindicated in

a. AF
b. Atrial flutter
c. CCF
d. HOCM

15. Which of the following is not a class 1B drug

a. Tocainide
b. Phenytoin
c. Mexiletine
d. Encainide

16. Most common adverse effect of quinidine therapy is

a. Hypotension
b. Thrombocytopenia
c. Diarrhoea
d. Cinchonism

17. All the following produce torsade de pointes except

a. Terfenadine
b. Sotalol
c. Amiodarone
d. Lignocaine

18. Which of the following statements regarding adenosine is not true

a. Used in PSVT
b. Administered as rapid IV
c. Activates Ach sensitive K channels
d. Disopyramide increases its therapeutic effect

19. Among the following prodrug is

a. Clonidine
b. Methyldopa
c. Guanabenz
d. Guanfacine

20. Ganglion blockers like hexamethonium act by

a. Increase release of Ach
b. Competing for Ach receptor
c. Transmission block
d. Inhibition of Ach destruction

21. The action of diazoxide is blocked by

a. Metformin
b. Nifedipine
c. Nitrates
d. Glibenclamide

22. ACE inhibitors and aldosterone antagonists are not used together because of danger of

a. Hyperglycemia
b. Hypokalemia
c. Hyperkalemia
d. Hypoglycemia

23. Hyperkalemia caused by potassium sparing diuretics is increased by

a. Beta blockers
b. NSAIDs
c. ACE inhibitors
d. All the above

24. In case of overdose with beta blockers the drug used is

a. Verapamil
b. Spironolactone
c. Glucagon
d. Digoxin

25. Metabolic acidosis is produced by

a. Furosemide
b. Acetazolamide
c. Indapamide
d. Hydrochlorothiazide

26. Acetazolamide is useful in treatment of all except

a. Acute mountain sickness
b. Calcium stones
c. Glaucoma
d. Metabolic alkalosis

27. Carbonic anhydrase inhibitors are avoided in

a. Gout
b. Epilepsy
c. Liver failure
d. UTI

28. Mannitol is useful in all except

a. Cerebral edema
b. To prevent anuria
c. Pulmonary edema and CCF
d. A/c congestive glaucoma

29. Allergic reactions are less common with use of

a. Furosemide
b. Bumetanide
c. Ethacrynic acid
d. Torsemide

30. Diuretic activity of loop diuretics is reduced by co administration of

a. Cotrimoxazole
b. Thiazides
c. Indomethacin
d. Aminoglycosides

31. Which of the following is not associated with thiazide therapy?

a. Hyponatremia
b. Hypokalemia
c. Hypercalciuria
d. Hyperuricemia

32. HIV patient treated with which antibiotic will cause hyperkalemia

a. Ciprofloxacin
b. Cotrimoxazole
c. Ceftazidime
d. Cefoperazone

33. Megaloblastic anaemia due to inhibition of dihydrofolate reductase is seen with use of all except

a. Methotrexate
b. Trimethoprim
c. Triamterene
d. Phenytoin

34. Diuretic of choice in treatment of ascites and edema due to liver failure

a. Mannitol
b. Furosemide
c. Spironolactone
d. Bumetanide

35. A patient was diagnosed as having SIADH the drug you will use to treat the condition is

a. Haloperidol
b. Chlorpropamide
c. Vincristine
d. Demeclocycline

Immunopharmacology

1. TNFα inhibitor used in rheumatoid arthritis is

a. Etanercept
b. Anakinra
c. Omalizumab
d. Leflunomide

2. Side effects of cyclosporine are all except

a. Nephrotoxicity
b. Bone marrow suppression
c. Hypertension
d. Hirsutism

3. Leflunomide acts by inhibiting

a. Dihydroorotate dehydrogenase
b. Inosine monophosphate dehydrogenase
c. mTOR
d. LFA-1

4. Aldesleukin used in treatment of renal cell carcinoma is a

a. Interferon β
b. IL-2 inhibitor
c. Lymphocyte proliferation enhancer
d. IL- 1

5. The most common side effect of cyclosporine is

a. Hyperglycemia
b. Hirsutism
c. Neurotoxicity
d. Nephrotoxicity

6.Which of the following can be used in head and neck carcinoma

a. Basiliximab
b. Bevacizumab
c. Cetuximab (Erbitux)
d. Certolizumab

7. Major toxicity of Bevacizumab is

a. Hypertension
b. Pancytopenia
c. Cardiomyopathy
d. Hepatotoxicity

8. Cetuximab is a monoclonal antibody directed against

a. EGFR
b. VEGF
c. TNF alpha
d. IL 2

9. The target for Denosumab is

a. RANKL
b. RANK receptor
c. M-CSF
d. NF-kB

Antimicrobials

1. All the following act on the cell membrane except

a. Daptomycin
b. Teicoplanin
c. Amphotericin B
d. Gramicidin

2. Resistance of pneumococci to penicillins is by

a. Alteration of D-Ala –D-Ala
b. Production of penicillinase
c. Altered PBP
d. Decreased pemeability

3. A diabetic patient developed cellulitis due to staphylococcus aureus which was found to be methicillin resistant .All can be used in this patient except

a. Vancomycin
b. Imipenem
c. Teicoplanin
d. Linezolid

4. A 60 yr old female is admitted with bacteremia due to gram negative bacilli, she has a h/o allergy to penicillins. Drug safely used in this patient is

a. Ceftriaxone
b. Imipenem plus cilastatin
c. Aztreonam
d. None

5. Imipenem acts mainly by inhibition of

a. Beta – lactamases
b. Protein synthesis
c. Transpeptidation
d. Transglycosylation

6. All are Polypeptide antibiotics except

a. Bacitracin
b. Cyclosporine
c. Polymyxins
d. Vancomycin

7. Synthesis of D-ala-D-ala is blocked by

a. Vancomycin
b. Cyclosporine
c. Bacitracin
d. None

8. About vancomycin true statement is

a. It is bacteriostatic
b. It binds to PBP
c. Binds to D-Ala-D-Lactate building blocks
d. Not susceptible to β lactamases

9.Which of the following does not have antipseudomonal activity

a. Aztreonam
b. Vancomycin
c. Piperacillin
d. Ceftazidime

10) Characteristic feature of Piperacillin is

a. Acid labile & Penicillinase resistant
b. Acid resistant & Penicillinase labile
c. Acid labile & Penicillinase labile
d. Acid resistant & penicillinase resistant

11. Which of the antibiotics is susceptible to β lactamases

a. Methicillin
b. Vancomycin
c. Ticarcillin
d. Oxacillin

12. All are therapeutic uses of penicillin G except

a. Bacterial meningitis
b. Rickettsial infection
c. Syphilis
d. Anthrax

13. Which of the statements about ampicillin is not accurate?

a. Causes maculopapular rashes
b. Used in Listeria infection
c. Eradicates most strains of MRSA
d. May cause pseudomembranous colitis

14. All are third generation cephalosporins except

a. Ceftizoxime
b. Cefixime
c. Cefamandole
d. Moxalactam

15. Disulfiram like reaction and hypoprothrombinemia is a adverse effect of

a. Cefuroxime
b. Cefoxitin
c. Cefotetan
d. Cefaclor

16. Cefotetan is mainly effective against

a. MRSA
b. Community acquired pneumonia
c. Bacteroides fragilis
d. Streptococcus

17. In a patient with history of cholelithiasis the drug you will avoid is

a. Cefazolin
b. Cefuroxime
c. Cefditoren pivoxil
d. Ceftriaxone

18. The CNS penetration is poor for

a. Ceftriaxone
b. Cefepime
c. Cefazolin
d. Ceftazidime

19. Aztreonam should not be used in treating pseudomonas infection if the patient is allergic to

a. Cefepime
b. Ceftazidime
c. Cefoperazone
d. Imipenem

20. The most appropriate treatment of gonorrhea in a patient allergic to penicillin is

a. Ceftriaxone
b. Doxycycline
c. Spectinomycin
d. Ciprofloxacin

21. For Beta lactamase producing enterococci all are used except

a. Imipenem
b. Ampicillin /sulbactam
c. Ceftriaxone
d. Vancomycin

22.β lactam antibiotic not useful in treatment of anaerobes

a. Penicillin G
b. Imipenem
c. Cefoxitin
d. Aztreonam

23. Tetracyclines inhibit protein synthesis by

a. Misreading of mRNA
b. Binding to 50s subunit and inhibiting the binding of t RNA to A site
c. Inhibiting peptidyltransferase activity
d. None of the above

24. Aminoglycosides are not useful in treatment of

a. Pseudomonas
b. E.coli
c. Klebsiella
d. Cl.difficile

25. Gram -VE organism not inhibited by aminoglycosides is

a. Shigella
b. Salmonella
c. Streptococci
d. Proteus

26. Which of the following is not associated with pseudomembranous colitis

a. Tetracyclines
b. Aminoglycosides
c. Clindamycin
d. Cephalosporins

27. The adverse effects Amikacin which is irreversible

a. Ototoxicity
b. Nephrotoxicity
c. Neuromuscular paralysis
d. Hypersensitivity

28. For eradication of meningococcal carrier state the tetracycline used is

a. Minocycline
b. Doxycycline
c. Rifampicin
d. Demeclocycline

29. Compared to tetracyclines chloramphenicol is more effective in typhoid fever but ineffective in

a. B.fragilis
b. H.influenza
c. Rickettsia
d. Chlamydia

30. A 26 yr old pregnant suffering from Rickettsial infection is treated with

a. Doxycycline
b. Penicillin
c. Cotrimoxazole
d. Chloramphenicol

31. Macrolide with least drug interaction is

a. Erythromycin
b. Azithromycin
c. Clarithromycin
d. Roxithromycin

32. Not an adverse effect of erythromycin

a. Torsades pointes
b. Ototoxicity
c. Constipation
d. Myopathy with statins

33. Long term abministration of which of the drugs is associated with thrombocytopenia

a. Daptomycin
b. Linezolid
c. Vancomycin
d. Quinupristin/Dafopristin

34. Antibiotic interfering with β subunit of DNA Gyrase is

a. Cinoxacin
b. Nalidixic acid
c. Novobiocin
d. Ofloxacin

35. The antibacterial activity of quinolones in staphylococcus is mainly by inhibition of

a. DNA gyrase
b. Topoisomerase II
c. Topoisomerase IV
d. Topoisomerase I

36. Fluoroquinolones are useful against all except

a. Anthrax
b. Pseudomonas
c. Syphilis
d. Chlamydia

37. All the following methenamine are true except

a. It is used in chronic suppressive therapy of UTI
b. It has major antibacterial effect at alkaline pH
c. It is contraindicated in renal insufficiency
d. It may cause gastric disturbances

38. Metronidazole acts by

a. Cell wall damage
b. Inhibition of protein synthesis
c. DNA damage
d. None

39. Hepatitis is seen with all except

a. INH
b. Rifampin
c. Ethambutol
d. Pyrazinamide

40. INH causes all except

a. Reduces absorption of B6
b. Psychosis
c. Optic neuritis
d. Seizures
e. Arthritis

41. Most common major toxic effect with INH is

a. Hepatotoxicity
b. Peripheral neuropathy
c. Memory loss
d. Hematological

42. Most common adverse effect of Zidovudine is

a. Macrocytic anemia
b. Peripheral neuropathy
c. Hepatotoxicity
d. Cardiomyopathy

43. The following is a side effect of Didanosine

a. Myocarditis
b. Pancreatitis
c. Aplastic anaemia
d. Seizures

44. The drug with maximum propensity to cause peripheral neuropathy

a. Didanosine
b. Zidovudine
c. Stavudine
d. Lamivudine

45. Peripheral neuropathy is not seen with

a. Lamivudine
b. Stavudine
c. Didanosine
d. Zalcitabine

46. Resistance to zidovudine develops due to

a. Mutation at reverse transcriptase
b. Active efflux
c. Increased metabolism
d. Reduced metabolism

47. Dose limiting toxicity of amphotericin B is

a. Nephrotoxicity
b. Fever and chills
c. Ototoxicity
d. Anaemia

48. The most common toxicity of flucytosine is

a. Nephrotoxicity
b. Ototoxicity
c. Bone marrow depression
d. Toxic enterocolitis

49. Not used in treatment of aspergillus

a. Amphotericin
b. Voriconazole
c. Fluconazole
d. Capsofungin

50. Systemically administered antifungal not useful in systemic fungal infection

a. Itraconazole
b. Griseofulvin
c. Amphoericin B
d. Voriconazole

General Pharmacology

1. Ames test in salmonella typhimurium is a test to detect

a. Teratogenicity
b. Delayed hypersensitivity
c. Genotoxicity
d. Promoters

2.Among the following statements choose the wrong one`

a. For a drug to be safe TI >1
b. Higher the therapeutic index safer the drug
c. TI is the ratio of median effective dose to median lethal dose
d. TI is a indicator of safety

3.True regarding Log Dose Response curve

a. Wide range of doses can be plotted
b. Log dose response is sigmoid shaped
c. Comparison between agonists and antagonists easier
d. All the above

4.Therapeutic confirmation of a drug is done during

a. Phase I
b. Phase II
c. Phase III
d. Phase IV

5.Good clinical practices need not be done in

a. Phase I
b. Phase II
c. Phase III
d. Preclinical testing

6.Postmarketing surveillance is associated with

a. Pharmacoeconomics
b. Pharmacovigilance
c. Pharmacodynamics
d. Pharmacogenetics

7. All are true about Bioavailability except

a. Determined from plasma concentration
b. Bioavailbility) = AUC (oral)/AUC IV X 100
c. Low bioavailability always means poor absorption
d. Comparison of bioavailability of two drugs is bioequivalance

8.Displacement of drug from plasma protein binding sites would usually be expected to

a. Decrease tissue levels of the drug
b. Increase tissue levels of drug
c. Decrease volume of distribution
d. Decrease metabolism of the drug

9.The renal clearance of a drug is determined to be 60 ml/min. Which of the following most likely explains this result

a. Extensive reabsorption
b. Drug is not bound to plasma protein
c. The drug is both filtered and secreted

d. Drug is filtered but not reabsorbed

10.A drug given as 80 mg single dose results in a peak plasma conc of 20µg/ml. The volume of distribution is

a. 1L
b. 2L
c. 3L
d. 4L

11.The most important factor governing loading dose is

a. Half life
b. Volume of distribution
c. Clearance
d. None of the above

12.Rate of elimination of a new drug is 40mg\hr at a steady state plasma concentration of 10mg \L , then its clearance will be

a. 2.0 L/hr
b. 4.0 L/hr
c. 8.0 L/hr
d. 1.0 L/hr

13.In determining the maintenance dose the most important pharmacokinetic term to be considered is

a. Loading dose
b. Volume of distribution
c. Clearance
d. Half life

14.What would be the maintenance dose for oral administration of a drug every 8 hrs if the dosing rate were 20mg/hr and the bioavailability were 0.5

a. 40mg
b. 75mg
c. 110mg
d. 320mg

15. A volunteer receives a new drug in a phase I trial. The clearance and Vd are 2 L/h and 80 L respectively. The half life in the subject would be

a. 22 hrs
b. 28 hrs
c. 32 hrs
d. 36 hrs

16.Which of the following statements applies to ethyl alcohol

a. Steady state plasma concentration reached in 4-5 half lives
b. The fraction of drug eliminated per unit time is constant
c. Half life increases with dose
d. The rate of elimination is dependent on plasma drug concentration

17.Which of the following is not a prodrug

a. Enalapril
b. Levodopa
c. Diazepam
d. α methyl dopa

18. All the following are Phase II biotransformation reactions except

a. Deamination
b. Glucuronide conjugation
c. Methylation
d. Acetylation

19.Acetaminophen is mainly metabolized by

a. Glucuronic acid conjugation
b. Acetylation
c. Glutathione conjugation
d. Glycine conjugation

20. All of the following drugs are metabolized by acetylation except

a. INH
b. Sulfonamides
c. Ketoconazole
d. Hydralazine

21. True about competitive antagonism

a. Has both affinity and maximum intrinsic activity
b. Has affinity and sub maximal response
c. Has affinity but no intrinsic activity
d. Has affinity but opposite intrinsic activity

22. False about partial agonist

a. Can act as a Agonist
b. Can act as a Antagonist
c. Fails to produce maximum response
d. Increases potency of pure agonist

23. cAMP is second messenger for all except

a. β1
b. β2
c. α1
d. α2

24. Imatinib used in CML acts by

a. Inhibiting Bcr/Abl translocation via tyrosine kinase
b. Blocking P glycoprotein
c. Competitive inhibition of ATP binding site of Bcr/Abl oncoprotein
d. C-kit inhibition

25. Which of the following do not belong to steroid receptor superfamily

a. Vitamin D3 receptor
b. Thyroid receptor
c. Retinoid receptor
d. Epinephrine receptor

26.Severe physical dependence is seen with all except

a. Morphine
b. Barbiturates
c. Alcohol
d. Cocaine

27.Hypoglycemia induced by Glibenclamide is a type of

a. Type A adverse drug reaction
b. Type B adverse drug reaction
c. Type C adverse drug reaction
d. Type D adverse drug reaction
e. Type E adverse drug reaction

28.Side effects can be minimized by increasing its

a. Specificity
b. Solubility
c. Affinity
d. Hydrophobicity

29.The most vulnerable period of pregnancy for the fetal malformation is

a. 1 – 17 days of gestation
b. 18-55 days of gestation
c. 56-85 days of gestation
d. Third trimester

30. Uses of thalidomide include all except

a. Used in treatment of multiple myeloma
b. Used in treatment of ENL
c. Used in treatment Crohns disease
d. Used in treatment of peripheral neuropathy

ANS

1. The sympathetic and parasympathetic exert functionally same action in controlling

a. Heart rate
b. Pupillary size
c. Sexual function in male
d. Intestinal motility

2. Among the hypoglycemic symptoms which is not masked by beta blocker

a. Sweating
b. Palpitation
c. Tremor
d. Anxiety

3. All of the following are seen with cholinergic muscarinic receptor stimulation except

a. Sweating
b. Rise in blood pressure
c. Bradycardia
d. Micturition

4. If high dose of Ach(5 mg) is administered after atropinisation, one would expect

a. Increase in Blood pressure
b. Fall in blood pressure
c. No change in Blood pressure
d. Increased muscarinic activity

5. Which of the following is paired correctly

a. Hemicholinium – Prevents release of Ach
b. Botulinum – Increases Ach release
c. Vesamicol- Inhibits choline uptake
d. None of the above

6. Rate limiting step in synthesis of Acetylcholine is blocked by

a. Vesamicol
b. Hemicholinium
c. Botulinum toxin
d. Atropine

7. Therapeutic use of acetylcholine is not possible because it is

a. Highly protein bound
b. Highly toxic
c. Increases blood pressure
d. Rapidly degraded

8. One of the following is metabolized by pseudocholinesterase

a. Methacholine
b. Carbachol
c. Bethnechol
d. Mivacurium

9.

10. Drug producing mydriasis,bradycardia and urinary retension

a. Atropine
b. Pilocarpine
c. Neostigmine
d. Salbutamol
e. Phenylephrine

11. Shortest acting anticholinesterase

a. Edrophonium
b. Pyridostigmine
c. Neostigmine
d. Tabun

12. Ageing of enzyme is seen with

a. Edrophonium
b. Dyflos
c. Neostigmine
d. Pralidoxime

13. Antidote for organophosphorus poisoning is

a. Neostigmine
b. Atropine
c. Succinyl choline
d. D- Tubocurarine

14. Antispasmodic which acts by inhibiting PDE-4

a. Oxybutinin
b. Tolterodine
c. Flavoxate
d. Drotaverine

15. Maximum increase in heart rate with atropine is seen in

a. Young children
b. Young adults
c. Elderly females
d. All the above

16. Atropine is not used in treatment of poisoning with

a. Amanita muscaria
b. Inocybe
c. Clitocybe
d. All

17. No sympathetic innervation but only adrenergic receptors are seen for

a. Radial muscle of iris
b. Ventricular myocardium
c. Seminal vesicle
d. Liver cells

18. Exocytosis of NE is inhibited by

a. Guanethidine
b. Cocaine
c. Reserpine
d. Metyrosine

19. The rate limiting step in the synthesis of catecholamine is

a. Hydroxylation of phenylalanine
b. Hydroxylation of tyrosine
c. Decarboxylation of dopa
d. Hydroxylation fo dopamine

20. Among the following drugs which will not stimulate α_2 receptors directly

a. Clonidine
b. Methyl dopa
c. Guanabenz
d. Guanfacine

21. Uptake I & II inhibited by

a. COMT inhibitors
b. Cocaine
c. MAO Inhibitors
d. Phenoxybenzamine

22. Drugs that block neuronal catecholamine reuptake (e.g., tricycle antidepressants) are likely to block the antihypertensive action of which of the following drugs?

a. Diazoxide
b. Guanethidine
c. Hydralazine
d. Prazosin

23. The following are indirectly acting sympathomimetic except

a. Cocaine
b. Amphetamine
c. Tyramine
d. Phenylephrine

24. Sympathomimetic drugs are useful in the therapy of all the conditions except

a. A/c decompensated heart failure
b. Hypotension
c. Hypertension
d. Erectile dysfunction

25. Renal vasodilatation occurs when the rate of dopamine drip is

a. 2-5 microgram/kg/min
b. 5-10 microgram/kg/min
c. 10-20 microgram/kg/min
d. 20 microgram/kg/min

26. Drug not having actions on Dopamine receptors

a. Dopamine
b. Fenoldopam
c. Dobutamine
d. Dopexamine

27. Classification of adrenergic receptors was proposed by

a. Henry Dale
b. Von euler
c. Otto loewi
d. Raymond Ahlquist

28. Smooth muscle excitation by α receptors and relaxation by β receptors is seen in all except

a. Vascular smooth muscles
b. Uterus
c. Intestines
d. Spleen

29.α1 stimulation produce

a. Increase in heart rare
b. Decrease Blood pressure
c. Decrease in heart rate
d. Relaxation of dilator pupillae

30. Dales vasomotor reversal is due to

a. Stimulation of α_1 receptor
b. Stimulation of α_2 receptor
c. Stimulation of β_1 receptor
d. Stimulation of β_2 receptor

31. Hypokalemia can be caused by action of

a. Norepinephrine
b. Epinephrine
c. Dopamine
d. Propranolol

32. Which of the drugs has more Alpha 2 affinity than Alpha 1

a. Phenoxy benzamine
b. Phentolamine
c. Tolazolin
d. Terazosin

33. Alpha blocker given by intra cavernous injection for treatment of erectile dysfunction in male is

a. Tamsulosin
b. Phentolamine
c. Tolazoline
d. Prazosin

34. Local anaesthetic activity not seen with

a. Propranolol
b. Acebutalol
c. Celiprolol
d. Pindolol

35. Nonselective adrenergic antagonist which cause peripheral vasodilatation

a. Phenylephrine
b. Propranolol
c. Carvedilol
d. Sotalol

36. Beta blockers with maximum local anesthetic activity

a. Metoprolol
b. Acebutalol
c. Pindalol
d. Propranolol

37. One of the following has shortest plasma ½ life

a. Propranolol
b. Esmolol
c. Timolol
d. Atenolol

38. Labetolol has

a. More potent beta blocking action than alpha blocking action
b. More potent alpha blocking action than beta blocking action
c. No postural hypotension
d. No first pass metabolism

39. Plasma t1\2 longest for

a. Pindolol
b. Atenolol
c. Nadolol
d. Labetolol

40. False about Esmolol

a. It is a cardioselective β blocker
b. Ultrashort acting β blocker
c. Metabolized by esterase's in RBC
d. Has membrane stabilizing activity

Anticancer Drugs

1.All the antitumor antibiotics are cell cycle nonspecific except

a. Doxorubicin
b. Daunorubicin
c. Bleomycin
d. Mitoxantrone

2.Vincristine arrests cell cycle at

a. Prophase
b. Metaphase
c. Anaphase
d. Telophase

3.Alkylating agent having the highest incidence of producing secondary leukemia

a. Cyclophosphamide
b. Procarbazine
c. Cisplatin
d. Busulfan

4.Dose limiting toxicity of carboplatin is

a. Vomiting
b. Nephrotoxicity
c. Neurotoxicity
d. Myelosuppression

5.Neutropenia following cancer chemotherapy can be reversed by

a. Leucovorin
b. Filgrastim
c. Prednisolone
d. Vitamin B 12

6.Most neurotoxic alkylating agent is

a. Cyclophosphamide
b. Busulfan
c. Ifosfamide
d. Melphalan

7.Dose limiting toxicity of Busulfan is

a. Nephrotoxicity
b. Neurotoxicity
c. Bone marrow depression
d. Pulmonary fibrosis

8.Palifermin is used for preventing

a. Myelosuppression
b. Mucositis
c. Diarrhoea
d. Alopecia

9.Dacarbazine is the drug of choice in

a. Ca Pancreas
b. Melanoma
c. Ca adrenal
d. Multiple myeloma

10. A patient is being treated with allopurinol to control hyperuricemia resulting from chemotherapy.Which of the following would have to have its dose reduced to prevent toxicity

a. 5-FU
b. 6-MP
c. 6-Thioguanine
d. Cytarabine

11.Hand foot syndrome is more common with

a. Capecitabine
b. Tamoxifen
c. Vinblastine
d. Cyclophosphamide

12.Among the following inhibitor of topoisomerase I is

a. Paclitaxel
b. Irinotecan
c. Doxorubicin
d. Teniposide

13.Dose limiting toxicity of Irinotecan is

a. Peripheral neuropathy
b. Diarrhoea
c. Pulmonary fibrosis
d. Cardiomyopathy

14. Adverse effects seen with vincristine are all except

a. Constipation
b. SIADH
c. Alopecia
d. Profound myelosuppression

15.Secondary leukemia occurs early when treated with

a. Cisplatin
b. Etoposide
c. Bleomycin
d. Busulfan

16.Dose limiting toxicity of anthracyclines is

a. Cardiotoxicity
b. Myelosuppression
c. Pulmonary fibrosis
d. Diarrhoea

17.Bluish discoloration of skin and nails seen with

a. Tamoxifen
b. Vincristine
c. Cisplatin
d. Mitoxantrone

18.The combination of vinblastine, Bleomycin& cisplatin is used in testicular carcinoma because

a. The three have same mechanism of action
b. One of the three drugs can be given orally
c. Two agents are natural products
d. The three have different dose limiting toxicity

19.Most common adverse effect of Thalidomide is

a. Peripheral neuropathy
b. Thromboembolism
c. Sedation
d. Diarrhoea

20.Tyrosine kinase inhibitor used in treatment of renal cell carcinoma is

a. Imatinib
b. Gefitinib
c. Sorafinib
d. Erlotinib

CNS

<u>Antiepileptics</u>

1.The antiepileptic drug that acts by affecting the levels of GABA is

a. Ethosuximide

b. Phenytoin
c. Carbamazepine
d. Vigabatrin

2.Which antiepileptic drug acts on GABA ergic system to decrease the uptake of GABA into neurons

a. Vigabatrin
b. Progabide
c. Gabapentin
d. Tiagabine

3. Which of the following is not a side effect of phenytoin

a. Inhibition of insulin release
b. Inhibition of ADH release
c. Inhibition of Ca absorption
d. Inhibition of Vit K metabolism

4. Lymphadenopathy resembling Hodgkins associated with reduced IgA is seen with

a. Phenobarbitone
b. Valprote
c. Phenytoin
d. Gabapentin

5. Carbamazepine in elderly causes

a. Hypernatremia
b. Hyponatremia
c. Hyperkalemia
d. Hypokalemia

6. A/C pancreatitis and hyperammonemia is a frequent side effect of

a. Lamotrigine
b. Valprote
c. Carbamazepine
d. Phenytoin

7.Which of the following is a dose related adverse effect of phenytoin

a. Gingival hyperplasia
b. Megaloblastic anaemia
c. Fetal hydantoin syndrome
d. None of the above

8.Idiosyncratic reactions of valproate include all except

a. Hepatotoxicity
b. Thrombocytopenia
c. Alopecia
d. Pancreatitis

9.About Phenytoin all are true except

a. Maximum protein binding
b. Induces enzymes
c. In low doses excreted by first order kinetics
d. Half life decreases with increasing dose

10.Use of phenytoin can produce all except

a. Ataxia
b. Diplopia
c. Hirsutism
d. Hypoglycemia

11.Carbonic anhydrase inhibitor that can cause Glaucoma

a. Acetazolamide
b. Tiagabine
c. Vigabatrin
d. Topiramate

12. Which of the following drugs is minimally excreted in milk.

a. Phenytoin
b. Ethosuximide
c. Valproic acid
d. Carbamazepine

13.Carbamazepine is useful in the following conditions except

a. Grand mal epilepsy
b. Petit mal epilepsy
c. Psychomotor epilepsy
d. Trigeminal neuralgia

14.All of the following are indicated in the treatment of petitmal epilepsy except

a. Ethosuximide
b. Sodium valproate
c. Phenytoin
d. Clonazepam

15.All are correctly matched except

a. Myoclonus - Valproate
b. Lennox Gastaut Syndrome- Lamotrigine
c. Infantile spasm- Vigabatrin
d. Juvenile myoclonic seizures - Carbamazepine

16. Which of the following drugs cannot be used in status epilepticus

a. IV Fosphenytoin
b. IV Valprote
c. IV Carbamazepine
d. IV Lorazepam

17.Drug not used in treatment of Infantile spasm

a. Corticotropin
b. Vigabatrin
c. Clonazepam
d. Carbamazepine

<u>Sedative Hypnotics</u>

1.Which of the following does not bind to GABA receptor

a. Ethanol
b. Alphaxalone
c. Zolpidem
d. Buspirone

2.True about benzodiazepines are all except

a. Binds to both $GABA_A$ and $GABA_B$
b. CI in obstructive sleep apnea
c. Decreases nocturnal gastric secretion
d. Metabolised by CYP enzymes

3. All the following can be used safely in elderly with liver disease except

a. Lorazepam
b. Oxazepam
c. Temazepam
d. Diazepam

4.The benzodiazepine which is a prodrug

a. Flurazepam
b. Estazolem
c. Clorazepate
d. Oxazepam

5.Flumezanil a benzodiazepine antagonist

a. Blocks the action of diazepam
b. Blocks the action of β carboline
c. Has a short half life
d. All the above

6.Benzodiazepines cause produce except

a. Cognitive impairment
b. Retrograde amnesia
c. Muscle relaxation
d. Decrease in REM sleep

7.Regarding Phenobarbital wrong statement is

a. They may produce megaloblastic anaemia
b. They are enzyme inducers
c. They have a steep dose response curve
d. Tolerance to anticonvulsant activity occurs on prolonged use

8. Which of the following is not a side effect of barbiturates

a. Causes failure of OCPs
b. Porphyria
c. Hyperbilirubinemia
d. Exfoliative dermatitis

OPIOIDS

1.Opioids receptors are

a. Ionic receptors
b. G protein coupled receptors
c. Cytokine receptors
d. Nuclear receptors

2.In epidural analgesia morphine acts by acting on

a. Axons
b. Substansia gelatinosa
c. Ventral horn
d. Sensory nerve

3.Which is a side effect of opioid

a. Mydriasis
b. Increased Gastric acid secretion
c. Truncal rigidity
d. Diarrhoea

4.Opioids are contraindicated in all except

a. Adrenal insufficiency
b. Hypothyroidism
c. Cough
d. Biliary tract surgery

5.The Mu receptor is responsible for the following clinical conditions except

a. Miosis
b. Respiratory depression
c. Sedation
d. Diuresis

6.The mu(μ) receptor is responsible for all the following effects except

a. Miosis
b. Bradycardia
c. Hypothermia
d. Bronchodilatation

7.Buprenorphine is a partial agonist at

a. Mu
b. Delta
c. Kappa
d. Sigma

8.Pentazocine can cause all except

a. Dysphoria
b. Analgesia
c. Hypotension
d. Less respiratory depression

9.True regarding Naltrexone are all except

a. Used in Opioid dependence
b. Used in alcohol dependence
c. Opioid antagonist
d. Agonist at kappa receptor

Antipsychotics

1.Among the atypical antipsychotics EPS is highest for

a. Quetiapine
b. Clozapine
c. Risperidone
d. Olanzapine

2.The risk of type II diabetes is low with use of

a. Clozapine
b. Ziprasidone
c. Olanzapine
d. Quetiapine

3.Which of the following is an allergic reaction to chlorpromazine

a. Hypotension
b. Jaundice
c. Acute dystonia
d. QT prolongation

4.Which of the following adverse reactions of antipsychotics responds poorly to anticholinergic drugs

a. EPS
b. A/C Dystonias
c. Akathisia
d. Rabbit syndrome

5. Sedation is a feature of all except

a. Chlorpromazine
b. Haloperidol
c. Quetiapine
d. Olanzapine

6. Thioridazine differs from older antipsychotics in that it is

a. More likely to cause extrapyramidal dysfunction
b. Less likely to cause urinary retention
c. Less likely to cause dry mouth
d. More likely to cause ocular dysfunction

7.Among the following antipsychotics weight gain is most prominent with

a. Haloperidol
b. Ziprasidone
c. Olanzapine
d. Risperidone

8. Antipsychotics are not useful in management of

a. Tourettes syndrome
b. Huntingtons disease
c. Intractable Hiccoughs
d. Opioid withdrawl

9.Apart from lithium which of the drugs are useful for treatment of bipolar disorder

a. Carbamazepine
b. Valproic acid
c. Lamotrigine
d. All the above

10.Overdosage of lithium is usually treated with

a. Thiazides
b. Indomethacin
c. ACE I
d. Hemodialysis

11.Therapeutic blood levels of lithium is

a. 0.8- 1.2 meq/l
b. 2-4 meq/l
c. 0.2-1 meq/l
d. None of the above

12. For a pregnant women suffering from bipolar disorder which of the following is the best choice

a. Lithium
b. Sodium Valprote
c. Carbamazepine
d. Olanzapine

Cardiovascular drugs, Hypolipidemic agents, & Diuretics

1. B
2. C
3. D
4. B
5. D
6. A
7. C
8. D
9. B
10. B
11. C
12. B
13. C
14. D
15. D
16. C
17. D
18. D
19. B
20. C
21. D
22. C
23. D
24. C
25. B
26. B
27. C
28. C
29. C
30. C
31. C
32. B
33. D
34. C
35. D

Immunopharmacology

1. A
2. B
3. A
4. C
5. D
6. C
7. A
8. A
9. A

Antimicrobials

1. B
2. C
3. B
4. C
5. C
6. D
7. D
8. D
9. B
10. C
11. C
12. B
13. C
14. C
15. C
16. C
17. D
18. C
19. B
20. C
21. C
22. D
23. D
24. D
25. B
26. B
27. A
28. A
29. D
30. D
31. B
32. C
33. B
34. C
35. C
36. C
37. B
38. C
39. C
40. A
41. A
42. A
43. B
44. C
45. A
46. A
47. A
48. C
49. C
50. B

General Pharmacology

1. C
2. C
3. D
4. C
5. D
6. B
7. C
8. B
9. A
10. D
11. B
12. B
13. C
14. D
15. B
16. C
17. D
18. A
19. A
20. C
21. C
22. D
23. C
24. C
25. D
26. D
27. A
28. A
29. B
30. D

ANS

1. C
2. A
3. B
4. A
5. D
6. B
7. D
8. D
9.
10. E
11. A
12. B
13. B
14. D
15. B
16. A
17. D
18. A
19. B

20. B
21. D
22. B
23. D
24. D
25. A
26. B
27. D
28. C
29. C
30. D
31. B
32. C
33. B
34. C
35. C
36. D
37. B
38. A
39. C
40. D

Anticancer Drugs

1. C
2. B
3. B
4. D
5. B
6. C
7. C
8. B
9. B
10. B
11. A
12. B
13. B
14. D
15. B
16. B
17. D
18. D
19. C
20. C

CNS

Antiepileptics

1. D
2. D

3. D
4. C
5. B
6. B
7. D
8. C
9. D
10. D
11. D
12. C
13. B
14. C
15. D
16. C
17. D

Sedative Hypnotics

1. D
2. A
3. D
4. C
5. D
6. B
7. D
8. C

OPIOIDS

1. B
2. B
3. C
4. C
5. D
6. D
7. A
8. C
9. D

Antipsychotics

1. C
2. B
3. B
4. C
5. B
6. D
7. C

8. D
9. D
10. D
11. A
12. D