This book is dedicated to Hazrat Muhammad s.a.w....
Special thanks to my Parents who encouraged me to do this and especially. My father Muhammad Boota who always and always supported me in my works and motivated me. And My Friends and my Class fellows (Nishtar Medical College Batch N62) who encourage me to complete this work

(Muhammad Ramzan Ul Rehman)
This book contains Mnemonics and short notes for pharmacology. Helpful for both students and teachers of Pharmacology for learning and teaching purposes. Pharmacology is one of the most boring and difficult subject considered in MBBS and is base of Clinical treatment.

In usual the stuff is present But you have to memorise that stuff by either way making concepts or by using Ratta. But still you have to remember the names of drugs, classifications, some special uses, side effects, contraindications and Bla Bla Bla......

Another problem is if you remember them then there will be mixing because there are a lot of Drugs and each drug will have a lot of uses, side effects, contraindications etc. The student is left with three methods one is to make concepts and everything understandable (This is the Best method), second method is to remember them all by ratta and clear your exams (but this will result in mixture in your mind) third last method is using some mnemonics or your emotions or your thoughts and relate them to Drugs and this will result increased retention power and this book is all about third method

This book contain
- Short notes
- Mnemonics
- Pictures related to mnemonics
- Tables
- Tricks to remember

I tried my best to make these things more and more palatable for ordinary students
For Suggestions, mistakes, spelling, mistakes, new mnemonics, additions, new ideas, and other things that can help to make this better are always welcomed

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Only Thing needed in Return is remember me in your Prayers If you find this Useful (This Book is FeSabeel ALLAH.)

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Γενεράλ Πηαρμαχολογψ
General Concepts

**Pharmacology** ➔ Study of substance that interact with living systems through clinical processes especially by binding to regulatory molecule

**Pharmacopeia** ➔ are the total of all authorized drugs available within the country.

**Medication** ➔ is a substance administered for diagnosis, cure, treatment, mitigation or prevention.

**Prescription** ➔ the written direction for the preparation and the administration of the drug.

**The therapeutic effect** ➔ is the primary effect intended that is the reason the drug is prescribed such as morphine sulfate is analgesia.

**Side effect** ➔ Secondary effect of the drug is one that unintended, side effects are usually predictable and may be either harmless

**Drug toxicity** ➔ deleterious effect of the drug on an organism or tissue, result from overdose or external use.

**Drug allergy** ➔ is immunological reaction to a drug.

**Drug interaction** ➔ occur when administration of one drug before or after alter effect of one or both drug.

**Drug misuse** ➔ is the improper use of common medications in way that lead to acute and chronic toxicity for example laxative, antacid and vitamins.
Drug abuse ➔ is an inappropriate intake of substance either continually or periodically.

Drug dependence ➔ is a person’s reliance on or need to take drug or substance there are two type of dependence:

1) **Physiological dependence**: is due to biochemical changes in the body tissue these tissue come to require substance for normal function.

2) **Psychological dependence**: is emotional reliance on a drug to maintain a sense of wellbeing accompanied feeling of need.

<table>
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<th>Pharmacokinetics</th>
<th>• is about how the body deal with drug (effect of body on drug)</th>
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<tr>
<td>Pharmacodynamics</td>
<td>• Is effect of drug on the body (d from dynamic drug on body).</td>
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<td>Pharmacotherapeutics</td>
<td>• Is a clinical using of drug.</td>
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<tr>
<td>Pharmacognosy</td>
<td>• The study of natural (plant and animal) drug sources.</td>
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### Sources of Drugs

1. Plants: such as digitalis (fox glove) and atropine (atropa belladonna)
2. Human and animals: such as epinephrine, insulin and adrenocorticotropic hormone.
3. Minerals: as iron, iodine and zinc
4. Synthetic and chemical substance: as sodium bicarbonate

Pharmacokinetics

Comprises Absorption, Distribution, Metabolism (Biotransformation) and Excretion.

A → Absorption
D → Distribution
M → Metabolism
E → Excretion

Absorption

Absorption is defined as the passage of a drug from the site of administration into the blood stream.

- Most drugs are absorbed (crosses cell membrane) by Passive diffusion (along concentration gradient with no carrier or energy).

Factors That Modify Drug Absorption

1) Factors related to the drug:
   a. Lipid solubility
      The higher the lipid solubility of the drug the higher the rate of drug absorption.
   b. Degree of drug ionization
      The greater the ionization, the lesser the absorption.
   c. pH of the medium
      Ionization depends on pH of absorbing media
- At acidic pH (stomach) weak acid drugs e.g. Acetyl salicylic acid (Aspirin) become more unionized → more lipid soluble → more absorbable, while weak basic drug e.g. amphetamine become less unionized (ionized) → less lipid soluble → less absorbable.
- At alkaline pH (Intestine) weak basic drugs become more un-ionized, more lipid soluble and more absorbable, while weak acidic drugs become less unionized, less lipid soluble and less absorbable.

d. Valency
Ferrous (Fe\(^{+2}\)) salts are more absorbed than ferric (Fe\(^{+3}\)), so vitamin C increases absorption of iron.
• Pharmaceutical form: Solutions are better absorbed than suspensions, the smaller the particle size of the powder, the more is the absorption.

e. Concentration at site of administration

2) Factors related to the Patient:
1-Route of Administration:
- Absorption from subcutaneous tissue is more rapid than absorption from mucous membranes EXCEPT pulmonary alveoli.
- Absorption from skeletal muscle is more rapid and complete than from subcutaneous sites.

2-State of absorbing surface
Diarrhea markedly decrease absorption of systemically acting drugs.

3-State of general circulation (Blood Flow)
During hypovolemic shock oral and subcutaneous rout are ineffective and drugs should be given intravenously.

Another way to enumerate these factors is (Modified form)

Chemical properties
- acid or base
- degree of ionization
• polarity
• molecular weight
• lipid solubility
• partition coefficient

**Physiologic variables**
• gastric motility
• pH at the absorption site
• area of absorbing surface
• blood flow
• presystolic elimination
• ingestion w/wo food

**Routes of drug administration**
Routs of Drug administration

Enteral
- Oral
- Rectal
- Sub lingual

Non-enteral
- Injection
- Inhalation
- Topical

Enteral Route of administration

Oral route

Drugs should be stable, non-irritant and adequately absorbed
• **Advantages (Oral is the most common)**
  1. Least expensive and most convenient route for most clients.
  2. Safe, does not break the skin.
  3. Conscious, able to swallow.

• **Disadvantages:**
  1- Variation in rate of absorption.
  2- Not in emergencies
  3- Not in unconscious patient
  4- Not for irritant drugs.
  5- Not in GIT disturbances (vomiting and diarrhoea).
  6- Not for non-absorbable drugs when systemic effect is needed e.g. streptomycin
  7- Not for drugs that undergo complete first pass metabolism e.g. lidocaine.

Governed by ➔ surface area for absorption, blood flow, physical state of drug, concentration.

- Occurs via passive process.
- In theory ➔ weak acids optimally absorbed in stomach, weak bases in intestine.
- In reality ➔ the overall rate of absorption of drugs is always greater in the intestine (surface area, organ function).
- Ingestion of a solid dosage form with a glass of cold water will accelerate gastric emptying: the accelerated presentation of the drug to the upper intestine will significantly increase absorption.
- Ingestion with a fatty meal, acidic drink, or with another drug with anticholinergic properties, will retard gastric emptying. Sympathetic output (as in stress) also slows emptying.

**Sublingual route**
Drug should be absorbed, stable, palatable and effective in small dose.

**Advantages:** Rapid absorption, escape first pass effect and proper control of dose by spitting or swallowing excess of drug.

Nitro-glycerine \(\rightarrow\) non-ionic, very lipid soluble. Because of venous drainage into the superior vena cava, this route “protects” it from first-pass liver metabolism.

**Rectal route**

- May be useful when oral administration is precluded by vomiting or when the patient is unconscious.
- Approximately 50% of the drug that is absorbed from the rectum will bypass the liver, thus reducing the influence of first-pass hepatic metabolism. Incomplete - irritation.

**Advantages:** Rapid absorption, useful in vomiting, unconscious patient, children, irritant drugs on stomach and drugs that undergo first pass effect.

**Disadvantages**
1. Psychological many patients refuse this route.
2. Rectal inflammation may occur with repeated use.
3. Absorption can be unreliable, esp. if the rectum is full of stool.
4. Irregular
5. Incomplete absorption
6. Irritation may occur
Parenteral Route of administration

Injections

Injection which should be sterile and are used in the following:

1. Drugs ineffective by other routes.

2. Drugs producing irritation.

3. Emergencies and to increase blood level rapidly.

Injections may be in the following sites:

a. Intradermal e.g., sensitivity tests and vaccination.

b. Subcutaneous: more rapid and complete than oral and is suitable for non-irritant drugs.

c. Intramuscular: for moderate irritant drugs.
**d. Intravenous:** drugs should be aqueous. It is suitable for too irritant drugs and rapidly destroyed drugs (e.g., lignocaine and nitroprusside). Usually has a rapid onset and produce immediate effective blood level.

**e. Rare** as in bone marrow, intra-arterial, intracardiac, intrathecal, intra-articular, intraperitoneal.

Intradermal

is the administering of a drug into the dermal layer of the skin just beneath the epidermis, usually small amount of liquid is used for example 0.1ml.

- **Advantage:** absorption is slow (this advantage test for allergy).
- **Disadvantage:** amount of drug administered must be small and breaks skin barrier

Subcutaneous

Hypodermic into subcutaneous tissue, just below the skin.
**Advantage:** onset drug action faster than oral.

**Disadvantage:**
1. Must involve sterile technique because breaks skin barrier.
2. More expensive than oral.
3. Can administer only small doses.
4. Slower than intramuscular injection.
5. Some drug can irritate tissue and can cause pain.

---

**Intramuscular**

Into in the muscle.

**Advantage:**
- Pain from irritating drugs is minimized.
- Can administer large volume of drug.
- Drug rapidly absorbed.

**Disadvantage:**
- Breaks skin barrier.
- Can be anxiety producing.

---

**Intravenous**

Intravenous (IV): allow injection of drugs and another substance directly into bloodstream through the vein.

- **Disadvantages of I.V.**
  * Allergic reaction as anaphylactic shock.
  
        * Velocity reaction, e.g. if aminophylline is given rapidly it can produce arrhythmia, hypotension and cardiac arrest.

        * Pyrogenic reaction.

        * Disease transmission.

        * Thrombophlebitis.

        * Extravasation (leakage) → severe irritation.
**Miscellaneous routes**

1-**Topical administration**
   Is useful in the treatment of patients with local conditions, there is usually little systemic absorption. Drugs can be applied to various mucous membranes and skin.

2-**Inhalation**
   Provides a rapid access to systemic circulation; it is the common route of administration for gases and volatile drugs.

3-**Subcutaneous pellet implantation**
   Pellet under skin induces fibrosis around it leading to slow absorption and long duration (e.g. contraceptives, steroid hormones)

4-**Transdermal delivery system**
   By applications of drugs to the skin for systemic effect. The drug is released through a rate controlling membrane into the skin and so into the systemic circulation.

5-**Hypospray gun** (jet injection syringe)
   Very convenient, no need for sterilization, not painful, offers self-medications. Used for giving insulin & for mass immunization.

6-**Intranasal**
   Calcitonin is used in treatment of osteoporosis as a nasal spray.
Drug Distribution

Process by which a drug reversibly leaves the circulation and enters the interstitium and cells of the tissue.

Drugs are distributed to the different tissues and body fluids, according to the compartmental models.

*One compartment model (intravascular)

- E.g. drugs with high molecular weight as heparin has Vd 3-4 L.

*Two compartment model (extracellular distribution)

- Drug with small molecular weight but ionized e.g. skeletal muscle relaxants have Vd average of 14 L.

*Multicompartmental model (extracellular and intracellular distribution)

- Drug with small molecular weight and lipid soluble as alcohol has Vd average of 42 L.

*Selective distribution

- Some drugs have special affinity for specific tissue. e.g. calcium in bones and iodide in thyroid gland.

Apparent volume of distribution (Vd)
• It is the hypothetical volume of the fluid into which a drug distributed

\[ V_d = \frac{\text{Amount of drug in body}}{\text{Plasma concentration of drug}} \]

\( V_d \) is not a real volume, small volume indicates extensive plasma protein binding, but large volume indicates extensive tissue binding.

\( V_d \) is increased by increased tissue binding, decreased plasma binding and increased lipid solubility.

**N.B.** in average 70 kg adult, the total body water is 42 liter, extracellular volume is 14 liter and plasma volume is 4 liter.

**A-Patterns of Drug Distribution**
The drug is transported in the blood in either 2 forms bound form OR free form

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<tr>
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<td>Diffusible</td>
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<tr>
<td>Cannot be metabolized</td>
<td>Can be metabolized</td>
</tr>
<tr>
<td>Cannot be excreted by kidneys</td>
<td>Can be excreted by kidneys</td>
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</table>

• The protein bound drug acts as a store from which a small amount of free drug is released.

• The protein responsible for binding of most drugs is albumin.

**B-Competition for Plasma Protein Binding Sites**
One drug may displace another from its binding sites on plasma proteins. The displaced drug will show higher free blood level with enhanced activity & possibly toxicity e.g. Aspirin can displace Warfarin (anticoagulant) → Hemorrhage.

**C-Passage of drug to CNS via BBB and to fetus via placental membrane**
Only un-ionized lipid soluble drugs can pass through BBB and placental membrane to exert central effects and affect the fetus respectively.

**Drug Metabolism (Biotransformation)**

It aims to eliminate the drugs by converting lipid soluble drugs into more polar and less lipid soluble compounds enhancing their renal excretion.

**Phases of biotransformation**

**Phase I (Non synthetic) reactions**

- **Oxidation**
  - Oxidation p450 dependant
    - Hydroxylation ➔ Barbiturates and phenytoin
    - N-dealkylation ➔ caffeine and morphine
    - N-oxidation ➔ Nico ➔ Nicotine
    - Deamination ➔ DA ➔ diazepam
  - Oxidation p450 independent
- Amine oxidation $\rightarrow$ catecholamine (as catecholamine have amine group)
- Dehydrogenation $\rightarrow$ ethanol

- **Reduction**
  - Easters $\rightarrow$ aspirin
  - Amides $\rightarrow$ Lidocaine

**Phase II (Synthetic) reactions**

- Functional group or metabolite formed by phase I is conjugated with natural endogenous constituent as glucuronic acid, glutathione, sulphate, acetic acid, glycine or methyl group.

- **Glucouronidation** $\rightarrow$ DAM Gluco
  - D $\rightarrow$ Diazepam and digoxin
  - A $\rightarrow$ Acetaminophen
  - M $\rightarrow$ Morphine

- **Glycine conjugation** $\rightarrow$ GlyciNe $\rightarrow$ Nicotine
- **Sulphation** $\rightarrow$ methyldopa
- **Methylation** $\rightarrow$ Dopamine, epinephrine, norepinephrine and histamine
- **Acetylation** $\rightarrow$ isoniazid

Most of drugs pass through phase I only or phase II only or phase I then phase II.

**Results of drug metabolism**

1. Conversion of **active** drug into an **inactive** metabolite.
2. Conversion of **active** to another **active** substance.
3. Conversion of **pro-drug** (drug given is inactive) to an **active** metabolite.
4. Conversion to a **toxic** compound.

**Liver** is the main organ for drug metabolism using liver microsomal $P_{450}$ enzymes.

**Hepatic Metabolism depends on**

1. Hepatic function: diseased liver is unable to metabolize drugs as healthy one.
2. Nutritional state as vitamins and minerals are cofactors for the metabolizing enzymes.
3. Presence of other drugs

**a) Activators (Enzyme Inducers)**

Some drugs can increase the activity of microsomal enzymes → their ability to detoxicate drugs.

GPRS Cell phone

- G ➔ Grisofulvin
- P ➔ Phenytoin
- R ➔ Rifampicin
- S ➔ Smoking
- Cell ➔ Carbamazepine

Phone ➔ Phenobarbitone (Benzodiazepines and barbiturates)

**b) Inhibitors (Enzyme Inhibitors)**

PC Games

- P ➔ P 450 inhibitors
- C ➔ Cyclosporine and Cimetidine
- G ➔ Grape fruit
- A ➔ Antifungals
- M ➔ Metronidazole
- E ➔ Erythromycin
- S ➔ SSRIs

**Hepatic First-Pass Metabolism**

Metabolism of drugs (usually oral) before reaching the systemic circulation (pre-systemic metabolism).

**Locations** ➔ liver and GIT linings

How to overcome hepatic first-pass metabolism?

1. Give a loading dose (high first dose).
2. Change route of administration e.g. sublingual or rectal.
3. Use alternative drug with less hepatic metabolism.
Drug Excretion and elimination

Drugs are eliminated from the body either unchanged or as metabolites.
⇒ Kidney is the major organ for drug excretion

• Kidney
  • Acidic urine ⇒ Excretion of basic drugs
  • Alkaline urine ⇒ excretion of acidic Drugs

First order kinetics
A constant fraction of drug is eliminated per unit of time.
When drug concentration is high, rate of disappearance is high.

Zero order kinetics
Rate of elimination is constant and is independent of concentration

Example ⇒ Alcohol

• Other routes of drug excretion include: Bile, Stool, Stomach (Morphine), Saliva (Iodides), Sweat (rifampicin), Milk (amphetamine) and Lungs (nitrous oxide).

Other pharmacokinetic Properties

Clearance
Volume of blood or plasma that can be freed of a drug in a specific time is called clearance
Formula

\[ \text{Cl} = \frac{\text{Rate of elimination of Drug}}{\text{Plasma concentration of drug}} \]

**Rate of Clearance**

First order kinetics ➔ constant

**Dependence of Clearance**

- Blood flow
- Condition of organ eliminating

Clearance of Drug by an organ = extraction capability of that drug x rate of delivery of that drug to that organ

**Bioavailability**

Is the percent of unchanged drug reaching systemic circulation after administration by any route.

In case of I.V. administration, bioavailability will be 100%.

**By other routes**

Absorption is less than 100

- Due to incomplete absorption
- Due to first pass metabolism
- Distribution into tissue before drug enters the circulation
- Drug formulation

Bioavailability ➔ measured by area under plasma concentration curve

**Plasma half-life (t1/2)**
It is the time needed to reduce drug plasma concentration by 50%. The longer the half-life of the drug the lesser the frequency of drug administration.

\[
\text{Half-life} = \frac{0.693 \times V_d}{\text{Clearance}}
\]

Half-life ➔ determines the rate at which blood concentration rises during constant infusion and falls after stopped

**Dosage regimens**

A plan of drug administration over a period of time

- Achieve therapeutic level of drug without achieving the minimum toxic level of the drug.

**Maintenance Dose**

Dose required for regular administration to maintain plasma level

\[
\text{Dosing rate} = \frac{\text{CL} \times \text{Desired plasma concentration}}{\text{Bioavailability}}
\]

Bioavailability for IV route is 1 so we can say that

Dosing rate = CL x Desired plasma level

**Loading dose (Love ➔ mean Loading dose have } V_d\)**

Dose required to achieve specific plasma level with single administration

- Therapeutic concentration must be achieved rapidly at the onset of therapy

\[
\text{Dosing rate} = \frac{V_d \times \text{Desired plasma concentration}}{\text{Bioavailability}}
\]

Bioavailability for IV route is 1 so we can say that

Dosing rate = V_d x Desired plasma level

- Clearance is not needed here because when clearance will start we will give patient maintenance dose
Adjusted dose for patient with impaired clearance

Dosing rate = \[
\frac{\text{Average dosage} \times \text{patient’s clearance}}{\text{Normal clearance}}
\]

**Therapeutic window**
Safe range between the minimum therapeutic concentration and minimum toxic concentration of a drug is called therapeutic window

- Helpful in designing dosage regimens

**Minimum effective concentration** ➔ determine the trough level of drug given intermittently

**Minimum toxic concentration** ➔ determines the peak concentration of the drug

Theophylline ➔ 8 to 16 mg/dL

**Pharmacodynamics**

Actions of Drug on body
- Mechanism of drug
- Receptor interactions
- Dose response phenomena
- Adverse effects of drug

**Mechanism of drug action**

a- Physical action, e.g., mannitol induces osmotic diuresis.

b- Chemical action, e.g., NaHCO₃ neutralizes excess HCl in hyperacidity.

c- Cytotoxic action (stop cell division) e.g., anticancer drugs.
d- Interfere with passage of ions as Na⁺ entry across cell membrane e.g. local anaesthetics.

e- Interference with normal metabolic pathway, e.g. sulphonamides compete with PABA which is essential for bacterial growth.

f- Enzyme inhibition. Enzyme inhibition could be:

1. Reversible e.g. neostigmine (cholinesterase inhibitor).

2. Irreversible e.g. irreversible anticholinesterases.

g- Action on specific receptors:

Most of drugs are effective because they bind to particular target proteins. Changes of intracellular molecular and biochemical events, responsible for drug action.

**Receptors**

Macro molecular structures present on cell membrane or within the cell that react specifically with ligand (drug, hormone or neurotransmitter) to produce a biological response.

\[
\text{Affinity} \quad \quad \text{Drug + Receptor} \quad \quad \rightarrow \quad \quad \text{D/R complex} \quad \quad \rightarrow \quad \quad \text{Response} \quad \quad (Efficacy)
\]

**Affinity** is the ability of the drug to bind to a receptor forming drug/receptor complex.

**Efficacy = response** is the ability of drug/receptor complex to produce a biological response or effect.

**Receptor interactions**

**Agonist**: A drug having affinity, efficacy and rapid rate of dissociation and is capable of fully activating the effecter system when it binds to the receptor

- e.g. adrenaline and acetylcholine.
**Antagonist**: A drug having affinity, no efficacy and slow rate of dissociation. It blocks the action of an agonist on the receptor e.g. Atropine and propranolol.

**Partial Agonist OR Antagonist**: A drug having affinity, efficacy less than that of agonist and moderate rate of dissociation. It blocks the action of an agonist on the receptor.

**Inverse agonist**: agonist have much higher affinity for the inactive state than for activated state and decreases or abolishes the constitutive activity (Activity in the absence of ligand is called **Constitutive activity**)

**Dose Response phenomena**

**Graded Dose Response Relationship**
A graph of increase response to increasing drug concentration

<table>
<thead>
<tr>
<th>Graded dose response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graph between</td>
</tr>
<tr>
<td>Graded</td>
</tr>
<tr>
<td>Increase of response</td>
</tr>
<tr>
<td>Dose response</td>
</tr>
<tr>
<td>Increase of dose of</td>
</tr>
<tr>
<td>drug</td>
</tr>
</tbody>
</table>

Data derived from this Graph
- Efficacy \( (E_{\text{max}}) \)
- Potency \( \text{EC}_{50} \) or \( \text{ED}_{50} \)
  Smaller the \( \text{EC}_{50} \) greater the potency of drug

**Quantal dose response**
A graph of fraction of population that shows a specific response at progressively increasing dose

<table>
<thead>
<tr>
<th>Quantal dose response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graph between</td>
</tr>
<tr>
<td>Quantal</td>
</tr>
<tr>
<td>Fraction of population showing that response</td>
</tr>
<tr>
<td>Dose response</td>
</tr>
<tr>
<td>Increase of dose of drug</td>
</tr>
</tbody>
</table>

Data derived from this Graph
- Median effective dose \( \text{ED}_{50} \)
- Median toxic dose \( \text{TD}_{50} \)
- Median lethal dose \( \text{LD}_{50} \) ➔ in animals

**Efficacy ➔ greatest effect**

is the greatest effect \( (E_{\text{max}}) \) an agonist can produce if dose is taken to highest tolerated level

**Determined by**
- Nature of the drug
- Nature of the receptor
- Nature of the effector system associated with it

➔ can be determined by graded response curve not by Quantal response curve
Potency ➔ amount required to produce required effect

The amount of drug needed to produce a given effect

Determined by

• Affinity of the receptor for drug
• No of receptor available

➔ can be determined by quantal and graded dose response curve

Spare receptors

Spare receptors are present if maximum response is obtained at less than 100% occupation of the receptors

Reasons

• Duration of activation of receptor may be greater than the duration of Drug receptor interaction
• Actual no of receptor may exceeds the no of effectors

⇒ Spare receptors increase the sensitivity of the receptors to the agonist

Therapeutic Index

This is the ratio of: \( \frac{LD_{50}}{ED_{50}} \)

• It measures margin of Safety for a drug.
• Safe Drug ➔ very large toxic dose and much small effective dose
• LD$_{50}$ or median lethal dose ➔ is the dose that kills 50% of experimental animals e.g. rats or mice.
• ED$_{50}$ or median effective dose ➔ is the dose that produces a certain pharmacological effect in 50% experimental animals.
• The higher the therapeutic index the safer the drug.

**Values of therapeutic index:**
1-So small therapeutic index means that the LD$_{50}$ is just above ED$_{50}$ e.g. digoxin.

2-So great therapeutic index means that it is impossible to kill a patient (the LD$_{50}$ is so great compared with ED$_{50}$ which is so small) e.g. Penicillin.

**Adverse Drug Effects**
“Each capsule contains your medication, plus a treatment for each of its side effects.”
Unpredictable

1- Allergy ➔ the drug is recognized by the immune system as an antigen ➔ allergic reaction e.g. anaphylactic shock in penicillin allergic patients.

2- Idiosyncrasy (pharmacogenetics) ➔ abnormal reaction to the drug due to genetic or enzyme defect e.g.
1-Hemolysis of RBCs in patients with G6PD deficiency due to administration of certain drugs as aspirin.

Predictable

1. **Carcinogenicity** ➔ drug induced cancer.

2. **Mutagenicity** ➔ drug induced gene mutations in parents or in their offspring.

3. **Teratogenicity** ➔ drug induced foetal defects in utero. Drugs are safely avoided as much as we can especially during the first trimester.

4. **Cumulation (Toxicity)** ➔ drug induced poisoning either due single large dose or several small doses.

5. **Tolerance** ➔ decreased drug response the usual dose on repeated administration of the drug. Tolerance may be congenital (inherited) OR Acquired.

   1. **Congenital:**

   a) **Racial:** Negroes are resistant to mydriatic effect of ephedrine.

   b) **Species:** rabbits are resistant to atropine due to presence of atropinase enzyme.

   c) **Individual variation.**
2. **Acquired**: e.g., morphine, ethyl alcohol, nitrates, ephedrine, and amphetamine.

   * It is reversible, so cessation of the drug will lead to loss of tolerance.
   
   * It may develop to some actions only and not to all actions. Tolerance occurs to analgesia and respiratory depression of morphine, but not to miosis and constipation.

**Special types of tolerance**

1) **Tachyphylaxis**

   (Acute acquired tolerance) e.g. ephedrine on B.P.

   **Reasons**

   - Intracellular molecules block access to G proteins ➔ Beta arrestins in case of beta agonists
   - Agonist bound receptor may be internalized ➔ like morphine receptors
   - Continuous activation may leads to depletion of some essential substrate required for downstream effects ➔ like depletion of thiol co-factors in case of tolerance to nitroglycerine

2) **Cross tolerance** (tolerance between related drugs), e.g. between ethyl alcohol and general anaesthesia.

   **Variation in drug response may be due to**

   1. **Alteration in drug concentration that reaches the receptors** due to an effect on absorption, distribution or elimination.
2. **Variation in concentration of endogenous transmitters** e.g. $\beta$-blockers will slow heart rate markedly in patients with excess endogenous catecholamines.

3. **Alteration in the number or function of receptors**, e.g. thyrotoxicosis increases the number and sensitivity of $\beta$-receptors.

   - Long use of agonists may decrease the number of receptors (down-regulation) and this may be responsible for overshoot phenomena which follows withdrawal of some drugs.

   - Long use of antagonists may increase the number of receptors by preventing down-regulation caused by endogenous agonists.

6. **Dependence**

   - Habituation: emotional or psychological dependence on the drug e.g. Tobacco smoking.

   - Addiction: both psychological and physical dependence on the drug e.g. Morphine addiction.
**Drug Interactions**

**DRUG-DRUG INTERACTIONS**

T - Tri cyclic anti depressants
H - Histamine antagonist
E - Erythromycin
M - MAO inhibitor
A - Aspirin
D - Digoxin diuretics
W - Warfarin
Z - Zole (antifungals)
A - Rifampin
A. Pharmacodynamic Interactions

When two or more drugs are combined, one of the following four phenomena may be observed.

I. **Addition or Summation** ➤ the combined effect of the two drugs given together equals the algebraic sum of their individual actions i.e. $A = 1, B = 1, A + B = 2$.

II. **Synergism** ➤ the combined effect of drugs is more than the algebraic sum of their individual actions i.e. $A = 1, B = 1, A + B > 2$. 
III. Potentiation ➔ one drug has no action on a system but increases the action of another drug on the same system i.e. A = 0, B = 1, A + B > 1.

III. Antagonism ➔ several types: (we discuss later after pharmacokinetic interactions)

B. Pharmacokinetic Interactions

- **Absorption** ➔ Salts of Mg, Ca & Al limit absorption of tetracycline.
- **Distribution** ➔ displacement from plasma protein binding sites (see interaction between aspirin & warfarin).
- **Metabolism** ➔ enzyme induction and enzyme inhibition (see pharmacokinetics)
- **Excretion** ➔ Probenecid inhibits renal excretion of penicillin.
Antagonism

1-Physiological

One drug has the opposite pharmacological action to another drug while the two drugs act on different receptors.

E.g. adrenaline antagonizes the effect of histamine on blood pressure.

2-Chemical/Physical

One drug chemically or physically combines with another drug and antagonizes its action.

E.g. Pralidoxime (antidote for Organophosphates) combine avidly to Phosphorous of organophosphate avidly.

3-Pharmacological

One drug bind to receptor without activating it and prevents the binding of agonist (thus prevent activation by agonist).

Types

- Competitive
• Non competitive

**Competitive**

A pharmacological antagonism in which effect of antagonist can be overcome by increase in concentration of agonist

• There is competition between antagonist and agonist ➔ whose concentration is more will dominate

➔ Drug will closely resemble the agonist and will bind reversibly to the receptor without activating the receptor

**Non-competitive**

A pharmacological antagonism in which the effect of antagonist cannot be overcome by increase in concentration of agonist

• There is no competition But antagonist bind irreversibly and do not allow the agonist to bind

➔ Drug will bind to receptor irreversibly
ANS Pharmacology
1. Introduction

Receptors Classification and their location and effects.

Adrenergic Receptors or sympathetic receptors

Alpha 1 receptors

imagine a Fish made of rope with a big Eye. And you pulled the rope and the Fish became smaller.

This means Alpha has big eye and other things generally constricted or contracted. So now we can move to the Functions Performed By Alpha..

- Fish with Big eye ⇒ mean sympathetic eye ⇒ Dilate Pupil (Mydriasis)
Other all almost will contract or constrict

- **Radial Muscles of eye** → contract → pupillary dilation
- **Blood vessels** → constrict (skin, Mucous membrane, viscera)
- **Bronchi** → constrict (Minor role as compared to Beta 2 receptors)
- **Uterus** → contract → Baby out
- **Sphincters** → contract
- **Erector Pilli** → contract → hair rising
- **Seminal vesicles** → contract → ejaculation of sperms

**Another mnemonic for remembering ejaculation and erection is**

Point and shoot
Point (erection) → parasympathetic
Shoot (ejaculation) → sympathetic

**Alpha 2 receptors**

Alpha 2 is like a Big fish and Alpha 1 was a small fish. There was rivalry between Alpha and others. Alpha 2 was swimming in water. And his enemies came to finish her. But as she is Big fish and Alpha 1 is too a fish so she recognize that alpha 2 is more powerful
so Alpha 1 ran away. But Beta 1 2 3 are batmez party so they decided to fight.

In the end Alpha 2 ended up eating all betas and with some poop.

So what happens is Alpha 2 have functions of opposing Batmez Betas

**Its functions will be**

- Heart rate ➔ decrease
- Secretions (slivery and from other Parts of GIT) ➔ decrease
- Insulin release ➔ decrease
- Weak opposition of effects of Betas because they are eaten up
- Weak favour of effects of alpha 1 because both are fishes
- There was PooP too ➔ mean increases platelet aggregation

**Beta 1 receptors**

Shape of Beta resemble heart and kidney so

- So effects of Beta will be

  **On heart ➔ (betay ko daikh kar man k dil ki dharkan taiz ho gai)**
  
  - Increase heart rate
  - Increase contractility
  - Increase Cardiac out put

  **On kidney ➔ increase Renin secretion**

**Beta 2 receptors**
Resemble expanding wings of Butterfly (Things will be expanding or relaxing here)

- Relax smooth Muscles \( \rightarrow \) decrease GIT motility
- **Expand Bronchi** \( \rightarrow \) Broncho dilation (Butterfly have two wings just like we have two lungs so Lungs function is important one)
- Expand Blood to Liver and skeletal muscles (vasodilation mean expand blood vessel calibre)
- Expand blood Glucose Level \( \rightarrow \) increase Gluconeogenesis
- Expand uterus \( \rightarrow \) keep baby inside
- Increase insulin release

Increase blood glucose mean blood glucose level is increased by them and increase insulin is for increase entry of Glucose into skeletal Muscles so we can fight or flight powerfully in sympathetic stimulation.

**Beta 3 receptors**

Resembles triglyceride \( \rightarrow \) so its function is in Lipolysis

**Cholinergic Receptors or Parasympathetic receptors**

**M 1 receptor**

M one \( \rightarrow \) mean Moan
M 1 ➔ increase Gastric secretions (increase proportion of water)

**M 2 receptor**

M 2 is just like M & M chocolate in shape of Heart. And you love them but this time you are having no chocolate.

**SO its Functions will be**

- Decrease heart Rate
- Decrease Force of contraction of Heart
- Decrease Cardiac output

**M 3 receptor**

*Anything that comes under parasympathetic control and not from M 1 (gastric secretions) and M 2 (Heart depression effects) will come here.*

*So let’s start*

**Most of the functions are reverse of sympathetic**

- Relax Sphincters (opposite to alpha 1 that contract them)
- Relax Blood Vessels ➔ vasodilation (opposite to alpha 1 that contract them)
- Increase GIT motility (opposite to beta 2 that decrease GIT motility by relaxing smooth muscles)
- Increase secretions ➔ increase water content of saliva (opposite to alpha 2 that decreases secretions)
• Broncho constriction (opposite to Beta 2 that expand bronchi)
• Eye ➔ Pupillary constriction ➔ Due to contraction of Sphincter muscles (opposite to Big eyed fish in alpha) Lead to miosis.

Location of these Receptors

You can guess their location from their effects in which they are working and if you want to remember them separately so here are some mne-

Monics

Muscarinic Receptors
• Muscles ➔ muscarinic receptors
• Not ➔ M 1 in Nerve endings (increase IP₃ DAG)
• Have ➔ M2 in Heart (decrease cAMP)
• energy ➔ M3 in Effector cells (increase IP₃ DAG)

Nicotinic Receptors
Nicotinic ➔ N ➔ Nerves
Nicotinic N ➔ ANS ganglia
nicotinic M ➔ neuromuscular end plate (M for muscle)

**Mechanisms:** they act on Na\(^+\)-K\(^+\) ion channels ➔ depolarize and evoke action potential

**Adrenergic Receptors**

- England ➔ alpha 1 in effector tissues
- Never ➔ alpha 2 in Nerve endings and smooth muscles
- Have ➔ beta 1 in heart
- Some ➔ beta 2 in smooth muscles
- Apology ➔ beta 3 in adipose tissue

Dopamine D1 receptor in renal vascular smooth muscles

**Mechanisms:**

First alpha 1 ➔ increases IP3 DAG (like M 1)
Second alpha 2 ➔ decreases cAMP (like M 2)
Rest betas and dopamine receptors all ➔ increase cAMP

**Adrenergic transmission**
Drug intervention -- Adrenergic transmission

- Stimulatory
- Inhibitory
- Solid: Agonistic
- Dotted: Antagonistic

Tyrosine → TH → Metyrosine
Dopa → DA
Reserpine

Vesicle (DA → NE)
Amphetamine, tyramine, ephedrine
Bretlyum, guanethidine
Cocaine
Tricyclic antidepressants (e.g. imipramine)

Release
Noradrenaline (NE)

Adrenergic antagonists
- Phentolamine (α-blocker)
- Propranolol (β-blocker)

Adrenergic agonists
- Isoproterenol
- Albuterol

Receptor + action
Recapture by Uptake-1

Cholinergic Transmission
Drug intervention -- Cholinergic transmission

(Rate-limiting)  Precursor transport

Cholinergic antagonists

Atropine (anti-M)
Succinylcholine (anti-Nm)
Trimethaphan (anti-Nm)

Cholinergic agonists (direct acting)

Carbachol
Pilocarpine

Receptor + action

Synthesis

Storage

Release

Ach

Degradation by AchE

Hemicholinium

↓: Stimulatory
⊥: Inhibitory
Solid: Agonistic
Dotted: Antagonistic

Vesamicol
Botulinum toxin

AntiChE

Reversible (neostigmine)
Irreversible (organophosphate)
2. Cholinergic or Parasympathomimetic or Cholinomimetic Drugs

**Members & Classification**

**Direct acting (agonists)**

**Direct acting cholinomimetics**

- On Both receptors
- Muscarinics
- Nicotinic

- Acetylcholine
- Carbacol
- Bethanecol
- Pilocarpine
- Nicotine
- Acetycholine

**Mnemonic**

Acetyl choline can bath pillow not succinylcholine (or you can use this ➔ aman can beat punon not succy)
Acetylcholine
Can ➔ Carbachol
Bath ➔ Bethanichol
Pillow ➔ Pilocarpine
Not ➔ nicotine
Succinylcholine

**indirect acting cholinomimetics**

<table>
<thead>
<tr>
<th>Carbamates</th>
<th>Alcohols</th>
<th>Organophosphates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neostigmine</td>
<td>Physostigmine</td>
<td>Edrophonium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parathion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malathion</td>
</tr>
</tbody>
</table>

**Indirect acting**

**Mnemonic** Newtonian physics ended para

Mathematics

Newtonian ➔ neostigmine
Physics ➔ physostigmine
Ended ➔ edrophonium
Para ➔ parathion
Mathematics ➔ malathion

**Drugs mnemonics**
**Direct acting cholinomimetics**

1 **Acetylcholine (both)**

   Not used therapeutically ➔ because rapidly destroyed by cholinesterase.

2 **Carbachol (both)**

   Glaucoma treatment

   Other uses are rare (due to high potency and long duration of action)

3 **Bethanichol (muscarinic)**

   B for Bladder atony

   B for Bowel atony

4 **Pilocarpine (muscarinic)**

   - Patient’s GCS
     
     G ➔ Glaucoma treatment

     C ➔ cystic fibrosis treatment

     S ➔ sojourn’s syndrome

   * Glaucoma treatment (increase drainage of aqueous humour)
     Chronically ➔ Open angle glaucoma (anterior chamber open
     Filtration drainage in tissue)

     Acutely ➔ angle closure glaucoma

   *Cystic Fibrosis

     Sweat test (to measure Na⁺ and Cl⁻ excreted in sweat)

**Indirect acting cholinomimetics**

1 **Neostigmine**    New Pump
New ➔ neostigmine
P ➔ Pseudo obstruction of colon
U ➔ Urinary retention resulting from General anaesthesia
M ➔ Myasthenia Gravis (improve Muscle tone)

P ➔ Pregnancy test (provoke menstruation in women with delayed Menstruation.)

2 Physostigmine

Phystostigmine is like pehelwan and mashoor pehelwan in Pakistan was Gama pehelwan

So

G ➔ glaucoma (acute)
A ➔ Atropa belladonna poisoning (atropine poisoning)
M ➔ Myasthenia gravis
A ➔ Alzheimer’s disease (improve short term memory)

3 Edrophonium

- Is end diagnosis of myasthenia gravis from cholinergic crisis
  Tension test is performed

Edrophonium is given to the patient and results are observed
- Myasthenia gravis ➔ reduce muscle weakness ➔ because it supply
Ach needed

- Cholinergic crisis $\rightarrow$ worsen weakness $\rightarrow$ because Ach is deficient

Patient

**Side-effects Produced By cholinomimetics**

**Mnemonic: DUMBLESS**

D $\rightarrow$ Diarrhoea.

U $\rightarrow$ Urination urgency

M $\rightarrow$ Miosis.

B $\rightarrow$ Bronchoconstriction

L $\rightarrow$ Lacrimation

E $\rightarrow$ emesis & excitation

S $\rightarrow$ salivation

S $\rightarrow$ sweetening

*From head to toe*

<table>
<thead>
<tr>
<th>System</th>
<th>Effect</th>
<th>Adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Excitation</td>
<td>Convulsions</td>
</tr>
<tr>
<td>Eye</td>
<td>Miosis</td>
<td>Miosis</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Dec heart rate $\rightarrow$ Dec contractibility Vasodilation</td>
<td>Bradycardia $\rightarrow$ reflex tachycardia</td>
</tr>
<tr>
<td>Bronchi</td>
<td>Bronchoconstriction</td>
<td>Aggravate asthma</td>
</tr>
<tr>
<td>GIT</td>
<td>Increase motility $\rightarrow$ Increase secretion $\rightarrow$</td>
<td>Diarrhoea Peptic ulcer</td>
</tr>
<tr>
<td>Glands</td>
<td>Sweetening lacrimation</td>
<td>Excessive</td>
</tr>
</tbody>
</table>
Contraindications

CAPI

C ➞ coronary insufficiency (because they dec heart rate) * this C also indicate these are contraindications of Cholinomimetics

A ➞ asthma (because they cause bronchoconstriction so...)

P ➞ Peptic Ulcer (because they cause increase in secretions)

I ➞ intestinal obstruction (they cause increase motility)
3. Cholinoreceptor Blockers and cholinesterase inhibitors
Or Parasympatholytic
Or Anticholinergics

Members and Classification

Anticholinergics

Non-selective muscarinic blockers
- Atropine
- Ipratropium
- Scopolamine

Ganglion Blockers
- Trimethopam
- Hexamethonium
- Nicotine

Mnemonic: **Aunty in school trimming her Nails**

Aunty ➔ atropine (nonselective muscarinic blocker)
In ➔ ipratropium (nonselective muscarinic blocker)
School ➔ scopolamine (nonselective muscarinic blocker)
Trimming ➔ trimethopam (ganglion blocker)
Her ➔ Hexamethonium (ganglion blocker)
Nails ➔ Nicotine (ganglion blocker)

**Drugs mnemonics**

<table>
<thead>
<tr>
<th>Non selective muscarinic Blockers</th>
</tr>
</thead>
</table>

**1 Atropine**

A 4 atropine

- A ➔ ankh (Eye) ➔ mydriatic and cycloplegic (used in measurement of refractory disorders because it will make you pupil big so disorders will be seen easily)
- A ➔ antispasmodic ➔ because they relax GIT and bladder
- A ➔ antisecretory agent in lower respiratory tract (Preanesthetic use)
- A ➔ Antidote ➔ in case of cholinesterase inhibitors
Organophosphate poisoning

Atropine overdose
- Hot as hare
- increase temperature
- mad as hatter
  (confused and delirium)

Red as beat
- (flushed face)
- dry as bone
- decrease secretions

2 Ipratropium
- Asthma (inhaler)
- COPD

3 Scopolamine
- SMS
  - S ➔ short term memory loss
  - MS ➔ Motion sickness

Ganglion Blockers

1 Trimethoprim
T for tension
Used in Hypertension caused by pulmonary hypertension

2 Hexamethonium
H for hypertension
Used in hypertension (obsolete)

3 Nicotine
N for no use

Toxicity
All parasympathetic effects Blocked + sedation + hyperthermia
opposite of DUMBESS

Ganglion Blockers ➔ Block all autonomic effects by Blocking the autonomic ganglia
04. Sympathomimetics
Drugs
adrenergic Drugs

Members and Classification

Sympathomimetics

Direct acting

- Alpha agonists
  - Phenylephrine
  - Clonidine
  - Norepinephrine

- Beta agonists
  - Dobutamine
  - Albuterol
  - Isoproterenol

Indirect acting

- Amphetamine
- Cocaine

Direct acting

Mnemonic: Please call Noor do all isoproterins

Please ➔ Phenylephrine (alpha 1)

Call ➔ Clonidine (alpha 2)
Noor ➔ Norepinephrine (alpha non selective)
Do ➔ Dobutamine (beta 1)
All ➔ albuterol (beta 2)
Isoproteins ➔ isoproterenol (beta 3)

**Indirect acting**

Mra aik friend hay name inam or mujhay wo tab hi yad karta hay jab usko loi kam ho
I remember this as
Inam ko cam (cocam)
   Coc ➔ cocaine
   Am ➔ amphetamine

**Effects produced from head to toe are**

<table>
<thead>
<tr>
<th>system</th>
<th>Effect produced</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Catecholamines ➔ do not enter brain Amphetamine ➔ stimulatory effect</td>
</tr>
<tr>
<td>Eye</td>
<td>mydriatic ➔ alpha one (Big eyed fish) decrease aqueous humour formation ➔ alpha 2</td>
</tr>
<tr>
<td>Bronchi</td>
<td>Alpha 1 ➔ Bronchoconstriction (less marked) Alpha 2 ➔ Bronchodilation (more marked)</td>
</tr>
<tr>
<td>Heart</td>
<td>Beta 1 and Beta 2 • inc firing of pacemaker • inc force of contraction • inc AV conduction velocity</td>
</tr>
</tbody>
</table>
Pharmacology Mnemonics and Short Notes
By Muhammad Ramzan Ul Rehman

<table>
<thead>
<tr>
<th>GIT</th>
<th>Relation of smooth muscles Sphincters ➔ tone increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Bladder</td>
<td>Increase sphincter tone</td>
</tr>
<tr>
<td>Uterus</td>
<td>Relaxation (beta 2 mediated)</td>
</tr>
<tr>
<td>Vascular effects</td>
<td>Vascular Effect</td>
</tr>
<tr>
<td></td>
<td>• A ➔ C for contraction (alpha 1 mediated)</td>
</tr>
<tr>
<td></td>
<td>• B ➔ D for dilation (beta 2 mediated)</td>
</tr>
<tr>
<td>Metabolic effects</td>
<td>Beta 1➔ renin secretion</td>
</tr>
<tr>
<td></td>
<td>Beta 2</td>
</tr>
<tr>
<td></td>
<td>• increase gluconeogenesis</td>
</tr>
<tr>
<td></td>
<td>• increase glycogenolysis</td>
</tr>
<tr>
<td></td>
<td>• increase insulin secretion (increase uptake of glucose by muscles)</td>
</tr>
<tr>
<td></td>
<td>Beta 3 ➔ Lipolysis</td>
</tr>
</tbody>
</table>

**Drugs Mnemonics**

**Direct acting Sympathomimetics**

1 **Phenylephrine (alpha 1)**

Two pherends (friends) Humpty dumpty & Super man went on alpha ones party

Pherends ➔ phenylephrine
Humpty ➔ hypertension
Dumpty ➔ nasal decongestant
Super ➔ supraventricular tachycardia
Man ➔ mydriatic (ophthalmic use)

2 Clonidine (alpha 2)
Clona said .....Hy two (to) Ben!
Two for alpha 2
Hy ➔ Hypertension
Ben ➔ minimize withdrawal symptoms of benzodiazepines

3 Norepinephrine (alpha non selective)
Noor shocked us by her marks
Norepinephrine is basically used in treatment of sock (septic and neurogenic)

4 Dobutamine (Beta 1 ➔ we have one heart in our body)
Used to increase cardiac output in congestive cardiac failure
◊ produces little change in heart rate
◊ Do not significantly elevate myocardial oxygen demand (advantage over other sympathomimetic

◊ Increase AV conduction ➔ caution for atrial fibrillation

5 Albuterol (beta 2 ➔ we have two lungs)
Albuterol lessens bronchospasm
6 Isoproterenol (beta 1 and beta 2) ➔ we have one heart and two lungs

- Stimulator of heart in emergency conditions
- Nebulizer for asthma (bronchodilator)
- In Bradycardia

7 Epinephrine or adrenaline (alpha and beta receptors)

ABCDE

- A 4 adrenaline
  - Anaphylactic shock
  - Asthma (acute attacks)
  - Anaesthesia (local ➔ increase duration)
  - Asystole
- B ➔ Bronchoconstriction
- C ➔ Cardiac arrest
D → dizziness and headache
E → Eyes (treatment of glaucoma → 2 percent solution is used)

**Side effect (C₃)**
- CNS → disturbance + anxiety + fear + headache + tremors
- Cardiac arrhythmias
- Cerebral haemorrhages (due to elevated Blood pressure)

**Interactions**
Person having cocaine or suffering from hyperthyroidism and you gave him epinephrine → he will have exaggerated cardiac effects of epinephrine

**8 Dopamine (alpha and beta effects)**

D for Dil walay
- + Inotropic effects (inward movements mean contractibility)
- + chronotropic effects (chronic time related mean rate of contraction)
- Blood flow → increase blood flow to viscera’s and kidneys

Used in Shock treatment. As it stimulate heart by beta 1 receptors
- Preferred over norepinephrine because it increases blood flow to viscera’s and kidney
- Increases glomerular filtration rate

While nor epinephrine decreases blood flow to kidney may lead to renal shutdown.

**Adverse effects**
- Excessive sympathetic effects
- Rapidly metabolized
9 Metoprolol and terbutaline ➔ beta 2 receptor ➔ bronchodilators

◊ Used in asthma.

**Indirect acting Sympathomimetics**

**1 Amphetamine**

Displace stores of nor epinephrine from nerve endings

**Uses**

A hyperactive naughty child depressed her Ant.

A ➔ amphetamine

Hyperactive ➔ *

Naughty ➔ Narcolepsy

Child ➔ CNS stimulant

Depressed ➔ Depression treatment

Her ➔ Hypotension

Ant ➔ Apatite control

**Adverse effects**

◊ Hypertension (sympathetic drug and sympathetic system increase blood pressure by increasing heart pumping)

◊ Dependence liability high (Amphetamine is like a Fanta bottle when I drink I liked so much that now I am dependent on it)

◊ Pregnancy ➔ developmental problems in child

**2 Ephedrine**

Like amphetamine
✧ Increase half life
✧ Less addiction liability.
05. ADRENOCEPTOR BLOCKERS or SYMPATHOLYTICS

Members and Classification.

Adrenoreceptor Blockers

<table>
<thead>
<tr>
<th>Alpha Blockers</th>
<th>Beta Blockeres</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non selective</td>
<td>Nonselective</td>
</tr>
<tr>
<td>Parabolemine</td>
<td>Parabolemine</td>
</tr>
<tr>
<td>Yohimbin</td>
<td>Yohimbin</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>Phentolamine</td>
</tr>
<tr>
<td>Phenoxylamine</td>
<td>Phenoxylamine</td>
</tr>
<tr>
<td>Beta 1</td>
<td>Beta 1</td>
</tr>
<tr>
<td>Beta 3</td>
<td>Beta 3</td>
</tr>
</tbody>
</table>

Mnemonic: pit-bull (dog name) par yonhi pathar maro at buttocks

Pit-bull

✧ Pit ➔ phentolamine (alpha nonselective) reversible
Pit-bull ➔ phenoxybenzamine (alpha nonselective) irreversible
Par ➔ parazosin (alpha 1)
Yonhi ➔ yohimbine (alpha 2)
Maro ➔ metoprolol (beta 1)
At ➔ atenolol (beta 1)
Buttocks ➔ butaxamine (beta 2)

This was one example from each group

**Beta Blockers**

The NEPAL prime minister

- The ➔ timolol
- N ➔ Nadolol
- E ➔ Esmolol
- P ➔ Pandolol
- A ➔ Atenolol
- L ➔ Labetolol
- Prime ➔ propranolol
- Minister ➔ metaprolol

**TRICK**

A to M are Beta 1 Blockers

Rest from N to Z are non-selective Beta Blockers

Beta 2 Blocker ➔ Butaxamine (only)

**Cardioselective Beta Blockers or Beta 1 Blockers**

Beta blockers acting exclusively at myocardium
Beta blocker ➔ butaxolol
Acting ➔ acebutalol
Exclusively ➔ Esmolol
At ➔ atenolol
Myocardium ➔ metaprolol

**Effects Produced by Alpha blockers**

Most important effects are of CVS effects

- No significant direct cardiac effects are produced by them
- They cause baroreflex mediated tachycardia (reflex activated due to decrease of arterial pressure)

**Epinephrine reversal phenomena**

*Blood Pressure effect of Epinephrine*

- Increase of Blood Pressure occurs (alpha mediated more alpha 1) (Presser effect)
- Because epinephrine act both on alpha and beta
  But effect of alpha is more so increase B.P occurs

But if Person is on Alpha Blockers and we gave him epinephrine then
- Decrease of Blood Pressure occurs (Beta mediated as alpha are on Block) (depressor effect)

**Effects**

<table>
<thead>
<tr>
<th>A ➔ Alpha</th>
<th>C ➔ Vasoconstriction</th>
</tr>
</thead>
<tbody>
<tr>
<td>B ➔ Beta</td>
<td>D ➔ Vasodilation</td>
</tr>
</tbody>
</table>
Selective alpha 1 blockers are more associated with cardiac symptoms than non-selective alpha blockers

But

Non-selective alpha blockers are more associated with reflex tachycardia than alpha 1 blockers

**Clinical Uses of Alpha Blockers**

**PMDC**

P<sub>4</sub>

- Pressure ➔ Blood Pressure ➔ Hypertension
- Pheochromocytoma
- Penile erection ➔ phentolamine and yohimbine mediated
- Peripheral vascular disease

M ➔ Migraine

D ➔ Disorders related to sleep & psychotic disorders

C ➔ Congestive cardiac failure

**Drugs Mnemonics**

1. **Phentolamine (alpha non selective and reversible blocker)**

   P ➔ Pheochromocytoma
   
   And antidote in alpha agonist overdose

2. **Phenoxybenzamine (alpha non selective and irreversible blocker)**

   PCR
   
   P ➔ Pheochromocytoma
C ➔ carcinoid use
R ➔ Reynard’s disease

3 Parazosin (alpha 1 Blocker)

P for parazosin
❖ Pressure ➔ increase B.P ➔ hypertension
❖ Benign prostate hyperplasia

4 yohimbine (alpha 2 blocker)

Obsolete use for erectile dysfunction

Side effects

OTG (OTG software is an android mobile software used to attach use to mobile) or you can use GOT

O ➔ orthostatic hypertension
T ➔ reflex tachycardia
G ➔ gastric distress

Beta Blockers
Clinical uses

MAG took MAHA

CNS
M ➔ migraine
A ➔ anxiety

EYE
G ➔ Glaucoma

Thyroid
Took ➔ thyroid storm

CVS (MAHA)²
M ➔ Myocardial infarction + Cardiomegaly
A ➔ Angina + arrhythmias
H ➔ Hypertension + Heart failure
A ➔ Aortic aneurysm + with alpha blockers to treat pheochromocytoma.
1 Non Selective Beta Blockers

- Uses are MAG took MAHA.
- Additionally Propranolol is also used in stage fright
- Timolol ➔ used in Eyes (Because it lacks local anaesthetic activity)
- Pandolol ➔ it is a partial agonist so can be used in asthmatic persons (while others are contraindicated)
- Nadolol ➔ longer duration

2 Beta 1 Blockers (Cardioselective beta blockers)(Atenolol)

- Used for MAHA
- Esmolol also used for thyroid storm treatment

3 Beta 2 Blocker (butaxamine)

No use (research purposes)

Side effects of beta blockers

(confused and delerium) BBC London TV

B ➔ Bradycardia and hypotension
B ➔ Blood Pressure drop
And Bronchoconstriction
C ➔ Cough
London ➔ lipid metabolism disturbance (Beta 3)
T ➔ Tiredness
V ➔ Vivid dreams and yawning

**Contraindications for Beta Blockers**

**ABCights**

A ➔ asthma
B ➔ Heart Block
C ➔ COPD and cough
D ➔ Diabetic (as beta 2 releases insulin and we are going to inhibit Beta 2 so patient will be on risk)
E ➔ electrolyte imbalance (hyperkalemic patient at risk)

**Usage in Asthma patient**

As Beta Blockers are contraindicated in asthmatic person because they causes bronchoconstriction

So there are some beta blockers with slight agonist activity and are going to least effecting asthmatic person so we are to use them they are

- Acebutalol
- Esmolol
- Metoprolol

In fact these are beta 1 selective and beta 1 receptor are only in heart not in lungs so safer for them

Full antagonist like propranolol (beta non selective ➔ also have beta Blockage effect on beta 2 receptor present in lungs) causes severe bronchospasm so contraindicated in asthmatic person
Usage in Glaucoma patient

Drugs lacking local anaesthetic activity like Timolol are used while other drugs causes local anaesthesia and result in loss of reflexes.
Drugs acting on Smooth Muscles
06. Histamine and Serotonin and Ergot Alkaloids

**Histamine Effects**

- **H** → HCl Production
- **I** → Inflammation
- **S** → Strong vasodilation
- **T** → Therapeutic value none
- **A** → Allergy
- **M** → By Mast cells
- **I** → Ig E
- **N** → Narrow air ways (bronchoconstriction)

**Location of Histamine Receptors**

**H1 Receptor**

Located in smooth Muscle (imagine shape of smooth Muscle just like one for me so H1 is in smooth Muscle)

**H2 Receptor**

Located in stomach (If I rotate stomach to 90 degree left then it make me shape of 2 so H2 is in Stomach)
H3 Receptor

Located in Endings of Nerves (Mean in Nerve Endings).

H4 Receptor

Located in Leukocytes (Do you remember Charlie ➔ Char for 4 and lie for Leukocytes)

Location of Serotonin Receptors

HT 1D Receptors

D for Dimag so they are located in Brain
HT 2 Receptors

Two mean second and second mean smooth Muscles
So second histamine is in smooth Muscles

HT 3 Receptors

Located in Endings of Nerves
And Third letter of ABC is C so I can say HT 3 is in Nerve endings of chemoreceptor Trigger zone.

5HT 4 Receptor

Enteric Nerve endings (khuch khud bhi yad kar lo)

Important Drugs and members from these Groups

H1 Blockers

First Generation

DiDi promotes cycling

Di ➔ Diphenhydramine
Di ➔ Dimenhydrinate
Promotes ➔ Promethazine
Cycling ➔ cyclizine

Mechanism

❖ Histamine receptor 1 Blockers
❖ Structurally resemble muscarinic and adrenergic receptors

Antihistamine + anticholinergic + antiemetics + antitussives
Clinical Uses

DiDi have mobile NGO

Have ➔ hay fever

Mobile ➔ anti motion sickness use

NGO ➔ angioedema

Side effects

DiDi have mobile NGO so stays away from home and many time she have to sleep in an automobile

So she sleeps in automobile

❖ Sleepy or sedation

❖ Automobile ➔ autonomic side-effects

Second generation

Its member is cetirizine and I remember this as SITRIZINE while so S for second, S for sitrizine this sounds fair

*Generation 2 lacks effects on Autonomic receptors and are not Antimotionsickness agent*

Another member is LORAtidine

Other all stuff remain same as that of First Generation

Side effects are less

H 2 Blockers

FRaNCeTidine

F ➔ Famo + tidine ➔ Famotidine

R ➔ Rani + tidine ➔ ranitidine

N ➔ Niza + tidine ➔ Nizatidine
C ➔ Cime + tidine ➔ Cimetidine

Femo rani niza (Nazia) Cime sounds just
Like Girl name
and tidine in Punjabi we say tid to abdomen so you can remember this as
Femo, Rani, Niza and Cime are Girls having Big Tids and there uses will in-
dicate that they are acting on tids

**Uses**

GPS Dr

G ➔ GERD
P ➔ Peptic ulcer
S ➔ Stress related gastroenteritis
Dr ➔ Dyspepsia

**5HT 1 agonists**

Suma Riza farva nay zalim nara lagaya (mnemonic from Fozia shafi from
Nishter Med college)

- Suma ➔ Suma + triptan ➔ Sumatriptan
- Riza ➔ Riza + triptan ➔ Rizatriptan
- Farva ➔ Frova + triptan ➔ Frovatriptan
- Zalim ➔ Zalmo + triptan ➔ Zalmotriptan
- Nara ➔ Nara + triptan ➔ Naratriptan

Or nara itnain zor ka tha k logon k sar main dard ho gia or unk chest main
dard shro ho gia

**Uses**
- Migraine
- Cluster headache

**Adverse effect**
- Chest pain
- Dizziness

### 5HT 2 antagonists

Two mean K2 (mountain in Pakistan)

K 2 → ketaserine (2 → 5HT2 antagonist)

**Uses**

Two for tension so used in hypertension

**Adverse effect**

Hypotension.

### 5HT3 Antagonists

Location of HT3 receptor is

- **HT 3 Receptors**
  - Located in Endings of Nerves
  - And Third letter of ABC is C so I can say HT 3 is in Nerve endings of chemoreceptor
  - Trigger zone.

So it will have role in vomiting
And its antagonists will stop vomiting

**Use**
- Antiemetic in chemotherapy
- Post-operative vomiting

**Drugs**
Imagine Granny is driving a Honda motor cycle and everyone saying hello! Hello!

- Granny ➔ Granisetron
- hONDA ➔ Ondasetron

Another member is Alosetron that is used in irritable bowel syndrome

**Adverse effect**
- Arrhythmias.

### 5HT4 Partial agonist.

5HT4 receptor location is

**5HT 4 Receptor**

Enteric Nerve endings (khuch khud bhi yad kar lo)

So its use will be somewhere in Git it increases GIT motility so used in Irritable bowel disease and adverse effect will be diarrhoea

**Drug** ➔ Tegaserod

**Ergot Alkaloids**

These are Partial agonists at
- Alpha adrenoreceptors
- 5HT receptors
- Dopamine receptors

### Drugs

They are ergot alkaloids and erg comes in their names

- Ergotamine
- Ergonavine
- Another member is bromocriptine

### Uses

HOME (I Built two homes in this book one in ergot alkaloids and another in Loop diuretics so you will visit my other Home in adverse effects of Loop diuretics)

- H ➔ Hyperprolectenemia (Bromocriptine is release inhibitor of prolactin)
- H ➔ Also used in Parkinsonism
- O ➔ Obstetric Bleeding ➔ Ergotamine and Ergonavine erg containing members are used because they causes strong vasoconstriction so they will stop bleeding
- M ➔ ergotamine used in migraine in acute attacks and in prophylaxis
- E ➔ expel baby out (abortion and miscarriage) ➔ because they produces powerful uterine contractions (Ergonavine is prototype)

### Adverse effects

- Ischemic gangrene (because they produces long lasting vasoconstriction
- Uterine effects ➔ sensitization of uterus to alkaloids
- Hallucination
- GIT effects
Pathways

- Lipoxigenase pathway \( \rightarrow L \rightarrow \text{Leukotrienes} \)
- Cyclooxygenase pathway \( \rightarrow \) others all
  - Prostaglandins
  - Prostacyclin
  - Thromboxane

Mechanism of action

Action are brought about by cell surface G protein coupled receptors

Some inhibitors to be remember

- Corticosteroids \( \rightarrow \) Phospholipase A\(_2\) (convert phospholipid \( \rightarrow \) Arachidonic acid)
- NSAIDS \( \rightarrow \) Inhibit COX (cyclooxygenase)
- Zeliuton \( \rightarrow \) Ze + Li \( \rightarrow \) Ze indicate this is Zeliuton and Li indicate it is lipoxigenase enzyme inhibitor
- Zafirlukast \( \rightarrow \) zafir+ Luko \( \rightarrow \) Zafir indicated this is zafirlukast and Leuko indicate that this inhibit Leukotriene receptor antagonist
- Montelukast \( \rightarrow \) Brother of zafirlukast

Effects Produced By Eicosanoids.

On Blood Vessels

Imagine a circle expanding

Circle \( \rightarrow \) Prostacyclin (PGI\(_2\))
Expanding ➔ PG E₁ and PGE₂

So their action will be vasodilation by expanding the calibre of the blood vessel

**On Bronchi**

Circle expanding again and here will be Bronchodilation.

**On Platelet aggregation**

PGI₂ and TXA₂ both are opposition leaders

- PGI₂ ➔ causes Bronchodilation that will help in making blood flow easy so they will decrease platelet aggregation
- TXA₂ ➔ is opposition leader so it will increases platelet aggregation

**On uterus**

PGE₂ ➔ analogue Dinopreston (have dual action on uterus)

- In lower concentration ➔ causes contractions
- In higher concentrations ➔ causes relaxation

Di mean two this mean Dinopreston is having dual action.

PGF₂ ➔ its analogue is Latinopreston.

*Dinopreston and Latinopreston ➔ are used in 2ходят trimester abortion*

**Chemotactic factor**

B for Bhago ➔ B₄ Bhago ➔ LTB₄ is leukocyte chemotactic factor

<table>
<thead>
<tr>
<th>Clinical Uses</th>
</tr>
</thead>
</table>

**Obstetrics**

Dinopreston

and latanopreston ➔ are used in 2 trimester abortion
• Dinopreston is PGE$_2$ analogue
• While Latanoprestone is PGF$_2$ analogue

So we can say E$_2$ and F$_2$ analogues are used in 2$^{nd}$ trimester abortion.

Later stages they induces labour but are not used clinically due to their side-effects.

**Paediatrics**

PGE$_1$ (Misoprostol) ➔ used to maintain patent ducts arteriosus before surgical cessation is done

MisoProstol ➔ maintain patent ducts arteriosus

**Dialysis**

PGI$_2$ (epoprostenen) ➔ prostacyclin analogue is used to prevent platelet aggregation in dialysis machine due to platelet aggregation antagonist.

**Pulmonary use**

PGI$_2$ (epoprostenen) ➔ used in pulmonary hypertension

**Peptic Ulcer**

PGE$_1$(Misoprostol) is used

**Genitourinary tract**

PGE$_1$ (Misoprostol) is used

**Ophthalmology**

PGF$_2$ (Latanoprostol) ➔lentina = Lenz + retina.

In glaucoma
Drugs which is which

\( \text{PGE}_2 \)
Dinoprostone \( \Rightarrow \) Di mean two and Die mean Di + E mean 2E

\( \text{PGE}_1 \)
Misoprostol \( \Rightarrow \) M for mono so it is 1 and if we rotate M it will Become E so it is 1E

\( \text{PGF}_2 \)
Latanoprost \( \Rightarrow \) Lat mean Laat mean Leg and leg has foot so from foot it is F two

\( \text{PGI}_2 \)
Epoprostenol \( \Rightarrow \) khudyadkarO

Eicosanoid antagonists

1 Leukotriene antagonist

Lipoxygenase inhibitors \( \Rightarrow \text{Zeliuton} \)

- Zeliuton \( \Rightarrow \) Ze + Li \( \Rightarrow \) Ze indicate this is zeliuton and Li indicate it is lipoxygenase enzyme inhibitor

- It Blocks the synthesis of leukotrienes
- Used in prophylaxis of asthma

Leukotriene receptor inhibitors \( \Rightarrow \) zafirlukast and Montelukast

- Zafirlukast \( \Rightarrow \) zafir + Luko \( \Rightarrow \) Zafir indicated this is zafirlukast and Leuko indicate that this inhibit \textbf{Leukotriene receptor antagonist}

- Montelukast \( \Rightarrow \) Brother of zafirlukast
Block cytoplasmic leukotriene receptors
Used in prophylaxis of asthma

2 Cyclooxygenase inhibitors (NSAIDS)

Nonselective COX inhibitors
- Ibuprofen (Reversible)
- Indomethacin (Reversible)
- Aspirin (Irreversible)

COX2 Selective
- Celecoxib (damage produced by cox₁ is prevented)

Will discuss NSAIDS in detail in NSAIDS section.
08. Nitric oxide donors and inhibitors

Nitric oxide synthase inhibitors

NCB (Nation commercial bank’s employers) in medical examination.

**Isoform 1**
- N $\rightarrow$ nNOS $\rightarrow$ neuronal
- C $\rightarrow$ cNOS $\rightarrow$ epithelial
- B $\rightarrow$ bNOS $\rightarrow$ epithelial

**Isoform 2**
- In $\rightarrow$ iNOS $\rightarrow$ Macrophages
- Medical $\rightarrow$ mNOS $\rightarrow$ muscles smooth

**Isoform 3**
- Exam $\rightarrow$ eNOS $\rightarrow$ endothelial

**NOS inhibitors**

NOS inhibitor is N-methyl arginase

Synthesis of NO can be inhibited by Heme and Hemoglobin
Effects Produced

Nitric oxide (NO) signaling pathway for SMC relaxation

- Smooth muscles ➔ vasodilator
- Cell adhesions ➔ decrease platelet aggregation and decrease neutrophil adhesion
Facilitate inflammation
Act as neurotransmitter

**Uses**
NO papa

NO → uses of NO
P → Pressure → Blood pressure control → hypertension
A → antianginal → nitro-glycerine
P → pulmonary hypertension and in penile erection maintenance in erectile dysfunction
A → antioxidant and antithrombic

**Risk factors**

- smokers
- Septic shock (may exaggerate)
- Hypotensive

**Side-effects**

TOTM

T → tachycardia → by baroreceptor reflex
O → orthostatic hypotension
T → throbbing headache
M → methemoglobinemia
09. Vasoactive Peptides

Renin-angiotensin antagonists

**Actions:**
- Renin inhibitors
  - Aliskiren
  - Renin inhibitor → reduce angiotensin 1, 2 and aldosterone

**Use:**
- Hypertension

**Adverse effects:**
- Angioedema and renal impairment
ACE Inhibitors

Pril sisters ➔ captopril and enapril

⇒ Inhibit ACE enzyme ➔ decreases AT₂ and aldosterone secretion and increases bradykinin secretion.

Use

⇒ Heart failure
⇒ Hypertension

Side effects HTC (mobile company)

H ➔ hyperkalemia
T ➔ teratogenic
C ➔ cough

AT receptor antagonists

Sartan brothers ➔ Losartan and Valsartan

⇒ AT₁ receptor inhibitors ➔ reduces effects of angiotensin II

Uses and adverse effects are almost same as Pril sisters
10. Drugs used in asthma treatment

Drugs used and classification

<table>
<thead>
<tr>
<th>A</th>
<th>Adrenergics</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>Steroids</td>
</tr>
<tr>
<td>T</td>
<td>Theophylline</td>
</tr>
<tr>
<td>H</td>
<td>Hygienic measures</td>
</tr>
<tr>
<td>M</td>
<td>Muscarinic antagonists</td>
</tr>
<tr>
<td>A</td>
<td>Antinflammatory</td>
</tr>
<tr>
<td></td>
<td>Antibiotics</td>
</tr>
</tbody>
</table>

Beta agonists

Asif is asthmatic person want to buy some Beta adrenergic drugs
A ➔ albuterol
S ➔ salmeterol
I ➔ indacaterol
F ➔ formoterol

First member Albuterol is short acting while other three are long acting beta agonists

And he run short of money so he goes to ATM now he can buy two other short acting beta agonists also.

A ➔ albuterol
T ➔ terbutaline
M ➔ metaproterenol

**Uses**

Short acting ➔ in acute treatment

Long acting ➔ in prophylaxis and chronic use

- Long acting are not used in acute attacks because of their slow onset of action

They are first line of treatment in asthma treatment and are used in combination with corticosteroids and are also effective in COPD

**Adverse effects**

Important adverse effects are

- Skeletal muscle tremors
- If used excess ➔ arrhythmias

**Non selective Sympathomimetics**

Epinephrine and isoproterenol ➔ were also used previously
**Indirect acting Sympathomimetics**

Ephedrin ➔ release stored catecholamines ➔ obsolete use

---

**Steroids ➔ Corticosteroids.**

Birthday party

- **Inhaled corticosteroids**
  - Birth ➔ bachlomethasone
  - Day ➔ dexamethasonium

- **Systemic corticosteroids**
  - Party ➔ prednisone (oral) and prednisolone (I/V)

Corticosteroids inhibit phospholipase A<sub>2</sub> that results in decrease formation of inflammatory mediators

- Corticosteroids ➔ Phospholipase A<sub>2</sub> (convert phospholipid ➔ Arachidonic acid)

**Side effects**

- **Inhaled**
  - Pharyngeal candidiasis
  - Other effects are minimal because of lesser systemic absorption

- **Oral and Parenteral**

  Cushingoid
  - C ➔ cataract
  - U ➔ ulcers
S ➔ skin stria + skin thinning + salt retention
H ➔ Hirsutism + hypertension + hyperglycaemia
I ➔ infections
N ➔ necrosis (avascular necrosis of femoral head)
G ➔ GIT ulcers
O ➔ obesity (buffalo hump obesity) + osteoporosis
I ➔ immune suppression
D ➔ diabetes mellitus

Theophylline.
(Methylxanthine derivative)

Theophylline inhibit phosphodiesterase inhibit degradation of cAMP increase level of cAMP relax bronchial smooth muscles

It also inhibit synthesis of leukotrienes and inhibit TNF alpha slowing the inflammatory process

**Uses**
- Prophylactic agent in asthma treatment
- COPD
- Infant apnea (in premature baby)

**Adverse effects**

**TAAS**

- T $\rightarrow$ tremors (T also indicate this drug is theophylline)
- A $\rightarrow$ arrhythmias
- A $\rightarrow$ anorexia and asleep
- S $\rightarrow$ seizures

Caffeine also produces similar effects

**Hygienic measures.**

This is just to make word for asthma best method to avoid asthmatic attacks is to avoid trigger (stimulant of asthmatic attacks) Like allergens, pollutants etc.

**M uscarinic antagonists.**
Ipratropium

- Asthma
- COPD

Prevent bronchoconstriction mediated by vagal discharge

⇒ Have no effect on chronic inflammation

Side effects

Minimum side effects of inhaler (minimum atropine like)

1) Leukotriene antagonists
1 Leukotriene antagonist

Lipoxygenase inhibitors ➔ Zeliuton

- Zeliuton ➔ Ze + Li ➔ Ze indicate this is zeliuton and Li indicate it is lipoxygenase enzyme inhibitor

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- Montelukast ➔ Brother of zafirlukast

- Block cytoplasmic leukotriene receptors

Used in prophylaxis of asthma

2) Mast cell stabilizers

After a long fight with foreign invaders masto cell got exhausted he started watching cartoon network (CN) to stabilize himself.

C ➔ cromolyn

N ➔ nedocromil

- They reduce release of inflammatory mediators from sensitized mast cells.
- Used especially in children (as children watch cartoon network profoundly)
- Rarely used for prophylaxis
• Also used in other allergies like ophthalmic, nasopharyngeal and GIT allergies

May cause cough as adverse effect.

3) Antibodies (Omalizumab)

Aik mali tha to usko severe asthma hogia or us nain har kisam ki drug li and no response tu aik dr bola O mali! Antibody lay lo us say thk ho jaey ga

Omalizumab ➔ Bind to IgE antibodies on mast cells ➔ reduce reaction to allergies

• Used as prophylaxis of severe respiratory asthma not responsive to all other drugs

Precipitating factors of asthma

Diplomat

D ➔ Drugs (Aspirin + NSAIDS + Beta antagonists) and DNA mean genatic factors

I ➔ Infections (URTIs and LRTIs)

P ➔ Pollutants (at work and at home)

L ➔ laughter (emotions)

O ➔ Obesity

M ➔ Mites

A ➔ activity (exercise) + atopic disease

T ➔ temperature (cold) + Tabaco (smocking)

Causes of asthma

A ➔ Allergens (most of the precipitating factors)

S ➔ small airways
T ➔ Tracheal obstruction
H ➔ heart failure
M ➔ mastocytosis
A ➔ anaphylaxis

**Treatment strategies.**

1) Avoidance of antigen or causative factor
2) Twice attacks or less per weeks
   a. Short acting beta agonists (SABA)
3) More than twice a weak
   a. Add inhaled corticosteroids to treatment (ICS)
4) Daily ➔ moderate attacks
   a. Long acting beta agonists added (LABA)
5) Multiple attacks per day
   a. ICS + SABA dose increased
6) Severe multiple attacks per day
   a. Systemic corticosteroids added hospitalized if needed
Cardiovascular Pharmacology
11. Drugs used in Hypertension

- A: Adrenergics, ACE inhibitors, Angiotensin receptor inhibitors, Aliskiren
- B: Beta blockers
- C: Calcium channel blockers
- D: Diuretics
- E: Endothelial antagonists
- F: Facilitate Vasodilation
- G: Ganglion blockers
Alpha adrenoreceptor agonists (centrally act on Alpha 2 receptors)

2 Clonidine (alpha 2)

Clonidine said ..... Hy two (to) Ben!

Two for alpha 2

Hy ➔ Hypertension

Sudden discontinuation causes rebound hypertension due to salt retention as compensatory mechanism.

Rebound increase in blood pressure can be controlled by reinstitution of the clonidine therapy or administration of alpha blockers such as phentolamine
Alpha adrenoreceptor inhibitors

3 Parazosin (alpha 1 Blocker)

P for parazosin

❖ Pressure ➔ increase B.P ➔ hypertension

❖ Benign prostate hyperplasia

ACE Inhibitors

ACTION— ↓ PERIPHERAL VASCULAR RESISTANCE WITHOUT:

❖ • ↑ CARDIAC OUTPUT
❖ • ↑ CARDIAC RATE
❖ • ↑ CARDIAC CONTRACTILITY
ACE Inhibitors

Pril sisters’ ➔ captopril and enapril

⇒ Inhibit ACE enzyme ➔ decreases AT2 and aldosterone secretion and increases bradykinin secretion.

Use

⇒ Heart failure
⇒ Hypertension

Side effects HTC (mobile company)

H ➔ hyperkalemia
T ➔ teratogenic
C ➔ cough

AT receptor antagonist.

AT receptor antagonists

Sartan Brothers ➔ Losartan and Valsartan

⇒ AT1 receptor inhibitors ➔ reduces effects of angiotensin II

Uses and adverse effects are almost same as Pril sisters
Aliskiren

Renin inhibitor ⇒ reduce angiotensin 1, 2 and aldosterone

Use

Hypertension

Adverse effects

Angioedema and renal impairment

Beta antagonists.

B-Blockers: LOLS

Beta Blockers
- Reduces cardiac output
- Reduction in renin release

Propranolol atenolol and labetalol are used commonly

**CVS (MAHA)**

M ➔ Myocardial infarction + Cardiomegaly

A ➔ Angina + arrhythmias

H ➔ **Hypertension + Heart failure**

A ➔ Aortic aneurysm + with alpha blockers to treat pheochromocytoma.

**THE “LOL” TEAM**

The “LOL” team blocks hypertension by “blocking” (decreasing) the contractility in the heart, the renin release from the kidneys, and the sympathetic output from the vasomotor center of the brain.
For further reading go to chapter of beta blockers

Side effects of beta blockers

(confused and delerium) **BBC London TV**

- B ➔ Bradycardia
- B ➔ Blood Pressure drop
  And Bronchoconstriction
- C ➔ Cough
- London ➔ lipid metabolism disturbance (Beta 3)
- T ➔ Tiredness
- V ➔ Vivid dreams and yawning

![BBC London TV]

**C**

\( \text{Ca}^{+2} \) Channel Blockers.
**Actions**

ACTION - BLOCKS CALCIUM ACCESS TO CELLS

CAUSING:
- \( \downarrow \) CONTRACTILITY +
- \( \downarrow \) CONDUCTIVITY OF THE HEART
- \( \downarrow \) DEMAND FOR OXYGEN

**Uses**

**Ca mash**

- C ➔ cerebral vasospasm
- A ➔ angina
- M ➔ migraine
- A ➔ atrial flutter and fibrillation
- S ➔ supraventricular tachycardia
- H ➔ hypertension
Adverse effects

Happy Dec. (happy December)
Happy → hypotension and heart failure
D → cardiac depression + dizziness
E → pulmonary oedema
C → constipation

Diuretics.

Loop diuretic → furosemide (lofer drug)
Thiazide diuretic → hydrochlorothiazide
Both are used in hypertension and heart failure

Endothelial Antagonist.

Busentan (Endothelial A and B receptor antagonist)

Use in pulmonary hypertension

Facilitate vasodilation.
## NO Releasers

### Hydralazine

- **Release NO by endothelial cells** → NO causes vasodilation

### Uses
- Hydralazine is used in hypertensive emergencies
- Also used in heart failure

### Nitroprusside

- **Release NO from drug molecule**

### Uses
- Hypertensive emergencies
- Cardiac decompensation

⇒ Adverse effects for NO releasers will be TOTM from chapter of NO

## K⁺ channel Openers

### K⁺ channel Openers

- **minoxidil (oral)**
- **Diazoxide (parenteral)**
- **Ca²⁺ channel blocker**

### NO releasers

- **Hydralazine** (oral)
- **Nitroprusside** (parenteral) name have P so.

### K⁺ channel openers

- **minoxidil** (oral)
- **Diazoxide** (parenteral)

### Ca²⁺ channel blocker

- detail above
**Minoxidil** (prodrug)

Open K⁺ channels ➔ atrial smooth muscles hyperpolarization and vasodilation

**Uses**

Hypertension and male pattern baldness

**Adverse effects**

Hirsutism and tachycardia

**Diazoxide**

Open K⁺ channels in smooth muscles and in glands

**Uses**

Hypertension and hypoglycaemia

**Adverse effects**

Opposite of use (hypotension and hyperglycaemia)

---

Ganglion Blockers.
Ganglion Blockers

1 Trimethoprim
   T for tension
   Used in Hypertension caused by pulmonary hypertension

2 Hexamethonium
   H for hypertension
   Used in hypertension (obsolete)

Antihypertensive drugs contraindicated in Pregnancy
Dr from NASA
D ➔ Diuretics
R ➔ Reserpine
N ➔ Non selective Beta blockers
A ➔ ACE inhibitors
S ➔ sodium Nitroprusside
A ➔ AT₁ antagonists
12. Drugs used in Heart failure

Cardiac failure

Decrease cardiac function as compared to needs of the body

Homeostatic responses of the body to decrease cardiac output

- By sympathetic nervous system
- By renin angiotensin mechanism

Drugs used in Cardiac failure.

Same drugs as hypertension are used in cardiac failure but finished before F (F mean failure finish) and C there was for Ca^{2+} channel blockers and here C is for Cardiac glycosides

| A | • ACE inhibitors  
|   | • Angiotensin receptor inhibitors  |
| B | • Beta agonists  
|   | • Beta antagonists  |
| C | • Cardiac glycosides  |
| D | • Diuretics  |
| E | • Endothelial factor releasers  |
**ACE and angiotensin receptor inhibitors.**

Same as hypertension

**Beta agonists.**

**Dobutamine**

4 Dobutamine (Beta 1 ➔ we have one heart in our body)

- Used to increase cardiac output in congestive cardiac failure
- Produces little change in heart rate
- Do not significantly elevate myocardial oxygen demand (advantage over other sympathomimetic

- Increase AV conduction ➔ caution for atrial fibrillation

**Beta antagonists.**
Cardioselective beta blockers are used

- Cardevalol and labetalol also

**Cardioslective Beta Blockers or Beta 1 Blockers**

- Beta blockers acting exclusively at myocardium
  - Beta blocker → butaxolol
  - Acting → acebutalol
  - Exclusively → esmolol
  - At → atenolol
  - Myocardium → metaprolol

**Cardiac Glycosides.**

**Cardiac glycosides**

- Steroid nucleus + Lactone ring + one or more sugars.
- Digitoxin is prototype and is obtained from foxglove plant

**Mechanism**
Effects Produced

Mechanical effects

Normal process → Cell memb have Na⁺ & K⁺ channels → Pump Na out and K in

Na out came in and Ca from in goes out → Ca moves out → Digitoxin is given

Na/K channel in inhibited → Na/channel also inhibited → inside Ca increased

causes Muscle contraction
**Electrical effects**

**Early response** (parasympathetic effects)

- Inc PR interval ➔ due to decrease AV conduction velocity
- Flattening of T wave

**Toxic effects**

- Inc automaticity caused by intracellular $\text{Ca}^{2+}$ overload
- Premature ventricular beats

**Clinical Uses of cardiac glycosides**

**Cardiac glycosides**

C ➔ congestive cardiac failure
Aatrial fibrillation

**Congestive cardiac failure**
+ Inotropic effects are produced
  ⇒ So used in chronic heart failure

**Atrial fibrillation**
  ⇒ Dec velocity of conduction
  ⇒ Inc refractory period

### Interactions

- **Factors that increase toxicity**
  - Hypercalcemia + hyperkalemia + hypomagnacemia

- **Digitalis induced vomiting**
  - Loss of Mg ⇒ increase toxicity

- **Loop diuretics and thiazide diuretics**
  - Reduce serum Ca^{2+} level ⇒ Dec toxicity

### Toxicity

Very And (very Andy drug)

- Very ⇒ vomiting + ventricular fibrillation
- A⇒ arrhythmias + AV node block and SA node block
- N ⇒ Nausea
- D ⇒ diarrhoea
Diuretics.

Same as hypertension

** First line of therapy for cardiac failure**

Endothelial factor releasers.

Hydralazine and Nitroprusside → same as hypertension

Non Pharmacological methods.

- Remove non-functional regions of myocardium.
- Resynchronization of left and right ventricles by pacemaker.
- Revascularization of coronary artery
13. Drugs used in Angina pectoris.

- **Nitrates**
- **Ca++ channel blockers**
- **Beta blockers**
- **metabolism modifiers**

Or you can Use National commercial bank.

Mechanism
Effects produced by Nitroglycerine

NO VCR

N ➔ nitroglycerine effects
O ➔ reduce oxygen requirements
V ➔ venodilation ➔ veins are more sensitive
R ➔ Reduce cardiac size and preload

Side effects

Totm (same as side effects of NO)
**Side-effects**

**TOTM**

- T ➔ tachycardia ➔ by baroreceptor reflex
- O ➔ orthostatic hypotension
- T ➔ throbbing headache
- M ➔ methmoglobinemia

**Uses of nitroglycerine**

A man has spasm

- A ➔ angina pectoris
- Man ➔ myocardial infection
- Has ➔ severe hypertension
- Spasm ➔ coronary artery spasm

**Interactions**

**With sidenaphil**

- Sidenaphil is used for Erectile dysfunction ➔ act by inhibit breakdown of cGMP ➔ result inc of cGMP
- Nitrates ➔ also inc cGMP by increase production by release of NO
  ➔ So Net effects produced by cGMP will be more marked
    - And will result high level of hypotension

**Cyanide poisoning**

- **Cyanide + iron of cyt P450** ➔ complex is formed ➔ oxidative metabolism is blocked
Nitrates $\Rightarrow$ oxidize Hemoglobin iron (ferrous $\Rightarrow$ ferric) and result methmoglobin formation $\Rightarrow$ cyanide bind to methmoglobin avidly $\Rightarrow$ result release of cyanide from cytochrome oxidase.

Methmoglobin $\Rightarrow$ carry less oxygen $\Rightarrow$ treated with methylene blue to revert this effect.

**C**a$^{+2}$ Channel Blockers.

Do this from hypertension

**B**eta blockers.

Same as hypertension

**Uses**

- Prophylactic treatment of angina
- Prevent exercise induced angina
- In vasospastic angina
- Combination with nitrates

**O**ther drugs.
Ronalazine

Effects are produced by alteration of intracellular levels of Na⁺

roNAalazine ➔ Na⁺ channel effects.

- Increase Ca²⁺ expulsion by Na⁺-Ca²⁺ channels
- Moderately effective in angina
  - Dec angina episodes and increase exercise tolerance.

Ivabradine.

Inhibit SA node ➔ result hyper polarization ➔ dec heart rate

- Symptomatic treatment of angina

Nitrates + Ca²⁺ channel blockers + Beta blockers ➔ reduce oxygen requirements

Nitrates + Ca²⁺ channel blockers ➔ increase O₂ delivery also

Arrhythmias

Heterogeneous group of conditions in which there is abnormal electrical activity in heart.

Drugs and classification

Sodium beta k calcium channel blockers married

<table>
<thead>
<tr>
<th>Sodium</th>
<th>Na⁺ channel blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta</td>
<td>Beta blockers</td>
</tr>
<tr>
<td>K</td>
<td>K⁺ channel blockers</td>
</tr>
<tr>
<td>Ca</td>
<td>Ca⁺² channel blockers</td>
</tr>
<tr>
<td>married</td>
<td>miscelaneous → adenosine + K⁺ + Mg⁺²</td>
</tr>
</tbody>
</table>

Group 1. Na⁺ channel Blockers.

Group 1A

Queen proclaimed this pyramid
Queen ➔ Quinidine
Proclaimed ➔ procainamide
This pyramid ➔ dispyramide

- Queen belongs to royal family so she belongs to first class people.
- A group indicate ➔ these are active people and active people have more potential and this indicate that this group prolongs the action potential (mechanism)
  - Na⁺ channel blockers block channels in abnormal tissue more effectively
    - Use dependent and state dependent they selectively depress tissues that is frequently depolarizing.

**Use**

Atrial arrhythmia and ventricular arrhythmia

**Group 1B**

B for Bili ➔ Bi + Li ➔ li mean lidocaine
B for bored ➔ bored people are not active people and have less or reduce potential

- Group B people decrease action potential because they reduce recovery of Na channels from inactivation. (mechanism)

**Lidocaine**

Li ➔ I indicate it is used in ischemic ventricular arrhythmias (for example after MI)

- Orally not administered because of high first pass metabolism and metabolites produced are cardiotoxic

**Toxicity**

- Local anaesthetic toxicity
- Cardiovascular depression
- Allergy
Drug interaction

Hyperkalemia ➔ increase cardiac toxicity

**Group 1C**

Ham darwazay ko Cafal kehtay hain tu us hisab say chota darwaza Cafle bana

Cafle ➔ C indicates this is C group and Fle indicates its drug Flecainide

Ab caflee chota darwaza hota hay tu logon k guzarnain k speed kam ho jaey gi

- Group 1C drugs lower conduction velocity
- Have no effect on action potential.
• They are powerful depressants of Na\(^+\) current and they increase QRS duration

**Uses**

Refractory arrhythmia

⇒ Use is restricted to persistent arrhythmias fail to response other therapies

**Group 2. Beta Blockers**

Prototype drugs propranolol and Esmolol

**Mechanism**

- AV nodes are selective to beta blockage
- PR interval is usually prolonged

⇒ Amiodrone and sotalol are from group 3 but have some activity of group 2

**Group 3. K\(^+\) channel blockers**

Bachy parh nh rhay thy tu **ami sota lai** or sab ki **kutt** laga di

Ami ⇒ amiodrone
Sota ⇒ sotalol
Lai ➔ lides ➔ ibutilide and dofetilide
Kutt ➔ K channel blockers

**Mechanism**

Block $K^+$ channel ➔ result prolongation of action potential and refractory period.

- Also show activity of other groups like sotalol also blocks Beta blocker & amiodrone show activity of group 1, 2 and itself is 3 and of 4

**Amiodrone**

Most efficacious of all antiarrhythmic drugs

- Block $Na^+$ channel
- Block beta adrenoreceptor
- Block $K^+$ channel
- Block $Ca^{+2}$ channel

**Use is restricted why?**

⇒ Extensive toxic effects are produced ➔ used only where other drugs are not responding

**Adverse effects**

Micro ppts of amiodrone

Micro ➔ microcrystalline deposits

P ➔ pulmonary fibrosis

P ➔ paraesthesia

T ➔ thyroid dysfunction

S ➔ skin sensitivity to light

**Dronedrone**
Similar to amiodrone but is toxic and used for atrial flutter and fibrillation.

**Group 4. Ca\(^{+2}\) channel blockers**

Discussed previously.

**Uses**

- AV nodal arrhythmias (prophylaxis)

**Group 5. Miscellaneous.**

**Adenosine** ➔ in acute nodal tachycardia

**K\(^+\) and Mg\(^{+2}\) ion** ➔ in digitalis toxicity and other arrhythmias
15. Diuretics.

Classification and sites of action

- Diuretics decrease Na absorption at various sites of nephron resulting increase rate of urination

**Carbonic anhydrase inhibitors**

**CIA**

⇒ Carbonic anhydrase inhibited by Acetazolamide.

**Site** ⇒ Proximal convoluted tubule

**Site of action** ⇒ carbonic anhydrase enzyme

**Loop diuretics**

**LEFT**

 L ⇒ Loop diuretics

 E ⇒ Ethacrinic acid

 F ⇒ Furosemide

 T ⇒ Torsemide

**Site** ⇒ Thick ascending limb of loop of henle

**Site of action** ⇒ Na / K / 2Cl channels

**Thiazide diuretics**

Thiazide came in their names

- Hydrochlorothiazide
- Chlorothiazide
Chlorothalidone
Site ➔ distil convoluted tubule
Site of action ➔ Na / Cl channel

Potassium sparing diuretics
PotASSium ➔ ASS of diuretics
   A ➔ amiloride
   S ➔ spironolactone
Site ➔ collecting duct
Site of action ➔ aldosterone receptor

Osmotic diuretics
OSMO ➔ Mo ➔ manitol
Osmotically retain water in tubule
Site ➔ dec absorption of water in dLOH, proximal tubule and CT.

Uses and adverse effects

Carbonic anhydrase inhibitors
Gem made a small dp with zola (acetazolamide)

**Use**

G ➔ glaucoma (chronic treatment)
E ➔ edema with alkalosis & Epilepsy in conjugation with antiepileptic drugs
M ➔ mountain sickness ➔ prophylactic

- They are less used as diuretics because they are less efficient than thiazide and loop diuretic.

**Adverse effects**

Made ➔ metabolic acidosis (hyperchloremic)
Small ➔ sedation and stone (renal)
D ➔ depletion of K
P ➔ paresthesia

**Loop diuretics**

Loop have **Hope for Home**

⇒ (my second home in this book first was in ergot alkaloid uses)

**Uses**

H ➔ Hypertension
Heart failure
Hypercalcemia (**Loop loose calcium**)  
O ➔ oedema associated with heart failure, hepatic cirrhosis and renal impairment
PE ➔ Pulmonary edema associated with congested heart
Adverse effects

H ➔ Hyperkalemia ➔ increase exchange of Na for K
    Hypovolemia
    Hyperuricemia

O ➔ ototoxicity ➔ especially when used with aminoglycoside antibodies.

M ➔ metabolic hypovolemic alkalosis.

E ➔ efficiency decreased by NSAIDS.

Thiazide diuretics

Hard hyper and hypoes

Uses

Hard
You have to remember Hard hyper and Hypoes

For Thiazide Diuretics

H ➔ hypertension
Heart failure
Hypercalciuria (dec urinary Ca excretion)
A ➔ syndrome of inappropriate ADH secretion
R ➔ Renal impairment (nephrotic syndrome accompanied by edema)

D ➔ Diabetes insipidus (produces hyper osmolar urine and urine volume drop from 11 litre to 3 litre per day)

**Adverse effects**

**Hypoes**
- Hypovolemia
- Hypokalemia
- Hypernatremia

**Hypers**
- Hypercalcemia (opposite of Loop)
- Hyperuricemia
- Hyperlipidaemia
- Hyperglycaemia
- Hypersensitivity (vasculitis & dermatitis)

**K⁺ sparing diuretics**

**Uses**
- Excessive K loss due to other diuretics
- Aldosteronism

**Adverse effects**

Hyperkalemia

Gynecomastia (spironolactone)

**Osmotic diuretics**

**Uses**
OSMO

O → oedema of brain (due to inc intracranial P)
S → Shock
M → GlaucoMa
O → solute Overload

**Adverse effects**

- Hyponatremia followed by hypernatremia
- Nausea
- Vomit
16. Anticoagulant Drugs.

Anticoagulant drugs
They are classified into three groups

- anticoagulants
- Thrombolytics
- antiplatelets

**Anticoagulants**
Anticoagulant diseased have defective wounds
Diseased ➔ Direct thrombin inhibitors
Have ➔ heparin
Defective ➔ Direct factor Xa inhibitors
Wounds ➔ warfarin

**Thrombolytics**
Smart thrombolytics
Smart → streptokinase
Thrombolytics → tPA activators

**Antiplatelet drugs**

APA g antiplatelet lo
- A → ADP inhibitors
- P → phosphodiesterase inhibitors
- A → aspirin
- G → glycoprotein IIB and IIIa inhibitors

**Members of each group**

1) **Direct thrombin inhibitors**
   Anty thrombin loves BD anatomy
   - Anty thrombin → antithrombin drugs
   - Loves → lepirudin
   - B → bivalirudin
   - D → dabigatran
   - Anatomy → argatroban

2) **Heparin**

3) **Direct factor Xa inhibitors**
   Ten A → TA
   Mnemonic is TARA
   - T A → Direct factor Xa inhibitors
R ➞ Rivaroxaban
A ➞ apixiban

<table>
<thead>
<tr>
<th>4) Warfarin</th>
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<tbody>
<tr>
<td>5) Streptokinase</td>
</tr>
<tr>
<td>6) tPA derivatives ➞ Thrombolytic agents</td>
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</table>

- tPA derivatives (Plases)
  - Alteplase ➞ normal
  - Reteplase ➞ human mutated form
  - Tenectiplase ➞ mutated and with increased half life

<table>
<thead>
<tr>
<th>7) ADP receptor inhibitors</th>
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<tbody>
<tr>
<td>Ticlo</td>
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<tr>
<td>Ticlo ➞ Ticlopidine</td>
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<tr>
<td>Clo ➞ Clopidogrel</td>
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<table>
<thead>
<tr>
<th>8) Phosphodiesterase inhibitors</th>
</tr>
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<tbody>
<tr>
<td>Phosphodiesterase inhibitors ➞ diasesterase ➞ Dipyridamole</td>
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<tr>
<th>9) Aspirin</th>
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<tr>
<th>10) Glycoprotein IIb and IIIa inhibitors</th>
</tr>
</thead>
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<tr>
<td>GTA vice city (game name)</td>
</tr>
<tr>
<td>G ➞ Glycoprotein IIb and IIIa inhibitors</td>
</tr>
<tr>
<td>T ➞ Tirofiban</td>
</tr>
<tr>
<td>A ➞ Abciximab</td>
</tr>
</tbody>
</table>

Detail of each of them
Anticoagulants

1) Direct thrombin inhibitors

Based on Protein hirudin (Leach protein)

Drugs ➔ Anty thrombin loves BD anatomy

- Lipirudin ➔ recombinant form of Hirudin
- Bivaluridin ➔ modified form of hirudin
- Dabigatran ➔ orally active
- Argatroban ➔ small molecule with lesser half life

Mechanism ➔ Bind to thrombin and thrombin substrate (argatroban only to thrombin)

Clinical uses

- tHrombin ➔ alternative to heparin in patients with heparin induced thrombocytopenia
- with aspirin in coronary artery angioplasty

Activity ➔ measured by aPTT (activated prothrombin time)

Toxicity ➔ prolonged bleeding

2) Heparin

Mechanism

High molecular weight Heparin ➔ inhibit thrombin and factor Xa
Low molecular weight Heparin ➔ inhibit only factor Xa

**Uses and adverse effects**

**Uses**
- **P** ➔ pulmonary embolism
- And this indicate this drug is positive for Pregnancy (Drug of choice in pregnancy ➔ acidic drug so cannot cross placenta and cane be used)
- **I** ➔ immediate coagulation
- **C** ➔ coronary artery stunts
- **D** ➔ DVT treatment
- **A** ➔ angioplasty and coronary stunts
- **M** ➔ acute myocardial infarction

**Adverse effects**

**HOTI**
- **H** ➔ Heparin induced thrombocytopenia (caused by an immunological reaction that make platelets a target of immunologic response result degradation of platelets leading to thrombocytopenia)
- **O** ➔ osteoporosis
- **T** ➔ two non-haemorrhagic side effects (elevation of serum amino transferase level and Hyperkalemia)
- **I** ➔ increased bleeding time

**Antidote** ➔ Protamine sulphate
3) **Direct oral factor Xa inhibitors**

Members of Drugs ➔ TARA (Rivaroxaban and Apixaban)

**Mechanism**

Bind to factor Xa free and bound to clotting complex

**Uses**

Ten A inhibitors

Ten ➔ T ➔ venous thrombosis after Nee (knee) surgery

A ➔ atrial fibrillation

4) **Warfarin**

Lipid soluble ➔ not given in Pregnancy

**Mechanism**

Vit K Epoxide ➔ activated Vit K under the action of enzyme **Vit K Reductase**

♀ Activated Vit K involve in the production of clotting Factor 2, 7, 9, 10 (II, VII, IX and X)

Warfarin ➔ inhibit Vitamin K Reductase enzyme ➔ result in loss of production of these factors and Result in antithrombic activity.

**Reversal of effects**

Effects of warfarin can be reversed by Vit K ➔ will result in synthesis of cofactors in 6 to 24 hours
- For emergency cases fresh frozen Plasma that have normal clotting factors is given

**Uses**

Warfarin is a chronic anticoagulant in clinical situations Except Pregnancy

*Warfarin have low therapeutic window

**Warfarin in Pregnancy**

**Toxicity**

- Increase bleeding time

- Dermal and vascular necrosis (it causes deficiency of protein C that is endodermal Vit K dependant anticoagulant

**Lab tests for for warfarin and Heparin**
Thrombolytic agents

Mechanism

Members

tPA (Tissue plasminogen activator)

• Selective for plasminogen that is already bound to fibrin (convert it into plasmin)
Protective layer is form to prevent loss by widespread production of plasmin

**Alteplase**
- Normal human plasminogen activator

**Retepase**
- Mutated form of human tPA (fast + longer duration of action)

**Tenectiplase**
- Human mutated form with longer half life

**Streptokinase**
- Obtained from bacteria
- Non selective to fibrin bound to plasmin

**Uses**
- PCR
  - P $\rightarrow$ pulmonary embolism
  - C $\rightarrow$ coronary artery angiography in coronary artery thrombosis
  - R $\rightarrow$ recanalize coronary artery

**Adverse effects**
- ABC
  - A $\rightarrow$ antibody formation against streptokinase
  - B $\rightarrow$ increased bleeding
  - C $\rightarrow$ cerebral haemorrhage

**Antiplatelet drugs**
1) **ADP receptor inhibitors**

Ticlo (Ticlopidine and clopidogrel)

Irreversibly inhibit platelet ADP receptor

**Uses**

Ticlo Cap

- C ➔ acute coronary syndrome
- A ➔ prevent and treat arterial thrombosis
- P ➔ after PCI (percutaneous coronary intervention) to prevent restenosis

2) **Phosphodiesterase inhibitors**

Diaseterase ➔ Dipyridamole

- Inhibit adenosine uptake
- Inhibit phosphodiesterase that degrade cAMP.

**Uses**

- Prevention of thromboembolic complications of cardiac valve replacement
- With Aspirin to prevent secondary ischemic stroke

3) **Aspirin**

**Mechanism**

Non-selective irreversible inhibitor of COX enzyme

⇒ Result reduced production of thromboxane A₂ by platelets (TxA₂ is potent stimulator of platelets)

**Uses as anticoagulant**

- P° myocardial infarction
Uses of aspirin are

- Antiplatelet ⇒ conc less than 300 mg/dl
- Antipyretic ⇒ conc 300 to 2400 mg/dl
- Analgesic ⇒ conc 300 to 2400 mg/dl
- Anti-inflammatory ⇒ 2400 to 4000 mg/dl

**Adverse effects**

Aspirin
A ➔ asthma

S ➔ salicylism

P ➔ peptic ulcer

I ➔ intestinal blood loss

R ➔ ray’s syndrome ➔ Aspirin given to children with viral infection (Rapid liver degeneration and encephalopathy)

I ➔ idiosyncrasy

N ➔ noise ➔ tinnitus

**Contraindication**

As aspirin belongs to NSAIDS so same contraindications as that of NSAIDS

N ➔ nursing and pregnancy

S ➔ severe blood loss
A₃ ➔ Allergy + Asthma + Angioedema

I ➔ impaired renal function

D ➔ drugs (when patient is allergic to ibuprofen and naproxen), (with warfarin produces intestinal blood loss)
17. Drugs used in Hypertlipidemias

Friend drugs

<table>
<thead>
<tr>
<th>F</th>
<th>• Fibrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>• Resins</td>
</tr>
<tr>
<td>E</td>
<td>• Ezetimibe</td>
</tr>
<tr>
<td>N</td>
<td>• Niacin</td>
</tr>
<tr>
<td>D</td>
<td>• Drugs that inhibit HMG CoA ➔ Statins (most imp)</td>
</tr>
</tbody>
</table>

Treatment strategies

**Diet**
- Dec intake of cholesterol and saturated fats
- Avoid alcohol ➔ as they increase Tg and VLDL

**Drugs**
- Drugs effective at lowering LDL cholesterol ➔ HMG CoA reductase inhibitors, Resins, Ezetimibe and Niacin.
• Drugs effective at lowering VLDL and rising HDL cholesterol ➔ Fibric acid derivatives, Niacin and marine Omega 3 derivatives.

**Fibrates ➔ Gemfibrozil and fenofibrate**

Are ligands for PPAR alpha (peroxisome proliferator activated receptor alpha) ➔ regulate transcription of genes involved in Lipid metabolism ➔ Increase synthesis of Lipoprotein lipase ➔ associated in capillary endothelial cells ➔ enhanced clearance of Tg rich lipoproteins.

**Uses**

- Hypertriglyceridemia
- Low HDL cholesterol

**Resins**

Also called bile acid binding resins

Colestipol and cholestyramine ➔ are large non-absorbable polymers that bind to bile acids and similar steroids in intestine and prevent their absorption ➔ prevent recycling of bile acids ➔ Divert hepatic cholesterol to Bile acid synthesis resulting in decrease in cholesterol in triglyceride regulatory pool.

- Resins ➔ modest reduction of LDL cholesterol
- No effect on HDL and Triglycerides
Uses

- Hypercholesterolemia
- To reduce pruritus in patients with bile salts accumulation

Niacin

- Reduces VLDL cholesterol synthesis ➔ in turn decreases LDL cholesterol
- Activate signalling pathway in adipose ➔ reduce lipoprotein lipase activity ➔ Decrease plasma free fatty acids and Tg level ➔ LDL formation decreased
- Reduces catabolic rate for HDL

Uses

- Hypercholesterolemia
- Hypertriglyceridemia
- Low level HDL

Toxicity
- Cutaneous flushing
- GIT irritation
- Hyperuricemia
- Reduce glucose tolerance

**Drugs that inhibit HMG CoA → Statins**

Semi loves rose flavour

- Semi → Simva + statin → Simvastatin
- Loves → Lova + statin → Lovastatin
- Rose → Rosuva + statin → Rosuvastatin
- Flavour → Fluva + statin → Fluvastatin

HMG CoA is formed from acetyl CoA and is converted into cholesterol under the action of enzyme **HMG CoA reductase**,

להלן איור שמתאר שלושה בני אדם, אחד מהם חסון בחרק, השני בחום, והשלישי בחול. המילים "HDL" מציינות את המבנה הchiolesterolי של האדם החוסן, "LDL" הוא המבנה של האדם החום, ובין השניים יש אנזים "HMG CoA reductase".

⇒ Statins are structural analogues of HMG CoA → competitively inhibit HMG CoA reductase enzyme.

**Uses**

- Reduce LDL cholesterol
- Reduce risks of Coronary events
- Reduce mortality in patients with ischemic heart disease
- Reduce risk of ischemic attacks

**Toxicity**

Statin cat

C ➔ creatinine kinase increase ➔ release from skeletal muscles

A ➔ elevation of serum aminotransferases

T ➔ teratogenic ➔ should be avoided in pregnancy
18. NSAIDS and drugs used in treatment of Rheumatoid Arthritis and Gout

NSAIDs

Non-steroidal anti-inflammatory drugs

**Mechanism**

Inhibit COX (Cyclooxygenase enzyme) → decrease prostaglandin and thromboxane synthesis

**COX**<sub>1</sub> → in non-inflammatory cells → normal physiological cells

**COX**<sub>2</sub> → in inflammatory cells, activated lymphocytes and polymorphonuclear cells.

**Effects**

- **Anti-inflammatory effect** → decrease synthesis of arachidonic acid derivatives (important mediators of inflammation) → reduce manifestations of inflammation and have no effect on underlying tissue and immunological reactions

- **Antipyretic effect** → supress prostaglandin synthesis in CNS → reduces fever

- **Analgesic effect** → Reduced production of prostaglandins in injured tissues

**Classification**
**NSAIDs**

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
</table>
| N | • negligible anti inflammatory and good analgesics  
   • Acetaminophen |
| S | • Salicylates  
   • Aspirin  
   • Na salicylates |
| A | • Acid derivatives  
   • all other than salicylates  
   • Ibuprofen |
| I | • Indoles $\rightarrow$ indomethacin |
| D | • Drugs with long duration $\rightarrow$ Oxicams |
| S | • COX$_2$ selective $\rightarrow$ celecoxib and meloxicam |

**Aspirin and other NSAIDs**

Most of it is discussed in chapter of anticoagulants

**Uses of aspirin are**

- Antiplatelet $\rightarrow$ conc less than 300 mg/dl
- Antipyretic $\rightarrow$ conc 300 to 2400 mg/dl
- Analgesic $\rightarrow$ conc 300 to 2400 mg/dl
- Anti-inflammatory $\rightarrow$ 2400 to 4000 mg/dl

**Why?**
TXA$_2$ ➔ increases platelet aggregation (coagulant effect).

PGI$_2$ ➔ decreases platelet aggregation (anticoagulant effect).

- Aspirin conc below 100mg/dl ➔ only ThA$_2$ is inhibited and there is only anticoagulant effects that last upto 300 mg/dl
- TXA$_2$ is inhibited PGI$_2$ is also inhibited so anticoagulant effect is cancelled by coagulant effect and there will be no anti-coagulant effect.

**Adverse effects**

**Non selective NSAIDs**
- GIT disturbances
- Renal damage

**COX2 Inhibitors**
- Reduced GIT damage
- Same risk or renal damage
- Increase risks of Myocardial infarction and stroke ➔ have more effect on PGI$_2$ synthesis than on TXA$_2$ synthesis ➔ increased risks of thrombosis

**Aspirin and Acetaminophen**

<table>
<thead>
<tr>
<th>Aspirin</th>
<th>Acetaminophen (peracitamole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesic</td>
<td>yes</td>
</tr>
<tr>
<td>Antipyretic</td>
<td>Yes</td>
</tr>
<tr>
<td>anti-inflammatory</td>
<td>Not</td>
</tr>
<tr>
<td>Irreversible non selective COX inhibitor</td>
<td>Weak inhibitor of COX$_1$ and COX$_2$ (lack anti-inflammatory)</td>
</tr>
<tr>
<td></td>
<td>COX$_3$ (in CNS) ➔ inhibitors</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>Not</td>
</tr>
</tbody>
</table>
### Uses
- discussed already
- Substitute of aspirin especially in children with viral infection

### Toxicity of Acetaminophen
- Therapeutic dosage → negligible toxicity
- Overdose or in patient with liver impairment → Hepatotoxic drug toxic metabolites produced by phase I reaction if substrates of phase II reaction (acetate and glucouronate) are lacking
- Antidote → Acetyl cysteine

### Drugs used in treatment of Gout

#### Drugs used in Gout

#### Acute
- NSAIDs
  - Indomethacin

#### Chronic
- Colchicine
- Uricosurics
- Xanthine oxidase inhibitors
  - Probenicid
  - Allopurinol

#### Treatment strategies
- Gout → increase uric acid in serum → deposition of Uric acid crystals in Joints → inflammation

#### Treatment strategies will be
- Reduce inflammation → Colchicine, NSAIDs or Glucocorticoids
• Accelerate renal excretion of uric acids ➔ uricosuric drugs ➔ Probenicid and Sulfinpyrazone

• Reducing conversion of purines into uric acid ➔ by xanthine oxidase inhibitors ➔ allopurinol

**Anti-inflammatory drugs**

**NSAIDs** ➔ such as indomethacin ➔ inhibit inflammation of acute gouty arthritis ➔ reduce prostaglandin synthesis and phagocytosis by macrophages.

**Colchicine** ➔ inhibit microtubule assembly ➔ reduce migration of leukocytes and phagocytosis. ➔ Reduce inflammation

**Glucocorticoids** ➔ preferred for treatment of acute gouty arthritis

**Uricosuric Drugs**

90% of uric acid is reabsorbed in proximal convoluted tubule

Uricosuric drugs ➔ prevent reabsorption of uric acid in PCT
Mechanism ➔ compete with uric acid in PCT ➔ increase uric acid excretion.
- Used in chronically. No value in acute attacks.

Toxicity
- Uricosuric agents (weak acids) also inhibit the secretion of other weak acids like penicillin and methotrexate.
- Hypersensitivity because they are sulphonamides share allergenicity with other sulphonamides

<table>
<thead>
<tr>
<th>Xanthine oxidase inhibitors</th>
</tr>
</thead>
</table>

Mechanism ➔ inhibit enzyme xanthine oxidase (the enzyme that metabolize conversion of hypoxanthine into xanthine and xanthine into uric acid) ➔ result decrease production of Uric acid
- Allopurinol ➔ converted into alloxanthine ➔ inhibit enzyme irreversibly
- Fubuxostat ➔ reversible inhibitor (more effective drug) (non-purine inhibitor of xanthine oxidase)

Uses
- Chronic gout treatment
- In combination with colchicine or NSAIDs in acute attacks
- Adjunctive in treatment of cancer therapy ➔ slow the formation of uric acid from purines by death of neoplastic cells.

Toxicity
- GIT upset + rash + peripheral neuritis + bone marrow dysfunction + aplastic anemia
19. Drugs used in GIT Disorders

**Acid peptic disease.**

Drugs used in acid peptic disease are Hy papa

<table>
<thead>
<tr>
<th>hy</th>
<th>• H$_2$ inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>• Proton pumb inhibitors</td>
</tr>
<tr>
<td>A</td>
<td>• Ant acids</td>
</tr>
<tr>
<td>P</td>
<td>• Protectivegents</td>
</tr>
<tr>
<td>A</td>
<td>• Antibiotics</td>
</tr>
</tbody>
</table>

H$_2$ inhibitors
H 2 Blockers

FRaNCeTidine

- F → Famo + tidine → Famotidine
- R → Rani + tidine → Ranitidine
- N → Niza + tidine → Nizatidine
- C → Cime + tidine → Cimetidine

Mechanism

Blockage action of histamine on parietal cells

Uses

- GPS Dr
  - G → GERD
  - P → Peptic ulcer
  - S → Stress related gastroenteritis
  - Dr → Dyspepsia

Proton pump inhibitors

OLPER + parazole

- O → Ome + prazole → Omeprazole
- L → Lenzo + prazole → Lenzoprazole
- P → Pento + prazole → Pentoprazole
E ➔ esmo + prazole ➔ Esmoprazole
R ➔ Rabe + prazole ➔ Rabeprazole

**Mechanism**

Lipophilic weak bases that diffuses into parietal cell canaliculi.

- Irreversibly inhibit the parietal cells H/K ATPase the transporter that is primarily responsible producing stomach acid.

**Uses**

In GERD and peptic ulcer these agents are more potent than H₂ receptor antagonists

**Pharmacokinetics**

- Oral formulations are enteric coated to prevent destruction in stomach
- Half-life of 1-2 hours and effects last for 1 day and 3-4 days are required to achieve full effectiveness

**Adverse effects**

TIDA proton

T ➔ Vit B twelve (B₁₂) deficiency ➔ because of decrease absorption (need acidity for absorption)
I ➔ inc risk of respiratory and enteric tract infections
D ➔ Diarrhoea and sard (headache)
A ➔ Abdominal pain

**Antacids**

\[ \text{Al(OH)}_3 \text{ and Mg(OH)}_2 \]

- These are weak bases that react with protons in GIT
- Also stimulate protective function of gastric mucosa

\[ \text{Mg(OH)}_2 \text{ } \]
this is also found in syrup milk of magnesia that is a laxative
So this causes strong laxative effect

\[ \text{Al(OH)}_3 \text{ } \]
show constipating effect opposite to Mg(OH)$_2$

\[ \text{CaCO}_3 \text{ and NaHCO}_3 \] can also be used they are also weak bases

**Uses**

GPS dr with burning hurt

G ➔ GERD
P ➔ Peptic ulcer
S ➔ Stress related gastroenteritis (less used)
Dr ➔ Dyspepsia

Burning hurt ➔ heart burn

**Adverse effects**

- Excess Calcium absorption from milk and Calcium rich foods ➔ result in milk alkali syndrome
• Regular intake may lead to alkalosis
• Chemical reaction between antacid and acid → production of CO₂ → distended abdomen
• May cause headache
• Al(OH)₃ → constipation
• Mg(OH)₂ → laxative
• Al(OH)₃ → neurotoxic and contraindicated in pregnancy
• Mg(OH)₂ → in renal failure patients
body Mg level increase Mg → hypermagnecemia

Protective agents

Protective MSc
Protective → protective agents
M → misoprostol
S → sucralfate
C → colloidal bismuth

Misoprostol

Misoprostol → M for mono so it is 1 and if we rotate M it will Become E so it is 1E

Peptic Ulcer

PGE₁(Misoprostol) is used

Actions
• Inc. mucosal protection
• Dec. acid secretion

Uses

• Effective in Ulcers by NSAIDS

Not used widely because of multiple doses and poorly tolerated adverse effects

Side effects ➔ diarrhoea + GIT upset

• Should not be taken by pregnant women ➔ increase uterine contractions may cause abortion

• With mifepristone used vaginally ➔ to terminate pregnancy

Sucralfate

⇒ Aluminium sucrose sulphate

  o Poorly soluble molecule that polymerise in acidic environment of stomach and bind to injured tissue
  • form protective covering over ulcer beds
  • accelerate healing of the ulcer
  • Reduce reoccurrence rate

  o Systemic effects are very less ➔ too insoluble

⇒ Toxicity very low

Colloidal bismuth

⇒ Formation of protective covering on the ulcerative tissue

⇒ Stimulation of mucosal protection mechanism

Antibiotics

Chronic infection with H-Pylori (present in most of the patients with reoccurrence, Non NSAID induced peptic ulcer.
Dosage regime
Proton pump inhibitor + Clarithromycin + amoxicillin
⇒ Metronidazole is given for penicillin allergic persons.

Motility Promoters
Mnemonic for this is MMDC (Multan medical and dental college)

- **M**
  - motility promoters
- **M**
  - Metocloperamide
- **D**
  - Domperidone
- **C**
  - Cholinomimetics (Neostigmine)

Metoclopramide and Domperidone
Dopamine D₂ antagonist that increase the GIT motility
- Prevent emesis after surgical anaesthesia
⇒ Chronic use of metoclopramide causes symptoms of parkinsonism and other extrapyramidal side effects

Cholinomimetics
Neostigmine ⇒ is used for GERD and Gastropresis.

Drugs used in irritable bowel syndrome
Sir Alu said to aunty chalo chalain lubi k pas irritation ho rhi hay.

Sir  ➔ serotonin antagonist  ➔ alosteron

Aunty  ➔ anticholinergics

Chalo chalain  ➔ chloride channel activator  ➔ Lubiproston

**Serotonin antagonists**

Alosteron

- Potent 5HT₃ antagonist

**Drugs**

Imagine Granny is driving a Honda motor cycle and everyone saying hello! hello!

Granny ➔ Granisteron

hONDA ➔ Ondasteron

Another member is Alosteron that is used in irritable bowel syndrom

Used in treatment of women with severe IBM and diarrhoea

**Side effect** ➔ constipation and colitis

**Anticholinergics**

Hayoscyamine ➔ also known as dhaturine (an antispasmodic drug)

   **Antispasmodic** ➔ drug or herb that depress muscle spasm and relieve abdominal pain

Hayoscyamine ➔ is an anti-muscarinic drug

**Uses**

- Peptic ulcer
- Irritable bowel syndrome
- Pancreatitis and colitis
Side effects same as of atropine but weaker

**Chloride channel activators**

Lubiproston ➔ Chloride channel activator type 2

⇒ Treatment of women with IBS and constipation

**Drugs for inflammatory bowel disease**

Central intelligence agency of America

- **central**
  - Corticosteron

- **intelligence**
  - immunosuppresants

- **agency**
  - 5-aminosalisalic drugs

- **america**
  - anti TNF drugs

**Corticosteroids**

Glucocorticoids are used

- Inhibit prostaglandin synthesis
- Inhibit leukotriene synthesis

**Immunosuppressants**

Methotrexate’ azathioprine are used
Depress immune system

**5-aminosalisalate inhibitor drugs**

Used for topical therapy of inflammatory bowel disease

**Mechanism**

- inhibit synthesis of prostaglandins
- inhibit synthesis of inflammatory mediators
- interfere with the production of inflammatory cytokines

Generic name for 5ASA is Mesalamine

**Adverse effects** ➔ GIT upset, headache, nausea, bone marrow suppression and hypersensitivity reactions

**Anti TNF drugs**

⇒ Natalizumab

- Block integrins on circulatory leukocytes
- Used in severe Crohn’s disease

**Antiemetic drugs**

H₂Canada
<table>
<thead>
<tr>
<th>Letter</th>
<th>Mnemonic</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>5HT₃ blockers</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>H₁ blockers</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Corticosteroids</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Anti-muscarinics</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Nurokinin receptor antagonists</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>D₂ blockers</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
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</tr>
</tbody>
</table>

**5HT₃ antagonists**

Go to 5HT₃ antagonists in chapter of histamine and serotonin
Location of HT3 receptor is

**HT 3 Receptors**

*Located in Endings of Nerves*

And Third letter of ABC is C so I can say HT 3 is in Nerve endings of chemoreceptor Trigger zone.

So it will have role in vomiting

And its antagonists will stop vomiting

**Use**

- Antiemetic in chemotherapy
- Post-operative vomiting

**Drugs**

Imagine Granny is driving a Honda motor cycle and everyone saying hello! hello!

Granny ➔ Granisteron

hONDA ➔ Cndasteron

**H₁ blockers**

Go to chapter of histamine and serotonin for more details
**H1 Blockers**

**First Generation**

DiDi promotes cycling

Di → Diphenhydramine
Di → Dimenhydrinate
Promotes → Promethazine
Cycling → cyclizine

**Mechanism**

- Histamine receptor 1 Blockers
- Structurally resemble muscarinic and adrenergic receptors

Antihistamine + anticholinergic + antiemetics + antitussives

**Corticosteroids**

Dexamethasone is used → anti-inflammatory and immunosuppressant

For further readings read in Corticosteroids chapter

**Anti-muscarinics → scopolamine**

**3 Scopolamine**

SMS

S → short term memory loss
MS → Motion sickness

**Neurokinin receptor antagonists → apirepitant**

- Chemotherapy induced nausea vomiting used

**D2 blockers → prochlorperazine**
Antiemetic treatment of nausea and vomit

**Antidiarrheal drugs**

- Loperamide
- Colloidal bismuth compounds
- Pectin and Kaolin absorbent compounds

**Loperamide**

Activate opioid mu receptors → decrease tone of longitudinal muscles.

**Colloidal bismuth compounds**

Subsalicylate and citrate salts → effective in travellers’ diarrhoea

**Pectin and Kaolin** → absorbent compounds

**Laxatives**

- Mg(OH)₂ and other nonabsorbant s
- Bulk forming compds → methyl cellulose and psyllium
- Stool surfactants → mineral oils
- Stimulants → cenna
- chloride channel activators → lubiprostone
- Opiod receptor inhibitors
Drugs acting on CNS.
20. Sedative and Hypnotics

Benzodiazepines

Members and Classification

Benzodiazepenes

<table>
<thead>
<tr>
<th>Short acting</th>
<th>Intermediate acting</th>
<th>Long acting</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOM</td>
<td>Steal</td>
<td>chloro floro carbon drugs</td>
</tr>
</tbody>
</table>

Short acting
TOM

T ➔ Triazolam
O ➔ oxazepam
M ➔ Midazolam

Intermediate acting

STEAL

S ➔ skip
T ➔ Teniazepam
E ➔ Estazolam
A ➔ Alprazolam
L ➔ Lorazepam

Long acting

Chloro floro carbon drugs
Chloro ➔ Chlorazepam
Floro ➔ Flurazepam
Carbon ➔ Chlordiazepoxide
Drugs ➔ Diazepam

Benzodiazepines not metabolized by the liver

Outside the liver
Outside ➔ oxazepam
The ➔ tempazepam
Liver ➔ lorazepam

They can be used in patient with liver disease
Actions of Benzodiazepines

Ben SCAM not by brain but by muscles

- Ben ➔ actions of benzodiazepines
- S ➔ sedation and hypnosis (used in insomnia)
- C ➔ anti-Convulsant (used in seizures)
- A ➔ anti-anxiety (used in panic disorders and Generalized anxiety disorders)
  - Also produces short term amnesia (used in premedication for medical procedures)
M → Muscle relaxants (used to relieve muscle spasm)

BEN SCAM
- Ben hate alcohol
  - So you can use him to avoid alcohol

Other way you can use to remember this is

SAM said Aaaah
- S → Sedation → relief of anxiety
- A → Anti-convulsants → in seizures
- M → Medullary depression → lead to respiratory and cardiac depression
- Said → Sleep onset → hypnosis
- Aaaah → Anaesthesia → amnesia + conscious loss + Reflex loss

Ben have big muscle so can relax muscles

Ben have good body figure
- So he is confident and he says I am overly calm

Ben is a powerful man so he do his work in short time
- * Benzodiazepines used for shorter duration to avoid dependence
Side effects

ABCDE

A ➔ Ataxia
  Dec alertness
B ➔ behavioural disturbances
C ➔ coma
  Decreased concentration
  Decreased co-ordination
D ➔ Depression (resp and CNS)
  Drowsiness
  Diplopia
E ➔ Decrease erection

Antidote

Ben is off with flu (Ben ko flu tha is liay chuti par hay)

Effects of benzodiazepines are reversed by Flumazenil.

Barbiturates

Members and classification

Meray father ka name Boota hay. Jab wo chotay thay to aam k darakht par charh gaey or whan say aik second main 5 aam tor kar phenkay

So mnemonic will be
  Bootay nain aik sec main 5 aam phenkay
<table>
<thead>
<tr>
<th>Mnemonic</th>
<th>Description</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bootay nain</td>
<td>Buta + Barbital ( \rightarrow ) butabarbital</td>
<td>Buta + Barbital</td>
</tr>
<tr>
<td>aik Second</td>
<td>Seco + barbital ( \rightarrow ) secobarbital</td>
<td>Seco + barbital</td>
</tr>
<tr>
<td>5</td>
<td>Penta + barbital ( \rightarrow ) pentabarbital</td>
<td>Penta + barbital</td>
</tr>
<tr>
<td>Aam</td>
<td>Amo + barbital ( \rightarrow ) Amobarbital</td>
<td>Amo + barbital</td>
</tr>
<tr>
<td>phenkay</td>
<td>Pheno + barbital ( \rightarrow ) Phenobarbital</td>
<td>Pheno + barbital</td>
</tr>
</tbody>
</table>
Mechanism

Bootay nain aik sec main 5 aam phenkay

BarbiDURATES ➔ Duration
• Barbiturates increase the duration of Cl⁻ channel opening thus decrease neuron firing

**Effects**

Effects will be same as benzodiazepines except muscle relaxant effects

- S → sedation (Sedation at lower doses to anaesthesia at higher doses)
- C → anti-Convulsants
- A → anxiolysis and hypnosis

**Other uses**

- Physician assisted suicide
- Capital punishment by lethal injection
- Na-Pentothal → truth serum
- Weak analgesia

**Side effects**

- Children are annoying (hyperkinesis + irritability + Insomnia + Aggression)
- Adults are sleepy (Sedation Dizziness and Drowsiness)
- Or you can use same side effects here ABCDE. Benzodiazepines and Barbiturates have similar effects.

**Contraindications**

- Pregnant women → foetus
- Babies → see side effects
- Aged person → difficult to remove from body
- Breast feeding → can came in Breast milk
Mechanism of Benzodiazepines and Barbiturates

GABA mediated chloride channel have 5 subunits two alpha, two beta and one gamma subunit.

**Benzodiazepines and newer hypnotics (like zolpidem)**

Binding at single site between alpha and gamma subunits
- Benzodiazepines antagonist Flumazenil also bind to this site

**Barbiturates**

Bind to sites on alpha and beta subunits

**GABA**

Bind to site between alpha and beta subunits

**Tolerance**

- Decrease responsiveness when used chronically in larger amount.
- Reduction in drug effect to amount of drug that was previously effective

**Cross tolerance**

Cross tolerance occurs when a person is tolerant to effects of a Drug and he also develop tolerance to another drug
- This happens with two drugs with similar functions or effects for example acting on same cell receptor
• Cross tolerance also present in sedative and hypnotics (Benzodiazepines and barbiturates)

**Physiological dependence**
Dependence that involves persistent physical–somatic withdrawal symptoms

• (fatigue, anxiety, tremors and/or persistent insomnia depending on substance)

**Psychological dependence**
Dependence that involves emotional–motivational withdrawal symptoms.

• Loss of comfort
• Loss of pleasure etc.

Physiological and psychological dependence → result in compulsive use of these drugs

⇒ Tolerance, Cross tolerance, physiological and psychological dependence are common with sedatives and hypnotics

**Atypical sedatives and hypnotics**

**Buspirone**

• Minimal CNS depressant effects (it does not affect driving skills)
• No anticonvulsant and muscle relaxant properties

⇒ Partial agonist at 5HT and D₂ receptor

**Good things about this**

- Development of tolerance with chronic use is minimal
- Little rebound anxiety and withdrawal symptoms
BUSPAR BUS

Get on the Buspar Bus to decrease anxiety. The seats recline for the undesirable effect of dizziness and drowsiness. Smiles can be seen after taking the drug for a week.

- Safe in pregnancy

**Adverse effects** ➔ GIT distress + Tachycardia + pupil constriction

**Ramelton**

- Activate melatonin receptors in suprachiasmatic nuclei of the CNS
- Decrease latency (delay) of sleep with minimal rebound insomnia and withdrawal symptoms

**Good things about this**

- Minimal dependence liability
Minimal abuse liability

**Adverse effects** → dizziness, fatigue and endocrine changes
21. Alcohols

Metabolism

Ethanol $\rightarrow$ Acetaldehyde $\rightarrow$ Acetate

Ethanol $\rightarrow$ Acetaldehyde

- Concentration below 100mg/dl
  Alcohol dehydrogenase is active
    - Alcohol dehydrogenase is inhibited by Fomipizol
  - Concentration above 100mg/dl
    Microsomal ethanol oxidizing system is active

Acetaldehyde $\rightarrow$ Acetate

- Aldehyde dehydrogenase is working
  - Aldehyde dehydrogenase is inhibited by Disulfiram
Effects Produced by ethanol

- Acute effects
- Chronic effects

**Acute effects**

- 60 to 80 mg/dl ➞ impairment of driving ability
- 120 to 160 mg/dl ➞ Gross drunkenness
- More than 300 mg/dl ➞ Loss of conscious, anesthesia and coma
- More than 500 mg/dl ➞ Lethal

**Other effects**

- Sedation
- Sedation, inhibition loss, impaired judgment and slurred speech

- CNS effects mg/dl ➞ produce due to modulation of signalling proteins
• Heart mg/dl ➔ depressed
• Blood vessel mg/dl ➔ vasodilation
• Smooth muscles ➔ relaxed

Chronic effects

• Tolerance
  Tolerance develop due to
  o Due to CNS adaptations
  o Due to faster metabolism
• Fatty liver ➔ irreversible hepatitis, cirrhosis and liver failure
• GIT ➔ irritation, inflammation and bleeding
• CNS ➔ most common effect ➔ peripheral neuropathy
• Thiamine deficiency ➔ Wernicke Korsakoff syndrome ➔ CAP ➔ confusion, ataxia and paralysis extraocular muscles
• Endocrine ➔ gynecomastia and testicular atrophy
• CVS ➔ Hypertension, anemia and cardiomegaly
• Immune system ➔ increase inflammatory effects

Foetal alcoholic syndrome

Alcohol in pregnancy ➔ teratogenic

• If used ➔ can lead to
  ➔ Alcohol in MUG
    o M ➔ mentally retard and microcephaly
    o U ➔ underdeveloped mid face
    o G ➔ Growth deficiencies

Treatment
Ethanol.

- Used as antidote in methanol and ethylene glycol poisoning.

Methanol poisoning.

- Leads toxic level of formate ➔ visual disturbances, coma and seizures
- Death due to respiratory failure
- **Fomipizol** ➔ used in treatment of methanol and ethylene glycol poisoning
- Inhibit alcohol dehydrogenase **Fomipizol** ➔ used in treatment of methanol and
  - Inhibit the formation of toxic metabolites (formaldehyde and formate)
    - Fomipizol ➔ F ➔ formaldehyde and formate

Ethylene glycol poisoning.

- Toxic aldehydes and oxalates ➔ kidney damage and severe acidosis

Treatment of Acute ethanol withdrawal.

1) Benzodiazepines

- **If Liver is working fine** ➔ Long acting ➔ diazepam
- **If liver is abnormal** ➔ Drugs metabolized outside the liver are used
  - Lorazepam is used (outside the liver * From benzodiazepines)
- **Use** ➔ prevention and treatment of acute ethanol withdrawal syndrome

2) Thiamine (B₁₂)

- Coenzyme required for thiamine phosphatase
Use to prevent Wernicke korsakoff’s syndrome

Drugs used in treatment of chronic alcoholism.

1) Opioid receptor antagonist

- Naltrexone used non-selective competitive antagonist of opioid receptors
  - Reduce risks of relapse

2) Enzyme inhibitors

- Disulfiram inhibit aldehyde dehydrogenase accumulation of acetaldehyde increase acetaldehyde major cause of hangover
- Prevention of relapse in individuals with alcohol disorders
- **Symptoms**
  Symptoms include flushing of the skin, accelerated heart rate, shortness of breath, nausea, vomiting, throbbing headache, visual disturbance, mental confusion, postural syncope, and circulatory collapse.

3) Others

- Acamprosate block NMDA receptor
  - Reduce risks of relapse

Treatment of methanol poisoning

- Maintenance of vitals
- Administration of thiamine (for thiamine deficiency)
- Electrolyte (for electrolyte imbalance)
- Treatment of alcohol withdrawal syndrome by benzodiazepines
- Treatment of alcoholism by Disulfiram
22. Anti-seizure Drugs

Seizures

Partial seizures
- Simple PS
- Complex PS
- Partial generalized S

Generalized seizures
- G-tonic clonic s
- Abscence S
- tonic and Atonic
- Clonic and mayoclonic

Pharmacokinetics
- They are used for long time
- All have hepatic metabolism (except gabapentin and vigabatrin)

Classification of Drugs
# Antiseizure Drugs

## Partial and tonic clonic seizures
VLC players
- **V** → Valproate
- **L** → Lamotrigine
- **C** → Carbamazepine
- **Player** → phenytoin Na

## Absence seizures
Valproate and ethosuxamide are used

## Myoclonic seizures
- **V** → valproate
- **L** → Lamotrigine
- **C** → Carbamazepine

## Backup drugs
Lela feto got Vig

## Partial seizures and tonic clonic seizures

<table>
<thead>
<tr>
<th>VLC player</th>
<th>Absence seizures</th>
<th>Mayoclonic seizures</th>
<th>Backup drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>V</strong></td>
<td>VE</td>
<td>VLC</td>
<td>Lela feto got Vig</td>
</tr>
</tbody>
</table>
Lela fato got Wig (hairs wali)

Lela ➔ lamotrigine
Fe ➔ Felbamate
To ➔ Topiramate
Go ➔ Gabapentin
T ➔ Taigabine
Vig ➔ Vigabatrin

Sites of Drug action & Uses

Na⁺ channel blockers

Zoni found a car lamozin
  Zoni ➔ zonisamide
  Found ➔ phenytoin
  Car ➔ carbamazepine
  Lamozin ➔ lamotrigene

Uses
  • Tonic clonic seizures
  • Partial seizures

Ca⁺² Blockers

Cave
  Ca ➔ Ca channel blockers
  V ➔ Valproate
E ➔ Ethosuxamide

**Uses**
- Myoclonic seizures
- Absence seizures

**GABA related targets**

Baba G took vegan

- Ba ➔ benzodiazepine
- Ba ➔ Barbiturate
- G ➔ GABA-pentin
- Took ➔ Tiagabine
- Vegan ➔ Vigabatrin

**Uses**
- Tonic clonic seizures
- Partial seizures

---

**Phenytoin**

**Mechanism**

Na⁺ Phenytoin ➔ this Drug block Na⁺ channels in neuronal membranes

**Clinical uses**

Drug of choice in
- Generalized tonic clonic seizures
- Partial seizures
  ➔ Elimination of Drug ➔ dose dependant
Adverse effects

Phenytoin

P ➔ P450 interactions
H ➔ Hirsutism
N ➔ Nystagmus
Y ➔ yellow brown skin
T ➔ teratogenic
O ➔ Osteomalsia
I ➔ Interfere B₁₂ metabolism (anemia)
N ➔ Neuropathies

Carbamazepine

Mechanism

Block voltage gated Na⁺ channels ➔ decrease glutamate release

Uses

• Generalized tonic clonic seizures
• Partial seizures

Adverse effects

Carbon on hand

Carbon ➔ Carbamazepines
H ➔ Headache
A ➔ Ataxia
N ➔ Nausea
D ➔ diplopia

Lamotrigine
Mechanism
Block Na\(^+\) and Ca\(^{2+}\) channels

Uses
- Generalized seizures
- Partial seizures
- Myoclonic seizures

Adverse effects
- Dizziness
- Diplopia
- Headache
- Rash

Valproate

Mechanism
- Block Ca\(^{2+}\) channels (T type)
- Beta block high frequency firing

Uses
- Used in all types of parkinsonism

Adverse effects
Valproate
- V ➔ Vomiting
- A ➔ Alopecia
- L ➔ Liver (Hepatotoxic)
- P ➔ Pancreatitis
- R ➔ Retention of fat (obesity)
O → Oedema
A → Appetite increase
T → Teratogenicity
E → enzyme inducer

**Ethosuxamide**

**Mechanism** → decrease Ca$^{+2}$ current (T type)

**Uses** → Absence seizures

**Adverse effects** → GIT distress and CNS effects

**Gabapentin**

Analogue of GABA

**Mechanism** → Block Ca$^{+2}$ channels

**Uses**
- Generalized tonic closure seizures
- Partial seizures

**Adverse effects** → ataxia and dizziness

**Benzodiazepines**

**Mechanism** → Bind GABA receptor subunit → opening of Cl$^{-}$ channels (increase frequency of opening of channels)

**Uses**
- All except absence seizures (Generalized tonic clonic, Partial and myoclonic seizures) [Clonazepam]

**Barbiturates**

Phenobarbitone
**Mechanism** ➞ Opening of chloride channels like benzodiazepines (increase duration of opening)

**Uses**
- Same as barbiturates

**GABA pentin**

Analogue of GABA
- Uses and adverse effects as barbiturates and benzodiazepines

**Vigabatrin**

**Mechanism** ➞ inhibition of GABA transaminase

V for vegan and vegan is used for transport So Transaminase is inhibited here

**Uses**
- Generalized tonic clonic seizures
- Partial seizures

**Side effects**

**D₂O**
- Drowsiness
- Dizziness
- Ocular side effects

**Tiagabine**

Tiagabine ➞ T ➞ inhibit GABA Reuptake by transporter

**Uses** ➞ Partial seizures

**Side effects** ➞ Dizziness, Depression and seizures
23. General anaesthetics

Stages of Anaesthesia.
Also called Guedel’s signs
Anny did some mistakes (or you can use this Annay di serial maan)

<table>
<thead>
<tr>
<th>Anny</th>
<th>• Analgesia</th>
</tr>
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<tbody>
<tr>
<td>Did</td>
<td>• Disinhibition</td>
</tr>
<tr>
<td>some</td>
<td>• surgical anaesthesia</td>
</tr>
<tr>
<td>mistakes</td>
<td>• Medullary depression</td>
</tr>
</tbody>
</table>

Stages of anaesthesia

1) **Analgesia**
   Decrease awareness of pain

2) **Disinhibition**
Delirious and exited

3) **Surgical anesthesia**
   Unconscious + no pain reflexes

4) **Medullary depression**
   Severe respiratory and CNS depression
   ➔ Dangerous stage

**Inhaled anesthetics.**

This English is having some nitrous oxide, ether and chloroform.

![Image of a person wearing a respirator and adjusting a machine]
Others either and chloroform were previously used not now.

**Mechanism**

FAN

- F ➔ Facilitate GABA mediated inhibition
- A ➔ Ach receptor blockage
- N ➔ NMDA receptor blockage

**Elimination**

Elimination of drugs through lungs for inhalational anaesthetics

Halothane ➔ liver metabolism (H for hepatic)

**Side effects**

- Increase ICP
- Respiratory depression
- CNS depression
- Cardiac depression
Intravenous anaesthetics

Barbie doll in Pacific Ocean

<table>
<thead>
<tr>
<th>Bar</th>
<th>• Barbiturates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bie</td>
<td>• benzodiazepenes</td>
</tr>
<tr>
<td>doll</td>
<td>• Dissociatives</td>
</tr>
<tr>
<td>in</td>
<td>• imedazole</td>
</tr>
<tr>
<td>pacific</td>
<td>• phenols</td>
</tr>
<tr>
<td>ocean</td>
<td>• opioids</td>
</tr>
</tbody>
</table>

Barbiturates

Thiopental, Thioamylal and methohexital
Effects (high lipid solubility and shorter duration of action)

- Respiratory and CNS depression
- Decrease ICP

Side effects

CNS depression extensions

Benzodiazepines

Midazolam, diazepam and lorazepam are used

Effects

- Less depression than barbiturates
- Shorter onset and longer duration of action than barbiturates

Side effects

- Respiratory depression

Dissociative ➔ Ketamine

Block excitation by NMDA receptor

- NMDA ➔ N methyl D aspartate

Effects

- Analgesia
- Amnesia
- Catatonia ➔ neurogenic motor immobility
- CVS stimulation

Dissociative anaesthesia

Dissociative are a class of hallucinogen in which distort perceptions of sight and sound and produce feelings of detachment (dissociation) from the environment and self.
• Complete unconsciousness is not present
• Generalize anaesthesia → characterized by catalepsy, catatonia and amnesia.

**Opioids**

Morphine and alfentanil

**Mechanism** → interact with mu, kappa and delta for endogenous opioid peptides.

**Effects**

Analgesia and respiratory depression

**Side effects**

Respiratory depression

**Effects produces by General anaesthetics**

Effects produced by general anaesthetics are $A_6$

- A → anaesthesia → hypnosis and conscious loss
- A → analgesia → loss of pain sensation
- A → Amnesia → Memory recall loss
- A → Autonomic areflexia → sympathetic Nervous control loss
- A → Areflexia → reflex loss
- A → anxiolysis → anxiety control
### 24. Local anaesthetics

#### Classification

**Local anesthetics**

<table>
<thead>
<tr>
<th>Easters</th>
<th>Amindes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short term</td>
<td>Medium action</td>
</tr>
<tr>
<td>Procaine</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>Long term</td>
<td>Long action</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>Bupivacaine</td>
</tr>
<tr>
<td>Surface action</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
</tr>
<tr>
<td>Benzocaine</td>
<td></td>
</tr>
</tbody>
</table>

**Easters**

Pakistan tele communication board

- Pakistan ➔ Procaine
- Tele ➔ Tetracaine
- Communication ➔ Cocaine
- Board ➔ Benzocaine
All members have one i in them examples ➔ Procaine, Tetracaine, cocaine and Benzocaine

**Amides**

All members have two i in them examples ➔ Lidocaine, Bupivacaine and Ropivacaine.

**Mechanism**

Local anesthetics ➔ block voltage gated Na\(^+\) channels ➔ prevent depolarization ➔ Block conductance of action potential

- Higher concentration of K\(^+\) in extracellular environment elevate their local activity
- Higher concentration of Ca\(^{2+}\) in extracellular environment antagonise the action of Local anesthetics

**Clinical uses**

- Minor surgical procedures
  - Mostly combined with vasoconstrictor (epinephrine)
    - Lee bleeding
    - Less dose of anesthetic required
    - Action prolonged
    - Less toxicity due to lesser systemic absorption
- Spinal anesthesia ➔ abdominal surgery
- Analgesia after surgery (post-operative analgesia) (slow epidural low concentration infusion)
- Surface anesthesia ➔ in dentistry and eye surgery
- Shoulder and arm surgery ➔ plexus anesthesia
• Surgery of skin ➔ topic anesthesia

**Adverse effects**

Sheda in L.A (Los Angeles)

S ➔ seizures
H ➔ hypotension
E ➔ CNS exited
D ➔ vasodilation
A ➔ arrhythmias
I ➔ localized impairment of Nerve
L ➔ Localized adverse effects ➔ prolonged anesthesia (numbness) and paresthesia (tingling, feeling pins)
A ➔ arrhythmias

**Cocaine**

Causes vasoconstriction and hypertension while for others effects remain the same
25. Skeletal Muscle Relaxants

Neuromuscular Blockers

- Non-depolarizing drugs
  - Long acting: tubocurarine
  - Short acting: mivacurium
- Depolarizing drugs: succinylcholine

Neuromuscular Blocking drugs

Block transmission on neuromuscular end plate of skeletal muscle

Non-depolarizing drugs

Antagonists and non-competitive
  - Less anesthetic is required to produce muscle relaxation

Mechanism of action

At Low doses
Non-depolarizing neuromuscular blocker ➔ prevent attachment of acetylcholine to nicotinic receptor ➔ prevent depolarization of muscle cell membrane ➔ inhibit muscle cell contraction

- Effects overcome by increase Acetylcholine ➔ by administration of cholinesterase inhibitors.

At higher doses

- Block the ion channel of the end plate ➔ further weakness of neuromuscular transmission.

- Effects not overcome by increase of acetylcholine ➔ because the ion channel is **Blocked**

**Actions**

Muscle relaxation from smaller to larger muscles

- Diaphragm Muscles are last to paralysed.

**Therapeutic usage**

Adjuvant drugs in anesthesia ➔ less anesthetic is needed to produce muscle relaxation

**Classification**

- Tubocurarine
- Mivacurium
- Metocurium
- Desocurium
- Rocuronium

Vacuronium and rocuronium ➔ are deacetylated in liver ➔ clearance is prolonged in hepatic disease.

LVR ➔ liver

**Drug inter actions**
1) Cholinesterase inhibitors

Neostigmine and physostigmine overcome action of nondepolarizing neuromuscular blockers

2) Halogenated hydrocarbon anesthetics

Increase neuromuscular blockage \( \rightarrow \) like halothane

3) Aminoglycoside antibiotics

Gentamicin and toberamicin \( \rightarrow \) inhibit Acetylcholine release by inhibiting \( Ca^{+2} \) release

4) Ca channel blockers

Increase neuromuscular blockage

---

**Depolarizing neuromuscular blockers**

Succinylcholine.

**Mechanism**

Attaches to Nicotinic receptors \( \rightarrow \) persist at high concentration in synaptic cleft and remain attached to the receptor for longer time \( \rightarrow \) provide constant stimulation.

**Phase I**

Membrane depolarization result in initial discharge which produces transient fasciculations followed by flaccid paralysis

**Phase II**

Full neuromuscular blockage is achieved and receptor is desensitized to effect of acetylcholine

- Now receptor is resistant to depolarization (closed or blocked)

**Actions**

Sequence of paralysis little different.
• Respiratory muscles are paralysed in last
Initially produce short lasting fasciculations ➔ followed within minute by paralysis

**Therapeutic usage** (rapid onset and short duration)
• When rapid endotracheal intubation is required ➔ to avoid aspiration of gastric contents to be avoided during intubation
• Electroconvulsive shock treatment

**Adverse effects**
• Hyperthermia
• Apnoea
26. Drugs used in Parkinsonism

TREATMENT OF PARKINSONS DISEASE

Causes of Parkinsonism

causes of Parkinsonism

<table>
<thead>
<tr>
<th>Natural causes</th>
<th>Drug induced causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>dec level of stratal dopamine</td>
<td>reserpine</td>
</tr>
<tr>
<td>degeneration of dopaminergic</td>
<td>Due to depletion of dopamine</td>
</tr>
<tr>
<td>neurons</td>
<td></td>
</tr>
</tbody>
</table>
Symptoms of Parkinsonism

RAFT

R ➔ rigidity of skeletal muscle
A ➔ akinesia (bradykinesia)
F ➔ flat face (expression less)
T ➔ tremors at rest

DRUGS USED IN PARKINSONISM

Mamu dp.com

Parkinsonism Drugs

<table>
<thead>
<tr>
<th>Ma</th>
<th>Mu</th>
<th>dp</th>
<th>Dot</th>
<th>Com</th>
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</thead>
<tbody>
<tr>
<td>MAO inhibitors</td>
<td>Muscarinic inhibitors</td>
<td>dopamine precursors</td>
<td>dopamine agonists</td>
<td>COMT inhibitors</td>
</tr>
</tbody>
</table>

MAO inhibitors

ISP or Pakistan international school

I ➔ isocarboxazid
S ➔ selegeline
P ➔ phenelezine

Mechanism
- Inhibit MAO (Monoamine oxidase enzyme) ➔ catabolism of amines (Dopamine) inhibited
- Used as adjuncts with levodopa in treatment of parkinsonism

Muscarinic Inhibitors
Muben ➔ Mu + ben ➔ Muscarinic inhibitors ➔ durug is benztropine

Mechanism
- Block muscarinic receptors

Uses
- Improve tremors and rigidity but not bradycardia

Adverse effect
- Muscarinic inhibitors (ANS section for side-effects)

Dopamine precursors
Levodopa and Carbidopa are used
- Levodopa ➔ metabolic precursor of dopamine and this restores the dopamine level in extrapyramidal centres
  - Provide symptomatic relief that last only when drug is present in body
- Carbidopa ➔ inhibit peripheral metabolism of Levodopa

Mechanism
Parkinsonism ➔ decrease level of dopamine in specific regions of brain
Dopamine ➔ cannot cross blood brain barrier

Levodopa ➔ immediate precursor of dopamine & can cross blood brain barrier

Carbidopa ➔ inhibit peripheral metabolism of Levodopa and cannot cross blood brain barrier SO metabolism inside brain will not be effected ➔ Lower dose of levodopa to 4 to 5 folds and decrease severity of side effects

**Therapeutic uses**

Levodopa in combination with Carbidopa is potent and efficacious drug regime currently available

- Decrease severity of disease for few years

**Absorption and metabolism**

- Absorbed rapidly from small intestine
- Half-life 2-3 hours
• Fluctuations in plasma concentration produces ➔ Fluctuations in motor response (ON OFF phenomena) ➔ sudden loss of mobility and tremors

Dietary interactions

• High protein meal ➔ interfere transport of levodopa (leucine and isoleucine compete with this drug for absorption and transport.
• Taken empty stomach 45 min before meal

Adverse effects

LEVODOPA

L ➔ lower blood pressure and loss of hairs
E ➔ emesis ➔ stimulate emetic centre
V ➔ ventricular extrasystole
D ➔ dyskinesia
O ➔ (°) ➔ o resemble eye ➔ Visual and auditory hallucinations
P ➔ protein interference with Levodopa ➔ nausea
A ➔ Anorexia

Interactions

• Vit B₁₂ ➔ increase peripheral breakdown of levodopa
• Antipsychotic drugs ➔ contraindicated in patients of parkinsonism ➔ exacerbate symptoms

Dopamine agonists

Bromocriptine (D₂ agonist) and pramipexol (D₃ agonist)

Uses

• Used in early treatment of parkinsonism
• Adjuncts to levodopa in treatment of parkinsonism
## COMT inhibitors (catechol o methyl transferase)

**Capones**
- Entacapone
- Tolcapone

**Mechanism**
- Block levodopa metabolism in periphery

**Uses**
- Prolong levodopa actions

## Tourette’s syndrome

- Haloperidol $\rightarrow$ D$_2$ blocker
- Clonidine $\rightarrow$ alpha$_2$ blocker

**Use**
- Reduce vocal and motor tic frequency
27. Antipsychotics and Lithium

Antipsychotics.

Classical Drugs (typical)
- Haloperidol
- Chlorpromazine
- Fluphenazine
- Thioridazine
- Risperidone

Newer agents (atypical)
- Olanzapine
- Zaprasidone
- Quetiapine

Classical agents \(\rightarrow\) D\(_2\) receptor affinity

Chlorine said! Hallo tharki fluorine
- Chlorine \(\rightarrow\) Chlorpromazine
- Hallo \(\rightarrow\) Haloperidol
- Tharki \(\rightarrow\) Thioridazine
- Fluorine \(\rightarrow\) Fluphenazine

Newer agents \(\rightarrow\) 5HT\(_2\) affinity

Chlorine said hy! to tharki Fluorine

Hy!
Roz (rose) from Quetta came

R ➔ Risperidone
O ➔ Olanzapine
Z ➔ Ziprasidone

From ➔ says ➔ 5HT₂ receptor affinity
Queta ➔ Quetiapine

USES

Antipsychotics ➔ AntiPSychotics

A ➔ treatment of agitated state
P ➔ Psychosis
S ➔ Schizophrenia

PHARMACOKINETICS

- Lipid soluble readily enter CNS
- Hepatic metabolism

Mechanism of action

- Dopamine hypothesis (older)
- Serotonin hypothesis (new)

1) Dopamine hypothesis

- Schizophrenia ➔ is due to excess of functional activity of neurotransmitter dopamine in specific brain tracts
  ➔ Dopamine tracts (multinational technical college)
  - Mesocortical & mesolimbic pathway
  - Nigrostriatal tract
  - Tuberoinfundibular tract
  - Chemoreceptor trigger zone
231

DOPAMINE receptors ➔ G protein coupled receptors

2) Serotonin hypothesis

These antipsychotics Block serotonin 5HT₂ receptor and also D₂ receptors

Clinical Uses of Antipsychotics

PAKISTANI BATS

- Pakistani ➔ psychotic and neurological disorders
- B ➔ bipolar disorders
- A ➔ antiemetic
- T ➔ Tourette’s syndrome
- S ➔ schizophrenia treatment

Side effects of Antipsychotics

Ramzan SHADED a new painting

Ramzan ➔ reversible neurologic effects (Bradykinesia, rigidity)

S ➔ sedation

H ➔ hypotension

A ➔ anticholinergic (autonomic effect)

D ➔ dermatologic effects

E ➔ endocrine (increased prolactin)

Extra pyramidal effects

D ➔ deposits in rating

New ➔ neuroleptic malignant syndrome

Painting ➔ Parkinsonism
Lithium.

**Uses**

Lithium ➔ ends on M ➔ used in manic phase of bipolar disorder

- Prevention and treatment of manic and depressive episodes

**Mechanism**

- Inhibit several enzymes involved in recycling of neuronal membrane phosphatides.
  ⇒ Result Suppress IP3 and DAG signaling

**Adverse effects**

Lithium

- L ➔ leucocytosis
- I ➔ insipidus (diabetes)
- T ➔ tremors and teratogenic
- H ➔ hypothyroidism
- I ➔ increased weight
- U ➔ v ➔ vomit
- M ➔ regular monitoring (because Li interfere Na⁺ and H₂O levels in body

**Other used as antipsychotic (VLC)**

- V ➔ valproic acid
- L ➔ lamotrigine
- C ➔ carbamazepine
28. Antidepressants

Members and Classification

Maria tanver sweet sweet hay

<table>
<thead>
<tr>
<th>Maria</th>
<th>• Mao inhibitors</th>
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<tbody>
<tr>
<td>Tanver</td>
<td>• TCAs</td>
</tr>
<tr>
<td>Sweet</td>
<td>• SSRIs</td>
</tr>
<tr>
<td>Sweet</td>
<td>• SNRIs</td>
</tr>
<tr>
<td>hay</td>
<td>• 5HT2 antagonists</td>
</tr>
</tbody>
</table>

MAO inhibitors.

⇒ Used in treatment of atypical depression
**Last line of treatment** ➔ due to lethal drug dietary interactions

Mao in ISP (international school of Pakistan)

I ➔ isocarboxazid

S ➔ selegeline

P ➔ phenlezine

**Mechanism**

Inhibiting the reuptake transport protein results in increased concentrations of serotonin and norepinephrine in the synaptic clefts, leading to improvement of depression symptoms.

Inhibit MAO enzyme (two isoforms A & B) ➔ prevent breakdown of monoamine neurotransmitters (example serotonin, dopamine and melatonin) ➔ increase their availability

**Uses**

In atypical depression.

**Interactions**

- **Catabolism of dietary amines is inhibited**
  - Food containing amines (cheese effect)
Hypertensive crisis are produced (tyramine displaces norepinephrine from storage vesicles) (or causes accumulation of catecholamines)

Examples ➔ liver, soyabean and aged cheese

- Food containing tryptophan ➔ hyperserotonemia ➔ fatal serotonin syndrome developed
- Should not be combined with other antipsychotics ➔ certain combination may prove lethal ➔ like with SSRIs and tricyclics
- Addictive potential of Nicotine (component of tobacco) is increased ➔ result difficulty in cessation of smoking.
- Cause hypertension with sympathomimetics

**Tricyclic antidepressants**

CIA is after cyclics

- C ➔ Clomipramine
- I ➔ imipramine
- A ➔ amitriptyline

**Mechanism**

Block nor-epinephrine and 5HT transporter

**Uses**

- Major depressive disorders
- Bipolar disorders
- Generalized anxiety disorders
- Post-traumatic stress disorders
- Body dysmorphic disorders
- Eating disorders (anorexia nervosa and bulimia nervosa)
• Borderline personality disorders
• Mood disorders
• Panic disorders
• Phobias (social phobias)

**Interactions**

TCAs are metabolized by cyt P450 ➔ drugs that inhibit cytP450 ➔ result increase TCA level and their toxicity is enhanced

**Side effects**

(TCAs)³

T ➔ Thrombocytopenia
  Tachycardia
  Tremors
C ➔ Cardiac (arrhythmias, MI and stroke)
  Comma
  Convulsions
A ➔ Anticholinergic effects
  Adipose ➔ obesity
  Appetite change
S ➔ Sedation
  Sweatening
  Seizures

**Selective serotonin reuptake inhibitors**

Sir Pera cita flu (or you can use this Pakistan chocholate factory)
  Sir ➔ sirotonin ➔ serotonin
Pera ➔ paroxetine
Cita ➔ citalopram
Flu ➔ fluoxetine and fluvoxamine

**Mechanism**

Block 5 HT transporter only

**Clinical applications**

Same from TCAs list

- In stroke
- Sidenaphil ➔ improvement in ejaculatory delay and sexual satisfaction

**Side effects**

SSRIs

S ➔ serotonin syndrome (It is a predictable consequence of excess serotonin on the CNS and/or peripheral nervous system.) (Symptoms ➔ increased heart rate, shivering, sweating, dilated pupils, myoclonus etc.)

S ➔ Stimulant CNS

- Stimulate CVS ➔ tachycardia
- Shorten weight (weight loss)
- Shorten appetite

R ➔ Reproductive dysfunction in males

I ➔ insomnia

S ➔ suicidal risks (usage is associated with increase suicidal risks in children and adults)
Selective norepinephrine reuptake inhibitors

SNRIs

Father and son ice-cream khanain gaey. Son nain two ice-creams li and father said

Son vanilla day do

Son ➔ SNRIs
Vanilla ➔ vanela ➔ vanla + fexine ➔ vanlafexine
Day ➔ des + vanlafexine ➔ desvenlafexine
Do ➔ dulextine

Mechanism

- Block norepinephrine reuptake
- Block 5HT transporter

Clinical applications

Major ➔ depression

Others from SSRIs

- Chronic pain (neuropathic pain)
- Anxiety disorders

Side effects

Same as SSRIs

- Less severe as compared to SSRIs

Sexual effects (decrease libido and difficulty to reach climax)

- Major cause of decrease compliance for both SNRIs and SSRIs
Additional side effects due to nor-epinephrine are

- Urinary retention
- Mydriasis
- Hypertension
- GIT motility

### 5HT₂ antagonists

Also called SARI (Serotonin antagonist and reuptake inhibitors)

Imagine ap nain 300 ki aik book kharedi and 313 ki baech di apko tera rupay ka nafa hoa

Tera + zodone → terazodone

Nafa + zodone → nafazodone

**Mechanism**

Block 5HT₂ receptor

Inhibit reuptake of serotonin and nor-epinephrine

**Clinical applications**

Same depression

**Adverse effects**

- Sedation
- Blurred vision
- Headache
- Fatigue
- Anticholinergic effects
29. Opioids

Opioids

Agonists

Strong
- morphine
- methadone
- meperidine

Moderate
- codeine
- oxycodone

Weak
- propoxyphene

Antagonists

Naloxon
naltrexon

Metabolism
To inactive glucuronide conjugates before excretion by kidney.

Opioid Receptors
functions of receptors

**Mu Receptors**
- Analgesia $\rightarrow$ produced by all types
- Mu cares
  - M $\rightarrow$ miosis
  - U $\rightarrow$ euphoria
  - C $\rightarrow$ constipation $\rightarrow$ decrease GIT motility
  - A $\rightarrow$ analgesia
  - R $\rightarrow$ respiratory depression
  - E $\rightarrow$ emesis
  - S $\rightarrow$ sedation

**Kappa receptors**
- Analgesia $\rightarrow$ produced by all types of receptors
• Kappa kiss
  o K ➔ kappa receptor
  o I ➔ inhibition of ADH
  o S ➔ Sedation
  o S ➔ stress
  o Other effects of mu receptor also weakly

**Delta receptor**

• Analgesia ➔ as others
• D delta
  o Dependence
  o Antidepressant

**Location of opioid Receptors**

**Located on**

• On Primary afferents
• Spinal cord pain transmission pathways
• Neurons in midbrain and medulla
• That involved in altering activities are located in Basal ganglia, hypothalamus and cerebral cortex

**Endogenous opioids**

Opioid-peptides that are produced in the body include:

• Endorphins
• Enkephalins
• Dynorphins
Ionic Mechanisms

Presynaptic membrane (all receptors)
- Decrease Ca influx \(\rightarrow\) decrease neurotransmitter release

Postsynaptic membrane (mu receptor)
- Increase K conduction \(\rightarrow\) inhibitory post synaptic potential developed

Members and classification

Strong agonists
Max effects \(\rightarrow\) M \(\rightarrow\) morphine, methadone and meperidine

Moderate agonists
Cods \(\rightarrow\) Codeine and oxycodone

Weak agonists
Propoxyphene \(\rightarrow\) partial mean weak

Effects produced

Acute effects
BAD Americans
- B \(\rightarrow\) Bradycardias and hypotension
- A \(\rightarrow\) Analgesia
  \[\text{treatment of moderate to severe pain}\]
- D \(\rightarrow\) Dependence
- A \(\rightarrow\) anorexia \(\rightarrow\) poor appetite and release of ADH hormone
- M \(\rightarrow\) miosis (characteristic of all opioids except meperidine)
- E \(\rightarrow\) euphoria \(\rightarrow\) state of excitement
R ➔ Respiratory depression
I ➔ increase smooth muscles activity ➔ biliary tract constriction (by increase contraction of biliary tract smooth muscles)
C ➔ constipation ➔ dec GIT motility ➔ effects of opioids on enteric nervous system (Used as antidiarrheal agents)
A ➔ antitussive ➔ suppression of cough reflex ➔ by inhibiting respiratory centres ➔ with decrease response to CO₂ challenge
N ➔ nausea and vomiting ➔ activate chemoreceptor trigger zone
S ➔ sedation and mental clouding (at higher doses)

Clinical Uses
- Analgesia ➔ fentanyl and morphine are used (Strong agonists)
- Cough suppression ➔ cods are used ➔ codeine
- Treatment of diarrhoea ➔ diphenoxylates are used
- Management of acute pulmonary edema ➔ morphine is used
- Anesthesia ➔ preoperative medicines are used

Opioid dependence
Methadone (longer acting opioids) ➔ used to manage withdrawal states of opioids and maintenance program in addicts.
- Prolonged usage of methadone ➔ block euphoric effects produced by short acting opioids (like heroin and morphine)
Side effects
Triad of toxic effects of opioids

Morphine
M → Miosis and mouth dryness
O → out of it → sedation
R → Respiratory depression
P → aspiration pneumonia
H → Hypotension
I → infrequent urination
N → Nausea
E → Emesis → vomiting

Opioid antagonists
Morph ran away with nelO
Morphine antagonist ➔ naloxone, naltrexone and nalmefene (antagonise opioid receptors)

- Treatment of opioid overdose
- Dependence maintenance
Endocrine Drugs
30. Thyroid and Antithyroid Drugs

Hypothyroidism

Levo thyroxine

Levo $\rightarrow$ T$_4$

Levo $\rightarrow$ have 4 letters $\rightarrow$ T$_4$ (Drug of choice for hypothyroidism)

Lio thyroxine

Lio $\rightarrow$ T$_3$

Lio $\rightarrow$ have 3 letters $\rightarrow$ T$_3$ (fast acting, shorter half-life and expansive)

Grave’s disease

Beta lymphocytes produces antibodies $\rightarrow$ that activates TSH receptors $\rightarrow$ result in production of thyroid hormone

- While TSH level in blood is low
$T_3$

$T_3$ is 10 times more potent than $T_4$

$T_4$

Converted into $T_3$ in target cells $\Rightarrow$ liver and kidney are examples of target cells

**Liothyroxine and Levothyroxine**

They activate nuclear receptor $\Rightarrow$ gene expression $\Rightarrow$ effects of Thyroid hormones are produced

$\Rightarrow$ Used in treatment of hypothyroidism

**Adverse effects**

Thyroidism

- T $\Rightarrow$ tremors and tachycardia
- H $\Rightarrow$ increase heart rate
- Y $\Rightarrow$ yawing
- R $\Rightarrow$ Restlessness
- O $\Rightarrow$ Oligomanuria
- I $\Rightarrow$ heat intolerance
- D $\Rightarrow$ diarrhoea
- I $\Rightarrow$ irritability
- S $\Rightarrow$ sweat
- M $\Rightarrow$ muscle wasting

**Antithyroid drugs**
**Bitar**

**Thioamides**
- PTU
- Propylthiouracil
- Methemazol

**Anion inhibitors**
- Thiocyanate
- Perchlorate

**Radioactive iodine**
- $^{131}$Iodine

**Beta blockers**
- Propranolol

**Iodide**
- Lugol solution
Mechanism

- Inhibit thyroid hormone synthesis
  - Block peroxide that catalyse iodination of thyroglobin
  - Block coupling of thyroglobin
  - Block coupling of MIT and DIT (mono iodo thyroxine and diiodo thyroxine)
  - Inhibit peripheral conversion of $T_4 \rightarrow T_3$

- **Methemazole** $\rightarrow$ preferred because can be administered per day

- **PTU (propylthiouracil)** $\rightarrow$ preferred in pregnancy + do not cross placenta + do not come in milk

Toxicity (reversible)

Rash + vaculitis + agranulocytopenia + liver dysfunction

<table>
<thead>
<tr>
<th>Anion inhibitors</th>
</tr>
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</table>

Thiocyanates and perchlorates

- Block uptake of iodide

Adverse effect $\rightarrow$ aplastic anemia

<table>
<thead>
<tr>
<th>Radioactive iodine</th>
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</thead>
</table>

Taken up by gland

**Dose** $\rightarrow$ is large enough to cause destruction of Gland

- Permanent treatment without surgery

<table>
<thead>
<tr>
<th>Beta Blockers</th>
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</thead>
</table>

Control tachycardia and other cardiac abnormalities produced by thyrotoxicosis

- Also inhibit peripheral conversion of $T_4$ into $T_3$
Use ➔ thyroid storm

Adverse effect ➔ BBC London TV (go to Side effects of beta blockers)

**Iodide salts**

They inhibit iodination and inhibit thyroid hormone release

- Result decrease size of the Gland

**Escape**

Thyroid gland escapes from iodide block after several weeks of treatment

**Uses**

- Thyroid storm
- Prepare patient for surgical resuscitation

**Adverse effects** ➔ rash + drug fever + metallic taste + rarely allergy
31. Corticosteroids and antagonists

Members and Classification

Corticosteroids

<table>
<thead>
<tr>
<th>Agonists</th>
<th>Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>Receptor antagonist</td>
</tr>
<tr>
<td>Mineralcorticoids</td>
<td>Synthesis inhibitor</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Glucocorticoid antagonist</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>Mineralcorticoid antagonist</td>
</tr>
<tr>
<td></td>
<td>Spironolactone</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole</td>
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<tr>
<td></td>
<td>Mifepristone</td>
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</tbody>
</table>

Mechanism

Enter the cell ➔ bind to cytosolic receptor ➔ transport corticosteroid into nucleus ➔ alter gene response by binding to gene response element ➔ specific response is made

Organ and tissue effects

- Stimulate gluconeogenesis
• Blood glucose rises
• Muscle protein is catabolized,
• Insulin secretion is stimulated
• Lipolysis and lipogenesis are stimulated → with net deposition of fat in face, shoulder and back.

Catabolic effects
• Muscle protein catabolism
• Lymphoid CT, fat and skin wasting under the influences of high concentration of steroids
• Can lead to osteoporosis

Immunosuppressive effects
• Inhibit cell mediated immunological functions
• Delay rejection reaction with organ transplant

Anti-inflammatory effects
• Increase neutrophils
• Decrease neutrophils, basophils and monocytes
• Migration of leukocytes is also inhibited

→ Induce synthesis of an inhibitor that decrease synthesis of Phospholipase A₂

• Decrease synthesis of inflammatory mediators

Clinical uses
1) Adrenal disorders.
• Chronic adrenal cortical insufficiency (Addison’s disease) Mineralocorticoids are used
• Congenital adrenal hyperplasia ➔ in which synthesis of hormone is stimulated by ACTH ➔ administration ➔ decrease synthesis of abnormal steroids

2) Non-adrenal disorders

• Inflammatory disorders and immunological disorders ➔ like asthma, transplant rejections, rheumatic diseases etc.

• Bachlomethasone ➔ hasten maturation of lungs in premature labour

Cushing syndrome ➔ Cortisol is Cushing

Addison’s disease ➔ cortisol do not add up

Adverse effects of corticosteroids

Cushingoid

C ➔ cataract
U ➔ ulcers
S ➔ skin stria + skin thinning + salt retention
H ➔ Hirsutism + hypertension + hyperglycaemia
I ➔ infections
N ➔ necrosis (avascular necrosis of femoral head)
G ➔ GIT ulcers
O ➔ obesity (buffalo hump obesity) + osteoporosis
I ➔ immune suppression
D ➔ diabetes mellitus
Antagonists

**Receptor Antagonist**

1) **Glucocorticoid antagonist** → mifepristone

Mifepristone → pharmacological antagonist of Glucocorticoid and progesterone antagonist

- **Use** → medical abortion and rarely in Cushing syndrome

2) **Mineralocorticoid antagonist** → Spironolactone

Spironolactone → pharmacological antagonist of mineralocorticoid receptor

- **Use** → aldosteronism + hypokalemia due to other diuretics

**Synthesis inhibitor**

**Ketoconazole**

Block fungal and mammalian Cyt P 450 enzyme

- **Use** → inhibit mammalian steroid hormone synthesis and fungal ergosterol synthesis.
32. Gonadal hormones and Inhibitors

Female Hormones

- Oestrogen
- Progesterone

Oestrogen

<table>
<thead>
<tr>
<th>Estrogens</th>
<th>Antiestrogents</th>
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</thead>
<tbody>
<tr>
<td>Estradiols</td>
<td>Receptor antagonist</td>
</tr>
<tr>
<td></td>
<td>Full antagonist</td>
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<tr>
<td></td>
<td>SERMs</td>
</tr>
<tr>
<td></td>
<td>Fulvestrant</td>
</tr>
<tr>
<td></td>
<td>temoxifen</td>
</tr>
</tbody>
</table>
Major is estradiol (have low oral bioavailability)

- Transdermal patches
- Vaginal creams
- IM injections are available

Oestrogen with max bioavailability ➔ Mestranol (max mean Mestra)

**Effects**

- Normal female reproductive development
  - Growth of genital structures
  - Sexual characters
  - Growth spurt associated with puberty

- Metabolic effects
Continuous administration result dec gonadotropin from anterior pituitary.

**Uses**

**Hot Chick**

H $\rightarrow$ HRT $\rightarrow$ hormone replacement therapy

O $\rightarrow$ Osteoporosis and prevent bone loss

T $\rightarrow$ Tiny gonads $\rightarrow$ hypogonadism

Chick $\rightarrow$ contraceptive $\rightarrow$ component of hormonal contraceptives

**Adverse effect**

Hot Chick reading ABC.

A $\rightarrow$ adenocarcinoma $\rightarrow$ vaginal adenocarcinoma.

B $\rightarrow$ Breast cancer $\rightarrow$ in post-menopausal women.

C $\rightarrow$ cardiovascular events $\rightarrow$ in post-menopausal women.

D $\rightarrow$ DVT.

E $\rightarrow$ endometrial cancer and in premature closure of epiphyseal lines (short stature).

**Progesterone**

Oral and vaginal creams
Effects

- Secretory changes in endometrium
- Maintenance of pregnancy
- Do not alter plasma proteins
- Result deposition of fats
- Suppression of gonadotropin secretions

Uses

PEC

P ➔ Promote and maintain pregnancy
E ➔ prevent endometrial cancer induced by oestrogen
C ➔ contraceptive with oestrogen

Toxicity

Lower than that of oestrogen

- Inc Blood pressure
- Dec HDL
- Decrease bone density

Hormonal contraceptives

Preparations ➔ progestin only and combination of progestin and oestrogen
Formulations ➔ Oral pills, transdermal patches, injections and vaginal rings

Preparations

- **Monophasic preparations** ➔ constant dosage throughout the menstrual cycle
• **Biphasic preparations** ➔ oestrogen and progesterone doses changes during month in two phases

• **Triphasic preparations** ➔ oestrogen and progesterone doses changes during month in three phases

• Progestin only preparations

**Post coital Contraceptives**

• These are emergency contraceptives that prevent pregnancy if administered within 72 hr of unprotected sex

• Preparations ➔ progestin only and combination preparations

**Mechanism of action of contraceptives**

• Primary ➔ inhibition of ovulation

• Effect glands (in cervix, uterine tubes) ➔ decrease likelihood of fertilization and implantation

• Progestin only ➔ do not inhibit ovulation ➔ act by other mechanisms

• Post coital ➔ by decrease survival of zygote

**Other clinical uses of Contraceptives**

Rida have hope (Rida umeed say hay)

R ➔ rheumatic arthritis

I ➔ iron deficiency anemia

D ➔ Dysmanuria

A ➔ acne treatment

Have ➔ Primary hypogonadism

H ➔ Hirsutism

O ➔ ovarian cyst & ovarian cancer
P ➔ pelvic inflammatory disease
E ➔ endometrial cancer

**Toxicity**

TB have (patient) some blood in mucous

- T ➔ thromboembolic effects
- B ➔ breast cancer
- Have ➔ headache
- Some ➔ skin pigmentation
- Blood ➔ nausea
- Mucous ➔ heavy menstrual bleeding

- Older preparation have high androgens (also causes acne, hirsutism and weight gain)

**Other adverse effects may be**
Anti-estrogens.
Fulvestrant

Estrogen receptor antagonist in all tissues
Full receptor antagonist ➔ fulvestrant

Use
- Adjuncts in hormone responsive breast cancer fail to response first line antiestrogen therapy

Adverse effects
- Hot flushes + headache

Tamoxifen
- Estrogen action in breast tissue and CNS
- Agonist effects in liver and bone

Uses
- Prevention and treatment of responsive breast cancer
Adverse effects

- Hot flushes
- Endometrial hyperplasia
- Thromboembolism

Tormifene ➞ same as tamoxifen

Raloxifene ➞ for osteoporosis and breast cancer prevention

Clomiphene

- Induces ovulation ➞ used in fertility

Anastrazole

Reduce estrogen synthesis by inhibition of aromatase enzyme

Aromatase ➞ A ➞ anastrazole

Use

- Adjuncts in hormone responsive breast cancer

Adverse effects

- Hot flushes
- Decrease bone mineralization
- Joint problems (arthralgia, arthritis etc.)

Danazole

Inhibit cyt P450 weakly and act as gonadotropin receptor antagonist

GnRH agonist ➞ Danazole

Uses

- Endometrial fibrotic breast disease

Adverse effects
• Act as partial agonist of androgens ➔ hirsutism, acne and weight gain
• Partial agonist of progestin ➔ menstrual disturbances

### Antiprogestins

Mifepristone (progestin antagonist)

**Mifepristone**

Progestin and glucocorticoid receptor antagonist

**Use**

• Combination with misoprostol for medical abortion

**Adverse effects**

• GIT disturbances
• Vaginal bleeding
• Atypical infections

### Male hormones
Androgens

Uses
- Male hypogonadism
- Weight gain in patients with wasting syndrome

Antiandrogens

Uses
- Benign prostate hyperplasia (reductase inhibitors → finasteride)
- Prostatic cancer (receptor antagonist → flutamide)
- Ketoconazole → used in advanced prostatic cancer that is resistant to first line anti androgen drugs
- Male pattern hair loss
### 33. Pancreatic hormones and antidiabatic agents

**Diabetes management drugs**

#### Drugs for diabetes mellitus

<table>
<thead>
<tr>
<th>Insulins</th>
<th>Non insulins</th>
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<tbody>
<tr>
<td>Rapid acting</td>
<td></td>
</tr>
<tr>
<td>lispro</td>
<td></td>
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<tr>
<td>Short acting</td>
<td></td>
</tr>
<tr>
<td>regular</td>
<td></td>
</tr>
<tr>
<td>Intermediate acting</td>
<td>NPH insulin</td>
</tr>
<tr>
<td>NPH insulin</td>
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</tr>
<tr>
<td>Long acting</td>
<td></td>
</tr>
<tr>
<td>galargine</td>
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</tr>
</tbody>
</table>

**Insulin preparations**

**Rapid acting**

Lispro, Aspart and Gluline insulins

- Taken just before meal
- Rapid onset and early peak activity
• In emergency treatment of diabetic ketoacidosis.

**Short acting**
Regular insulin
• Taken hour or more before meal
• Subcutaneous administered in ordinary maintenance regimens

**Intermediate acting**
NPH insulin ➔ Neutral protamine Hagedorn insulin

**Long acting**
Galargine insulin

**Production ➔** By bacterial recombinant DNA technology

**Mechanism**
Same as insulin (tyrosine kinase receptor)

**Insulin toxicity**
• Hypoglycaemia ➔ excessive insulin effect
• Insulin induced immunologic complications ➔ formation of antibodies to insulin
• Allergic reactions

| Non-insulin anti-diabetic drugs |
Non insulin anti diabetic drugs

**Insulin secretagogues**

⇒ Stimulate endogenous insulin release ➔ by premature closure of $K^+$ channels in the pancreatic beta cell membrane

<table>
<thead>
<tr>
<th>Insulin secretagogues</th>
<th>Biguinides</th>
<th>alpha glucosidase inhibitors</th>
<th>Thiazolidinediones</th>
</tr>
</thead>
</table>

Most of them belong to **Sulfonylureas**

**Second generation sulphonylureas**

- Gly (My pride – my bride)
- Gly + My Pride ➔ Glimepiride
- Gly + Pride (Pizide) ➔ Glipizide
- Gly + Bride ➔ Glyburide
Older sulphonylureas

Tolbut and Cleopatraan old couple

- Tolbut → tolbutamide
- Cleopatra → chlorpropamide

Rapid acting

(Rapa + nate) + Glinide → Rapaglinide and Nateglinide

- Rapid onset and short duration of action

Adverse effect

- Can precipitate hypoglycaemia
- Allergic reactions and weight gain

Biguinides → metformin

- Inhibit gluconeogenesis in liver and kidney
- Decrease absorption of Glucose in GIT
- Stimulation of glucose uptake in periphery

Metformin → decrease insulin production ability by increasing insulin sensitivity

- Do not increase weight

First choice in

Overweight patients or in Diabetes type II

Thialidinediones

Thai rose payo (in Urdu will be Thailand k rose dalna)
Thai ➔ thialidinediones
Rose ➔ Rosi + Glitazone ➔ Rosiglitazone
Payo ➔ pio ➔ Pio + Glitazone ➔ Pioglitazone

**Mechanism**

Activate PPAR gamma receptor ➔ activate transcription of gene ➔ proteins encoded that are involved in carbohydrate and lipid metabolism.

⇒ Increase glucose uptake in muscles and adipose

⇒ Inhibit hepatic gluconeogenesis

Reduce both fasting and post prandial hyperglycemia and are shown to reduce risks of diabetes in high risk patients

- PPAR ➔ peroxisome proliferator activated receptor

<table>
<thead>
<tr>
<th>Alpha Glucosidase inhibitors ➔ Acarbose</th>
</tr>
</thead>
</table>

**Acarbose**

Inhibit alpha glucosidase ➔ Glucose is not formed from more complex carbohydrates ➔ Less absorption of carbohydrates

**Alpha glucosidase**

Enzyme in conversion Oligosaccharides or disaccharides ➔ monosaccharaides in intestinal cells

- And monosaccharaides are absorbed into blood

<table>
<thead>
<tr>
<th>Comparison of type 1 and 2 diabetes</th>
</tr>
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<tbody>
<tr>
<td><strong>Feature</strong></td>
</tr>
<tr>
<td>Onset</td>
</tr>
<tr>
<td>Age at onset</td>
</tr>
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<td></td>
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<td>--------------------------</td>
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<tr>
<td><strong>Body size</strong></td>
</tr>
<tr>
<td><strong>Ketoacidosis</strong></td>
</tr>
<tr>
<td><strong>Autoantibodies</strong></td>
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<tr>
<td><strong>Endogenous insulin</strong></td>
</tr>
<tr>
<td><strong>Concordance in identical twins</strong></td>
</tr>
<tr>
<td><strong>Prevalence</strong></td>
</tr>
</tbody>
</table>
| **Drugs**                | Insulin required| • Non-insulin anti diabetic agents  
• Later stages also require insulin |
Chemothearapeutic Drugs
34. General concepts

Antimicrobial chemotherapy

Is the clinical application of antimicrobial agents to treat infectious disease

Types of antimicrobial chemotherapy:

- Antibacterial chemotherapy ➔ the use of antibacterial drugs (antibiotics) to treat bacterial infection
- Antifungal chemotherapy ➔ the use of antifungal drugs to treat fungal infection
- Antiviral chemotherapy ➔ the use of antiviral drugs to treat viral infection

Antimicrobial

- An agent that kills microorganisms or inhibits their growth

Types of Antimicrobials

- Microbicidal
- Microbiostatic

Microbicidal

Agents that kill microbes

Microbiostatic

Agents that inhibit their growth of microbes
Antimicrobial chemotherapy

The use of antimicrobial medicines to treat infection

Antimicrobial prophylaxis

The use of antimicrobial medicines to prevent infection.

Disinfectants

Nonselective antimicrobials such as bleach which kill a wide range of microbes on non-living surfaces to prevent the spread of illness

Antiseptics

Which are applied to living tissue and help reduce infection during surgery

Antibiotics

Which destroy microorganisms within the body

- Antibiotics are also called antibacterial

Classification of antibacterial drugs

- Bactericidal agents, which kill bacteria
- Bacteriostatic agents, which slow down or stall bacterial growth.

Bactericidal drugs ➔ irreversible

Very finely proficient at cell murder

- Very ➔ vancomycin
- Finely ➔ fluoroquinolones
- Proficient ➔ penicillin
At → aminoglycosides
Cell → cephalosporins
Murder → metronidazole

**Bacteriostatic drugs → reversible**

ECSTaTiC

E → erythromycin
C → Clindamycin
S → sulphonamides
T → tetracycline
T → Trimethoprim
C → Chloramphenicol

**Criteria for choosing antibiotic**

- Pharmacokinetics of drug
- Sensitivity to microorganism
- State of the patient
- Availability of the drug

**MIC (minimum inhibitory concentration)**

Minimum amount of drug needed that can inhibit growth within 15 to 20 hours

**Concentration dependant killing**

- Concentration of drug and killing ability of drug are proportional to each other below MIC
Aminoglycosides

**Time dependant killing**
- Time for which drug remains above MIC is proportional to killing ability of drug
  - Penicillin and cephalosporin

**Unwanted effects of antibiotics**
- Reactions due to toxic effects of antibiotic
- Hypersensitivity reactions
- Super infections (second infection superimposed on earlier one)

**Spectrums of Drug**

**Broad spectrum**
Antibiotic that acts against a wide range of disease-causing bacteria.
- Tetracycline, chloramphenicol etc.

**Narrow spectrum**
Agents that act on a single or limited group of microorganisms
- Isoniazid against mycobacteria

**Extended spectrum**
Agents that are effective against gram (+) as well as gram (-) bacteria
- Ampicillin

**Drug Combinations**
Most infections can be treated with a single agent.
Situations in which combinations are prescribed
- **To achieve broad antimicrobial activity**
  E.g. aminoglycoside plus a penicillin to treat septicaemia
- **To treat mixed bacterial infections**
E.g. following perforation of the bowel)

- **In cases where no single agent would affect all of the bacteria present**
- **To prevent the emergence of resistance**
  E.g. in treating tuberculosis
- **To achieve an additive or synergistic effect**
  E.g. use of **co-trimoxazole** in the treatment of *Pneumocystis carinii* pneumonia
THE ANTIBIOTIC TREE
35. Bacterial cell wall synthesis inhibitors

**Bacterial cell wall synthesis inhibitors** ➔ **Beta lactams**

### Penicillin

**Penicillin**

- **Narrow spectrum**
  - Penase susceptible
    - Penicillin G
    - Penicillin V
  - Penase Resistant
    - Nafcilin
    - Oxacillin
- **Wider spectrum**
  - Wider spectrum
  - Antipseudomonal Penicillin
    - Amoxicillin
    - Ampicillin
    - Ticarcillin
    - Piperacillin

### Mechanism

- Binding to specific proteins (penicillin binding proteins)
• Inhibition of transpeptidation reaction (cross linking of peptidoglycans is inhibited)

• Produce lesions in bacterial cell wall by activation of autolytic enzymes

**Mechanism of resistance**

• Formation of beta lactamases (penicillinases)

• Structural changes in penicillin binding proteins (PBPs)

• Changes in porin structure in outer cell wall

**Narrow spectrum**

• **Penase susceptible** (Penase $\rightarrow$ penicillinases)

  Mean penase is working here so Drugs will be with P

  $P \rightarrow$ Penicillin G

  $P \rightarrow$ Penicillin V $\rightarrow$ oral drug mainly used in oropharyngeal infections

  **Spectrums**

  - Gram (+) $\rightarrow$ streptococci
  - Gram negative cocci (-) $\rightarrow$ Neisseria
  - Spirochetes

  $\Rightarrow$ Penicillin $\rightarrow$ no Longer suitable for Gonorrhoea

  $\Rightarrow$ For syphilis $\rightarrow$ first line of treatment

• **Penase resistant**

  Means drug is resistant to penase enzyme $\rightarrow$ enzyme have **NO** action on drug

  $N \rightarrow$ Nafcillin

  $O \rightarrow$ Oxacillin

  **Spectrum**
This drug will be effective in those bacteria that are producing penase

- Staphylococcal infections (antistaphylococcal penicillin)

**Wider spectrum**

Wider spectrum of antibacterial activity but remain susceptible to penase

- Everything need ATP and mnemonic here is ATP

A ➔ ampicillin and amoxicillin

**Spectrum**

- Similar to penicillin G
- For other HELP
  - H ➔ Haemophilus influenza
  - E ➔ E.Coli
  - L ➔ Listeria monocytogenes
  - P ➔ Proteus mirabilis
- When used with Penase inhibitors its antibiotic activity is even more enhanced

- **Antipseudomonal Penicillin**
  - T ➔ Ticarcillin
  - P ➔ Piperacillin
  ➔ Still they are susceptible to penase

**Spectrum**

- Pseudomonas
- Enterobacter
- Klebsella
Penase inhibitors

- Inhibit penicillinases enzyme \( \rightarrow \) salbactam, tazobactum and clavulanic acid

Toxicity

- Allergic reactions (SAAF)
  - S \( \rightarrow \) joint swelling
  - A \( \rightarrow \) Hemolytic anemia
  - A \( \rightarrow \) Anaphylaxis
  - F \( \rightarrow \) fever
- GIT disturbances

Naficillin \( \rightarrow \) N \( \rightarrow \) neutropenia

Ampicillin \( \rightarrow \) AM \( \rightarrow \) allergic reaction maculopapular skin rash

Cephalosporins

Derivatives of 7-amiocephalosporanic acid

Mechanism

- Bind to penicillin binding proteins (PBPs) \( \rightarrow \) similar to penicillin (But structure is different from penicillin)

Resistance

- Decrease in membrane permeability
- Change in structure of PBPs
Methicillin resistant bacteria are resistant to Cephalosporins

**Classification and generations**

**First-generation drugs**

Mr. Fazol (cefazolin) is a lorry driver (cephaloridine). He works very hard and so became thin (Cephalothin). He has Red (cepharadine) Lux (Cephalalexine) soap.

Mr. Fazol ➔ Ce + fazol + in ➔ cefazolin
Larry driver ➔ Cefa + Lori + dine ➔ cefaloridine
Thin ➔ Cefalo + thin ➔ Cefalothin
Red ➔ Cef + Radine ➔ Cefradine
Lux soap ➔ Cefa + lexine ➔ cefalexine
In first generation drugs cef can also be spelled by ceph both are correct

**Spectrum**

**CEF THE GIANT**

Gram (+) ➔ more effective ➔ Activity against penicillinases-producing, methicillin-susceptible staphylococci and streptococci.

Gram (-) ➔ PEcK

- P ➔ proteus mirabilis
- E ➔ E.Coli
- K ➔ Klebsella pneumonia

Methicillin resistant ➔ not effective
Second-generation drugs

Mr. Foo (Cefotetan) wearing fox (cefoxitin) fur (cefuroxime) coat came into the party.

- Mr. Foo ➞ Ce + Fo + tetan ➞ Cefotetan
- Fox ➞ Ce + Fox + itin ➞ Cefoxitin
- Fur ➞ Ce + fur + oxime ➞ Cefuroxime

Spectrum

- Gram (+) ➞ less effected
- Gram (-) ➞ extended spectrum (HEN PEcK)
  - H ➞ H.Influenze
  - E ➞ Enterobacter
  - N ➞ Neisseria
  - PEcK ➞ from first generation
Third Generation Drugs

Mr. Aziz (Ceftazidime) is taking his ox (ceftizoxime) in a taxi (Ceftaxime) to slaughter. For this purpose he have three axon (ceftriaxon) blades.

Mr. Aziz ➞ Ceft + azi + dime ➞ Ceftazidime
Ox ➞ Ceftiz + ox + ime ➞ ceftizoxime
Taxi ➞ Cefa + taxime ➞ Ceftaxime
Three axes ➞ Cef + tri + axon ➞ Ceftriaxon

**Spectrum**

Gram (+) ➞ less effected

Gram (-) ➞ extended spectrum
- HEN PEcK
And PINS

- Providentia
- Influenza
- Neisseria
- Serratia

### Fourth generation Drugs

Mr. Fazol invited Mr. Aziz to coffee

Coffee ➔ Cefipime

**Spectrum**

Extended spectrum of activity against Gram-positive and Gram-negative bacteria, with greater activity against both types of organism than third-generation agents.

Gram (+) ➔ similar activity as 1<sup>st</sup> generation (Mr. Fazol is on coffee)

Gram (-) ➔ effective against wider spectrum of 3<sup>rd</sup> generation (Mr. Aziz is on coffee)

- Beta lactamase stable

**Cephalosporins are not effective against**

Lame

L ➔ Listeria

A ➔ Atypicals (mycoplasma)

M ➔ Methicillin resistant staph aureus

E ➔ Enterococci

**Adverse effects of Cephalosporins (ADP)**

- Allergic reactions
  - Skin rash to anaphylactic reactions
- But less frequent than that of penicillins
- Cross reactivity between penicillins and cephalosporins is incomplete (penicillin allergic can be treated with them but anaphylactic to penicillin should not be treated with cephalosporin)

- Drugs containing methylthiotetrazole group may cause Disulfiram like reactions (Cefamandole and Cefotetan)
- Pain at site of injection (I/M)

**Carbapnems**

(Imi boli dor maro) + Penem

- Imi → Imi + penem → Imipenem
- Boli → these are broad spectrum antibiotics
- Dor → Dori + penem → Doripenem
- Maro → Mero + penem → Meropenem

**Spectrum**

- Against penicillin resistant staphylococci
- Not against methicillin resistant strains
- Gram negative rods
- Have partial cross reactivity with penicillins

**Monobactams**

Mono → Mano

- M → monobactum group
- A → aztreonam Drug
No ➔ active against gram (-) bacteria (like pseudomonas and klebsiella)

**Glycopeptides**

Peptide mean ➔ active against gram (+) bacteria (even against penicillin and methicillin resistant strains)

Mnemonic for this is Red Guava (Gava)
Ga indicate this is glycopeptide and Va indicate its member Vancomycin

Red ➔ indicates this cause’s Red man syndrome

- Given parentally for Clostridium deficile colitis

**Lipopeptides**

Peptide mean ➔ active against gram (+) bacteria

Lipo mean Lipid ➔ D at the end of Lipid indicate its member Daptomycin

- All other groups in this chapter inhibit synthesis of cell wall but Lipopeptide (daptomycin) destabilizes the bacterial cell membrane
36. Bacterial Protein synthesis inhibitors

Protein synthesis inhibitors

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<th>Moderate spectrum (KM)</th>
<th>Short spectrum (L$_2$S)</th>
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<td>Macrolide</td>
<td>Lincosamide</td>
</tr>
<tr>
<td>Chlorampenicol</td>
<td>Ketolide</td>
<td>Streptogramins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linezolide</td>
</tr>
</tbody>
</table>

Mechanisms

**Tetracycline**

Tetracycline $\rightarrow$ tRNA $\rightarrow$ tries but cannot bind

- Prevent the amino acyl transfer RNA from attaching A site on ribosome.

**ChloramPhenicol**

Chloram + Phenicol $\rightarrow$ Phenicol $\rightarrow$ Peptide

- Inhibit the peptide bond formation by peptidyl transferase
**Macrolide**

Macro ➔ movement
- Prevent movement of ribosome
  - Prevent translocation

**Clindamycin**

Clinda ➔ Cling
- Make ribosome cling to mRNA
  - Prevent translocation

**Streptogramins**

Strepto ➔ sliped (in bathroom)
- Slipping of nacent polypeptide chains from ribosome

**Linezolid**

Line ➔ if you count lines in A₄ paper of a register they will be 23 (may differ but in my register they were 23)
- Bind to 23S RNA of 50S subunit

**Tetracycline** ➔ thirty ➔ 30S

Others ➔ on 50S

<table>
<thead>
<tr>
<th>Details of Each group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tetracycline</strong></td>
</tr>
</tbody>
</table>

**Members**

Tetra doxy minor tigers

- Tetra ➔ Tetracycline
Doxy → doxycycline
Minor → Minocycline
Tigers → Tigecycline (Tiger have broadest spectrum and resistance is less common)

Uses
Tetracycline vacuum her bed room
Tetracycline → Tularaemia
V → vibrio cholera infections
A → acne
   ⇒ Alternative in treatment of syphilis
C → chlamydia infections
U → urea plasma infections
M → mycoplasma pneumonia
Her → H-Pylori infection
Bed → brucecella infections
Room → Rickettsia infections

Doxycycline
   o alternative to Macrolide in community acquired pneumonia
   o Lyme disease
   o Malaria

Tigecycline → also used in case of those organisms resistant to other tetracycline
   o Penicillin resistant → yes
   o Methicillin resistant → yes
Vancomycin resistant → yes

Resistance

- Development of efflux pumps (for active extrusion)
- Formation of ribosomal protection proteins (interfere tetracycline binding)

⇒ But there is least resistance to tigecycline

Pregnancy contraindicated

Side effects

Kapil DeV
K → kidney toxicity (fanconi’s syndrome → Disease of the proximal renal tubules of the kidney in which glucose, amino acids, uric acid, phosphate and bicarbonate are passed into the urine)

A → Anabolic effect on body

P → Phototoxicity

I → increase ICP (intracranial Pressure)

L → Liver toxicity

De → Dental → enameal problems

V → vestibular problems

Others

- GIT effects (nausea, diarrhoea, enterocolitis etc.)
- Teratogenic → to be avoided in pregnancy

Contraindications

Tetra + cycline → Cycle → C₄

Children → bone and teeth mineralization problems

Child birth → Teratogenic (liver dysfunctions)

Chelates → form chelates in the presence of divalent ions in food → decrease oral absorption

Candidiasis → super infections

 Chloramphenicol

Wide spectrum drugs

Backup Drugs for severe infections

- RMP
R → rickettsia infection
M → meningitis
P → pneumonia
Not used in chlamydial infection

**Resistance**
- Plasmid mediated → formation of acetyltransferase that inactivates the drug

**Adverse effects**
- Smart boy in girl’s hostel
- Smart → super infection
- Boy → bone marrow infection
- In → irritational effects
- Girls → Grey baby syndrome → this occurs in infants characterized by decrease RBCs, cyanosis and CVS collapse
- Hostel → hypersensitivity

**Clindamycin** (Lincosamide)

**Uses**
PAST PAST
- P → Peritonitis and prophylaxis of endocarditis in valvular disease
- A → Aspiration pneumonia, Acne and Anaerobic infections
S ➔ Strep aureus infections
T ➔ AIDS related toxoplasma

**Adverse effects**

P ➔ Pseudomembranous colitis
A ➔ Abdominal pain
S ➔ Skin infections and rash
T ➔ Toxic mega colon
And Gray baby syndrome

---

**Macrolides**

Mr Aziz telephoned Rfida.

Mr. Aziz Telephoned Rfida

Mr ➔ Group is macrolide
Aziz ➔ Azithromycin
Tele-phoned ➔ telithromycin
R ➔ RBC ➔ erythrocyte ➔ Erythromycin
Fida ➔ fidaxomycin
Macro mean big ➔ act on big subunit ➔ 50S

**Uses**

(PC)²

- P ➔ pertussis
- C ➔ corynebacteria infection
- P ➔ Pneumonia
- C ➔ Chlamydia infection

- Azithromycin is effective in gonorrhea alternative to Ceftriaxone
- Azithromycin is effective in syphilis alternative to Penicillin G

⇒ Cross resistance between macrolides is complete

**Resistance**

- Formation of drug metabolizing easterase

**Adverse effects**

Macro GRAPES

- G ➔ Gastric discomfort
- R ➔ Rash
- A ➔ acute cholestatatic hepatitis
- P ➔ prolonged GT
- E ➔ eosinophilia
- S ➔ sensitivity
Linezolid

**Uses**
- Penicillin resistant ➔ yes
- Methicillin resistant ➔ yes
- Vancomycin resistant ➔ yes

**Resistance**
Decrease affinity of linezolid for binding site

**Adverse effects**
- STN
- S ➔ Serotonin syndrome
- T ➔ Thrombocytopenia
- N ➔ Neutropenia
37. Aminoglycosides

Members and Classification

STANG

S → Streptomycin
T → Tobramycin
A → Amikacin
N → Neomycin
G → Gentamycin

Mechanism → on 30S subunit of ribosome

Aminoglycoside → A is first letter of ABC
  o Block the initiation step → by blocking the formation of initiation complex

Other mechanisms
  o Inhibit translocation
  o Misreading of code on mRNA

amiNOglycosides

NO → no protein synthesis
NO → effective again Negative organisms
NO → Not used in Pregnancy
NO → Neomycin oral → Neomycin use is restricted to oral use to eliminate bowel flora (topical can also be used)
NO ➔ Not used alone (used in combinations with Beta lactams)

NO ➔ Nephrotoxic and Ototoxic

**Uses**

- HEN Peck (see from cephalosporins)
- Streptomycin combination with penicillin ➔ effective in enterococcal carditis, tuberculosis, plague and tularaemia
- Netilmicin ➔ for treatment of infection resistant to other aminoglycosides

**Resistance**

- Streptococcus pneumonia and enterococci ➔ Resistant due to failure of drug to penetrate the cell
- Primary mechanism ➔ Plasmid mediated formation of inactivating enzymes ➔ Group transferases that catalyse the acetylation of amine functions and transfer of phosphoryl or adenylyl group to oxygen atoms of Hydroxyl groups on aminoglycosides
  - Group transferase produced by enterococci ➔ resistant to gentamycin and toberamycin but not to streptomycin

**Adverse effect**

- Nephrotoxic
- Ototoxic
- Neuromuscular blockage
- Skin reactions
38. Sulphonamides, Trimethoprim and Fluoroquinolones

Sulphonamides and trimethoprim ➔ interfere folic acid synthesis
Fluoroquinolones ➔ inhibit microbial nucleic acid metabolism

**Sulphonamides**

Chemical nucleus resemble PABA (P amino benzoic acid)
- Less soluble in acidic urine

**Trimethoprim**

Structure similar to folic acid
- Weak bases and are trapped in urine

**Resistance**

**Sulphonamides** ➔ Decrease affinity of enzyme for drug + Decrease accumulation of drug

**Trimethoprim** ➔ Decrease affinity of enzyme for drug

**Mechanism**
Pteridine precursors

+ p-Aminobenzoic acid (PABA)

Sulfamethoxazole

Dihydropteroate synthetase

Dihydrofolinic Acid

Trimethoprim

Dihydrofolate reductase

Tetrahydrofolinic Acid

Members and classification

Antimetabolites

Trimethoprim

Sulphonamides

trimethoprim sulfamethazole

Long acting

Intermediate acting

Short acting

sulfadoxine

Sulfamethoxazole

sulfasoxazole
**Sulphonamides**

- **Long acting** ➔ dair tak act karta hay ➔ dair ➔ sulfa + doxine ➔ sulfadoxine
- **Intermediate acting** ➔ medium ➔ Sulfa + methoxazole ➔ Sulfamethoxazole
- **Short acting** ➔ short ➔ Sulfa + soxazole ➔ sulfasoxazole

**Clinical uses**

- **Gram (+)** ➔ yes
- **Gram (-)** ➔ yes
- **Norcardia** ➔ yes

**Simple urinary tract infection**

Urine ➔ came out of sex organs ➔ soxa used

- Sulfasoxazole

**Ocular infection**

Aankh (eye) ➔ actamide is used

- Sulfaacetamide is used

**Ulcerative colitis**

Coli Sala

Sulfa + Sala + zine ➔ sulfasalazine is used
**Trimethoprim sulfamethoxazole**

Luse

- L → Lungs → respiratory tract infections
- U → Urinary tract infections
- S → Sinusses infections
- E → Ears infections

- Drug of choice for Norcardia infection

**Backup drug**

Tv set

- T → typhoid
- V → vibrio cholera infection
- Set → Shigallosis

**Toxicity of Sulphonamides**

SAD Tang

- S → Sulphonamide side effects + Skin rash
- A → aplastic anemia
- D → Drug interactions
- T → Thrombocytopenia
- A → Acidic urine
- N → Nephrotoxic (Crystaluria and hematuria)
- G → GIT side effects (Nausea, diarrhoea and vomiting)

**Drug interactions**
BMW

B ➔ Displace bilirubin from proteins ➔ kernicterus in neonates if used in pregnancy
M ➔ Methotrexate ➔ compete with this for plasma proteins
W ➔ Warfarin ➔ compete with this for plasma proteins

**Adverse effects of Trimethoprim**

The male garments

The ➔ indicate these are side effects of trimethoprim
Ma ➔ magaloblastic anemia due to folate deficiency
Le ➔ leukocytopenia
Garments ➔ granulocytopenia

**Trimethoprim and sulfamethoxazole**

Same from sulfonamides
* also called **Cotrimoxazole** (sulfamethoxazole)

**Fluoroquinolones**
Drugs and classifications
Noor ciped orange and gemi loves maxico

fluoroquinolones

Generation 1
Nor → Norflroxacin

Generation 2
Ciped → Ciprofloxacin
Orange → Ofloxacín

Generation 3 and 4
Gemi → Gemifloxacin
Loves → Levofloxacin
Maxico → Moxiflaxacin

1st and last belong to 3rd generations and levo belongs to 4th generations

Generation 1 → Norfloxacín
Derived from Nalidixic acid
One is also called uni ➔ so they are used in urinary tract infections

**Generation 2 ➔ ciprofloxacin and Ofloxacin**

Use against

- Gram (+) ➔ yes
- Gram (-) ➔ no
  - Used in atypical pneumonia (mycoplasma pneumonia)

**Generation 3 and 4 ➔ gemifloxacin, levofloxacin and moxifloxacin**

Less active than generation 2 and have greater activity against gram (+) cocci

Effective against

- Strep pneumonia aureus
- Methicillin resistant staphylococci
  ➔ Also called respiratory fluoroquinolones

**Pharmakinetics**

Norfloxacin ➔ Nor Not ➔ Donot achieve adequate plasma level in most of infections

Moxifloxacin ➔ Eliminate also by bile Given in case of renal impairment

**Mechanism**

**Queen on top**

Fluoroquinolones ➔ inhibit topoisomerase

- Topoisomerase II ➔ in gram (-) (negative can be drawn between two dots)
- Topoisomerase IV ➔ gram (+) (positive can be drawn between four dots)
Topoisomerase II ➔ also called DNA gyrase

DNA gyrase ➔ causes relaxation of supercoiled DNA during replication and duplication (This step is inhibited by Fluoroquinolones)

- Inhibition of Topoisomerase causes death of bacteria

Post antibiotic effect

Fluoroquinolones and aminoglycosides show post antibiotic effects ➔ Growth is inhibited even after the plasma concentration of Drug is fall below Minimum inhibitory concentration

Resistance

- Efflux pumps ➔ Decrease intracellular accumulations
- Change in structure of porins ➔ in gram (-) organisms
- Change in sensitivity to target enzyme via point mutations

Clinical uses

Fluorquinolone surg

S ➔ Skin infections
U ➔ Urogenital tract infections
R ➔ Respiratory tract infections
G ➔ GIT infections
Examples
PEcK infections

P ➔ Pseudomonas auregenosa
E ➔ enterobacter and E.coli
K ➔ Klebsella pneumonia

- Should not use them unless no other safe drug is available to avoid development of resistance
**Adverse effects**

Boxer’s LAMP

- Boxer ➔ Black boxer warning ➔ Tendinitis and Tendon rupture
- L ➔ abnormal Liver function test
- A ➔ Allergic reactions (Rash and phototoxicity)
- M ➔ Exacerbation of myasthenia gravis
- P ➔ Prolongation of QT interval

**Contraindications**

CAP

- C ➔ CNS inflammation
- A ➔ Arrhythmias
- P ➔ Pregnancy ➔ if used in first trimester abnormalities are developed
39. Anti-mycobacterial Drugs

First line Drugs

International formula

2HREZ/4HR₃

- H → Isoniazid
- R → Rifampicin
- E → Ethambutol
- Z → Pyrazinamide

- HREZ daily for 2 months and then HR 3 times a week for 4 months

Second line Drugs

Cape

- C → Ciprofloxacin → Fluoroquinolone
- A → Amikacin → Aminoglycoside
- P → P amino salicylate
- E → Ethionamide → thioamide

Isoniazid

Mechanism

Inhibit mycolic acid (mycolic acid essential component of bacterial cell wall)
Resistance

Kat G gene \(\rightarrow\) encodes the catalase \(\rightarrow\) required for bioactivation of drug

- This Gene is deleted to develop resistance

INH-A Gene \(\rightarrow\) encodes the target enzymes

- This Gene is deleted to develop resistance

Pharmacokinetics

Drug \(\rightarrow\) penetrate inside the cell to act on intracellular mycobacteria

Clinical uses

- Prophylaxis of Tuberculosis
- Most important Drug in Tuberculosis regimes
- Given to persons in contact with diseased person

Toxicity

Jim Loves haseena

J \(\rightarrow\) jaundice

I \(\rightarrow\) Insomnia

M \(\rightarrow\) inhibit metabolism of Drugs in liver

Loves \(\rightarrow\) Abnormal Liver function Test

Haseena \(\rightarrow\) Hepatotoxic

- Hepatitis
- Hemolysis in G6P deficient persons

Rifampicin

Derivative of Rifamycin

Mechanism

Rifampicin \(\rightarrow\) R \(\rightarrow\) RNA \(\rightarrow\) inhibit RNA polymerase
Resistance

Change of drug sensitivity to polymerase

Pharmacokinetics ➔ enterohepatic recycling and orange metabolites are eliminated in feces

**REDMAN RIFAMPIN**

Meet Mr. Redman Rifampin. He is taking some r & r (rest and relaxation) and is at the beach eating many oranges. He has had so many oranges his pee and tears are orange. Rifampin is hard on the liver, so it has gotten larger. The oranges will help you recall the 6 D’s of rifampin.

Clinical uses

- Tuberculosis ➔ combination with others
- Prophylaxis tuberculosis
- Persons in close contact with Tuberculosis person
- Leprosy → delay emergence of resistance
- With Vancomycin → Methicillin resistant staph aureus

**Toxicity**

Rifampicin in NEPAL

N → Nephritis
E → Excite P450 metabolizing enzyme
P → Proteinuria
A → Anemia
L → Liver dysfunction

**Ethambutol**

**Mechanism**

Inhibit arabionosyl transferase (encoded by emb [ab] gene)

**Resistance**

Emb gene mutation

**Uses**

- Tuberculosis in combination with others

**Toxicity**

- Ethambutol → E → Eye
  - Visual disturbances
  - Optic neuritis
  - Red green colour blindness

**Pyrazinamide**

Require bioactivation
- Pyrazinamide ➔ Pyrazoic acid
- Bacteriostatic

**Uses**
- Component of many regimes
  ⇒ Avoided in pregnancy.

**Adverse effects**
Parazina + Mide ➔ (PM)$^2$
  - P ➔ phototoxicity and porphyria
  - M ➔ Maculopapular rash and myalgia
40. Anti-Fungal Drugs

Antifungal drugs

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<th>Block nucleic acid synthesis</th>
<th>Disrupt microtubule function</th>
<th>cell wall synthesis inhibitors</th>
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<tr>
<td>Azoles</td>
<td>Terbinafine</td>
<td>Polyenes</td>
<td>Flucytosine</td>
</tr>
<tr>
<td></td>
<td>Griseofulvin</td>
<td>Echinocandins</td>
<td></td>
</tr>
</tbody>
</table>

Azoles

Used for systemic mycosis **Members**

- Itra and imeda ko bht flu hay
- Itra ➞ itra + conazole ➞ itraconazole
- Imeda ➞ imeda + conazole ➞ Imedaconazole
- Ko ➞ keto ➞ Keto + conazole ➞ Ketoconazole
- Bht ➞ very ➞ Vori + conazole ➞ Voriconazole
Flu → Flu + conazole → Fluconazole

Mechanism
Azoles are pzoles
Azoles → inhibit cty p450 → disrupt synthesis of ergosterol
- P450 enzyme → produces 14 alpha demethylation of lanosterol that is converted into ergosterol component of fungal cell membrane

Clinical Uses
For all members
- Systemic mycosis
- Conazole → candidiasis

Ketoconazole
- Ket → Cut → cutaneous → mucocutaneous candidiasis
- Systemic mycosis as other azoles

Fluconazole
• Fluid flows in CNS ➔ so used in meningitides ➔ Cryptococcal meningitides

• If someone engulf his flu secretion it will first go to his oropharynx then into oesophagus
  o Oropharynx ➔ Oropharyngeal Candidiasis
  o Oesophageal ➔ Oesophageal candidiasis

Itraconazole

It is used in ABC
  A ➔ Aspergillus infection
  B ➔ Blastomycosis infection
  C ➔ Chromoblastomycosis & Candidiasis

Voriconazole

Vori ➔ invasive aspergilosis resistant to other drugs

Posaconazole

P ➔ used in prophylaxis of fungal infections

Toxicity

Voriconazole ➔ Visual disturbances

Ketoconazole ➔ munday ko kuri bna deti hay
  • Interfere synthesis of adrenal and gonadal hormones
    o Gynecomastia (enlarged breast in male)
  • In females ➔ menstrual disturbances

For all ➔ Diarrhoea, vomit, Rash and hepatotoxic
  • They all inhibit Cyt p450
Terbinafine

To remember this
Time square

Time ➔ terbinafine
Square ➔ inhibit squalene epoxide

- Time duration ➔ terbinafine is used in dermatophytosis

Toxicity

- Terbinafine and Grisofulvin ➔ both accumulates in Keratin
- Terbinafine ➔ Taste disturbances
- Others ➔ GIT upset and headache

Polyenes ➔ Amphotericin B

Used in systemic fungal infections

Mechanism

amphoTERIcin ➔ Amphotericin tearing cell membranes of Fungi

- Amphotericin ➔ produces holes in fungal cell membrane
  Bind with ergosterol ➔ form transmembrane channels that leads to movement of ions (Na, K and Cl) ➔ leads to cell death

Clinical Uses

ABCD

A ➔ Aspergillus infection
B ➔ Blastomycosis infection
C ➔ Candida albicans infection
D ➔ Dermatophytosis
Adverse Effects

Amphotericin

A ➔ Anemia
M ➔ Muscle spasm
P ➔ Phlebitis
H ➔ Headache and hypertension
O ➔ Ooh
T ➔ Thrombocytopenia
E ➔ Emesis
R ➔ Respiratory infections
I ➔ increase temperature
C ➔ Chills
I ➔ immune suppression
N ➔ Nephrotoxic (Most important side effect)

Or you can use this mnemonic

Amna ka blood pressure fall ki waja say fever chill or vomit hoi or uski red kamez neli ho gai

Amna says ➔ this is amphotericin B

Infusion related side-effects

- Blood pressure fall
- Fever
- Chill
- Vomit

Dose limiting side-effects
- Red ➔ Renal acidosis
- Kamez ➔ K ➔ potassium wasting
- Neli ➔ Nephrotoxic and neurotoxic

**Flucytosine**

**Mechanism**

Thymidylate synthase is inhibited by it ➔ inhibit nucleic acid synthesis

**Clinical uses**

As this Drug inhibit Nucleic acid synthesis and Nucleic acid is present in Chromosomes so for its uses C is used

C ➔ in combination with other antifungal Drugs in ABCD (above)
C ➔ Cryptococcus neoformans
C ➔ Chromoblastomycosis

**Toxicity**
- Bone marrow depression
- Liver dysfunction

**Grisofulvin**

**Mechanism**
Grass like microtubules
- They interfere the Microtubule synthesis (are fungistatic)

**Use**
Dermatophytosis

**Side effects**
P5
- P ➔ Peripheral neuropathy
- P ➔ Porphyria
- P ➔ P450 interactions (Activator)
- P ➔ Photosensitivity
- P ➔ Potentiation of alcohol (Disulfiram like reaction)

Other ➔ GIT disorders, Nausea and confusion

**Echinocandin**
Candin ➔ Din ➔ Gin ➔ Glycan inhibitors
• Caspofungin
• Micofungin

**Mechanism**
They inhibit the synthesis of Beta 1, 2 glycan
  • Glycan → component of Bacterial cell wall

**Clinical uses**
Caspofungin → C → Candida infections irreversible to Amphotericin B
Micafungin → Mico
  • Mi → Mucocutaneous candidiasis
  • Co → prophylaxis of candidiasis

Echinocandins → candy → Candidiasis

**Toxicity**
Diarrhoea, vomit, rash and Headache
  • Micafungin → release of histamine

---

**Systemic Drugs for Superficial Infections**

GTA (Grand theft auto games like Vice City)
  G → Griseofulvin
  T → Terbinafine
  A → Azoles

• These are used orally for Dermatophytosis of skin, hairs and nails

---

**Topical for superficial Treatment**
**Needed for**

- Candida infections
- Dermatophytosis

**Nystatin ➔ polyene**

Bind to ergosterol (Polyene so mechanism resemble Amphotericin B)

- Cutaneous, vaginal and mucosal candida infections (use)
- Nausea, diarrhoea and rash (side-effect)

**Others**

Miconazole and Clotrimazole are also available (azoles)
41. Anti-Viral Drugs

Mechanisms

Entry inhibitors
- Entry \(\rightarrow\) en \(\rightarrow\) Enfuveritide
**Uncoating inhibitors**
- Amantadine ➔ aam ka chilka just like coat of virus (a covering)

**Penetration inhibitors**
- Penetration ➔ mean movement in ➔ IN ➔ INF alpha (interferon)

**Nucleic acid synthesis inhibitors**

Far Far Drugs
- F ➔ Foscarnate
- A ➔ Acyclovir
- R ➔ they inhibit Reverse transcriptase enzyme

**Protein synthesis inhibitors**

**Viral release inhibitors**
- Release ➔ Nikalna ➔ Neuraminidase inhibitors

---

**Drugs for Herpes**

Her father got a cycle
- Her ➔ Drugs for Herpes
- Father ➔ Foscanate
- Got ➔ Guanithidine
- A cycle ➔ Acyclovir

If you reverse order then it will be choice based order

**Acyclovir**

**Mechanism**
Far far Drug ➔ inhibit nucleic acid synthesis
• It is competitive substrate for DNA Polymerase
• Also produces changes in DNA polymerase (alteration of structure)

**Pharmacokinetics** → short half live → multiple doses per day

**Clinical Uses**

• Mucocutaneous herpes
• AIDS
• Immunocompromised persons

**Adverse effects**

Cycle have two new designs
Cycle → Acyclovir side effects
Have → Hypertension
Two → Tremors
New → Nephrotoxicity
Designs → Delirium

**Ganciclovir**

Guanine derivative

**Mechanism**

Phosphorylated by thymidine kinase to produce nucleotide that inhibit DNA polymerase

• Inhibit DNA Polymerase → Inhibit nucleic acid synthesis

**Uses**

• In herpes as from above
• In DNA G pairs with C → G≡ C so
  ○ C → Cytomegalovirus infections
- Prophylaxis
- Treatment
- Treatment by this in immunocompromised persons

**Adverse effects**

**Bloody Effects**
- Thrombocytopenia
- Neutropenia
- Leukopenia

Also causes hepatic dysfunctions

**Cidofovir**

- Acyclovir and Ganciclovir $\rightarrow$ both are activated by viral enzyme thymidine kinase
- Cidofovir $\rightarrow$ activated by host cell kinase and do not require viral kinase
  - Used where resistant to first two $\rightarrow$ to treat herpes

**Uses**

- Cidofovir $\rightarrow$ C $\rightarrow$ CMV viral infection treatment

**Foscarnet**

Phosphor formate derivative
- Does not require phosphorylation for activity

Used where resistance to other drugs has been developed

**Mechanism**

foscarnet $\rightarrow$ inhibit RNA polymerase & also inhibit DNA polymerase
(Like previous discussed drugs)
Uses

- Herpes treatment
- Resistant Herpes in AIDS
- FosCARnet → Car → CMV viral infections

Anti-AIDS Drugs

<table>
<thead>
<tr>
<th>No new Indian entered Pakistan</th>
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</thead>
<tbody>
<tr>
<td>No</td>
</tr>
<tr>
<td>new</td>
</tr>
<tr>
<td>Indian</td>
</tr>
<tr>
<td>entered</td>
</tr>
<tr>
<td>Pakistan</td>
</tr>
</tbody>
</table>

- Non nucleoside reverse transcriptase inhibitors
- Nucleoside reverse transcriptase inhibitor
- Integrate strand transferase inhibitors
- Entry inhibitors
- Protease inhibitors

Nucleoside reverse transcriptase inhibitors (NRTIs)

**Mechanism**

Inhibit RNA dependant DNA polymerase (Reverse transcriptase)

Inhibit conversion of single stranded RNA into double stranded DNA

- Activate Host cell kinase → Triphosphates are formed → inhibit reverse transcriptase enzyme
• Act as chain terminators ➔ block attachment of next nucleotide

**Members**

Abay ka veer Lamba zidi hay

• Abacavir
• Lamivudine ➔ hep B and HAART (highly active antiretroviral therapy)

• **Zidovudine**

Also called azidothymidine (AZT)

• **Uses**
  - First Drug to be discovered for treatment of AIDS
  - Post exposure prophylaxis
  - Pregnancy prophylaxis

• **Side effects**
  - Zid ➔ zero RBCs ➔ Causes anemia (megaloblastic anemia) ➔ because this causes bone marrow suppression
  - Other effects ➔ GIT distress, CNS effects (headache) and hepatotoxic

**Non-Nucleoside reverse transcriptase inhibitors**

**Mechanism**

• Site of action different from NRTIs
• They doesnot require phosphorylation for activation
• Non-nucleoside ➔ do not compete for Nucleoside phosphate
• **Resistance** ➔ develop rapidly if used alone (monotherapy)

**Adverse effects**
• GIT distress (ulcers), CNS effects
• Nephrotoxic
• Electrolyte imbalance

Protease inhibitors

Mechanism
Aspartate protease ➔ enzyme that convert precursor polypeptides into final structural Proteins of Mature Virion
• They are used in combination with other Drugs

Drunavir
• Daro na ➔ used where resistance to other drugs is developed

Fosamprenavir
• Hydrolysis to produce Amprenavir
• Not used in children and pregnant women

Indinavir
• Good oral bioavailability (except in the presence of food)
• Side effects ➔ Indina ➔ India ➔ baharat
  o India ➔ insulin resistance
  o Baharat ➔ Increase Bilirubin (jaundice)

Effects Produced by Protease inhibitors
• Disorders of carbohydrate and lipid metabolism
• Insulin resistance
• Sex hormone abnormality ➔ gynecomastia

Entry inhibitors
Entry inhibitors → en → Enfuvirtide

- Attach to Gp41 unit of viral envelop → prevent conformational changes required for cellular fusion

Other anti-viral Drugs

**Fomivirsen**

- FOM → Bind to mRNA of CMV → Block initial step of protein synthesis
- Injected IV for treatment of CMV retinitis

**Etravirin**

- Newest drug → effective against HIV resistant strains

**Nevirapine**

- Metabolized by cyp3A4
- Nevirapin → N → Neonates → Prevent vertical transmission of HIV when given in single dose to mother at the onset of the labour

**Anti-Influenza Drugs**

1) Amantadine and Rimetadine
A man dine (Deen) ➔ deen is bat ki ijazat nh deta k naked hon kisi k samnain

- Prevent Virus from being naked ➔ Prevent uncoating of virus ➔ as a result inhibit replication because viral Nucleic acid will not be released until uncoating

**Uses**

Amantadine ➔ A man ➔ prophylactic against influenza A
- Reduce duration of symptoms if given within 24 hours

### 2) Oseltamivir and Zanamivir

Ozone ➔ O and Z inhibit Neuraminidase release in influenza A and B

**Uses**

- Alleviation of influenza symptoms
- More effective if used within 24hrs
- Prophylactic ➔ decrease influenza incidence

---

**Agents used in Viral Hepatitis**

Drugs used in treatment of Hepatitis B
Adela in entry test

- Ad ➜ Adefovir
- La ➜ Lamivudine
- In ➜ IFN (interferon) alpha
- Entry ➜ entecavir
- Test ➜ tenofovir (newer drug)

### Drugs used in Hepatitis C

Rabia in chakwal

- Rabia ➜ Ribavirin
- In ➜ IFN alpha

Chakwal ➜ these drugs are effective against Hepatitis C

### Details of Each Drugs

**Adefovir**

**Mechanism** ➜ competitively inhibit HBV DNA polymerase

- aDefovir ➜ D ➜ Inhibit DNA polymerase
  - Need phosphorylation for activation of drug
Uses
- Supress replication of HBV

Side-effect ➔ nephrotoxic

**Lamivudine**

Nucleoside inhibition of HIV reverse transcriptase

**Uses**
- Supress replication of HBV
- Used in HAART (highly active acute antiretroviral therapy)

**IFN alpha**

Interferon alpha

**Mechanism**
- Activates JACK & STATS ➔ formation of antiretroviral proteins is activated
- Activates host cell ribonuclease ➔ Degrade viral mRNA

**Pharmacokinetics** ➔ elimination ➔ proteolytic hydrolysis in kidney

**Uses**
- Hep B ➔ alone or in combination with others
- Hep C ➔ Combination with ribavirin to reduce progression
- CMV infection
- Herpes zoster infection

**Entecavir**

Guanicine nucleotide ➔ inhibit DNA polymerase

**Use** ➔ effective against HBV
Adverse effect ➔ fatigue, nausea and headache

**Tenofovir**

NRTIs (nucleoside analogue reverse transcriptase inhibitor)

Use ➔ effective against HBV

**Ribavirin**

**Mechanism**

Make the native nucleoside drug resemble adenosine or guanosine, depending on its rotation ➔ incorporated into RNA, as a base analogue of either adenine or guanine ➔ inducing mutations in RNA-dependent replication in RNA (Hypermutation) ➔ lethal to RNA viruses.

- Ribavirin ➔ R ➔ incorporated into RNA ➔ lethal mutations

**Uses**

- Adjuncts in chronic hepatitis C infection with IFN alpha
- Monotherapy not effective

**Toxicity**

Ribavirin ➔ R ➔ effect RBCs ➔ Dose dependant haemolytic anemia

- Teratogenic ➔ so contraindicated in pregnancy
### 42. Anti-Protozoal Drugs

#### Antimalarial Drugs

Prima queen celebrated many festivals

<table>
<thead>
<tr>
<th>Prima</th>
<th>• Primaquine</th>
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<tbody>
<tr>
<td>Queen</td>
<td>• Quinine</td>
</tr>
<tr>
<td>Celebrated</td>
<td>• Chloroquine</td>
</tr>
<tr>
<td>Many</td>
<td>• Mafloquine</td>
</tr>
<tr>
<td>Festivals</td>
<td>• Antifolates</td>
</tr>
</tbody>
</table>

Prima ➔ only tissue schizonticide  
Others ➔ Blood schizonticide  
Primaquine ➔ synthetic 8-amino quinoline  
Quinine ➔ alkaloid  
Chloroquine ➔ 4-amino quinoline derivative  
Mafloquine ➔ 4-quinoline derivative  
Quinine ➔ Quinoline + Quinuclidine
**Chloroquine**

**Mechanism**

Chloroquine ➔ accumulate in food vacuole ➔ Prevent polymerization of Heme into hemozin ➔ accumulation of Heme ➔ Cytotoxic to Parasite

**Resistance**

- Decrease intracellular accumulation by increased activity of membrane pumps
- Intravascular accumulation of Chloroquine via transporter encoded by pfcrt (Plasmodium falciparum Chloroquine resistance transporter)

**Uses**

- Non falciparum and sensitive falciparum malaria Treatment and prophylaxis
- In autoimmune diseases (rheumatic arthritis)
- Radiosenstizing in anticancer therapy

**Adverse effects**

G Rana sahib

G ➔ GIT irritation
R ➔ Renal damage
A ➔ Auditory damage
N ➔ Neuropathies
A ➔ attacks of porphyria
Sahib ➔ Skin rash and skin lesions

**Quinine**

**Mechanism**
Complexes with Double stranded DNA to prevent strand separation ➔ Block DNA Replication and transcription of RNA

**Clinical use**

- P falciparum infections resistant to chloroquine
- Used with doxycycline and clindamycin (to shorten duration of toxicity and limit toxicity)
- Should not be used for prophylaxis (to delay resistance emergence)

**Toxicity**

BC got his TV

- Black water fever ➔ Hematotoxic effects
- Cinchonism
  - Got ➔ GIT disturbances
  - His ➔ headache
  - T ➔ tinnitus (ringing in ears)
  - V ➔ Vision blurred

**Mefloquine**

- First line of drug taken for prophylaxis in all geographical areas with chloroquinine resistance
- Alternative to quinine in acute attacks
- In uncomplicated infection resulting from p falciparum
Toxicity

Psycho cat have some Gastric disease

Psycho ➔ psychiatric diseases
Cat ➔ CVS disorders
Have ➔ headache
Some ➔ skin rash
Gastric ➔ GIT disturbances
Disease ➔ dizziness

Primaquine

Form Quinoline quinone metabolites ➔ electron transferring redox compounds ➔ cellular oxidants ➔ killing of gametes of plasmodium

- Tissue schizonticide ➔ Gametocide

Clinical use

- Eradicate Liver stages of p vivax and P ovale
- Used in conjugation with blood schizonticides (Not active alone)
- 14day treatment of primaquine is standard after treatment with chloroquine
- Alternative for primary prevention

Anti-folate drugs

Pyrimethamine, Proguanil, sulfadoxine and dapsone are used

Mechanism

Act as antimetabolites of PABA and inhibit synthesis of folic acid

Clinical uses

- Blood schizonticide against p falciparum
• Pyrimethamine + sulfadoxine ➔ Fensidar (used in Chloroquine resistant p-falciparum)

• Proguanil + atvaquone ➔ Malarone (chemoprophylaxis of chloroquine resistant malaria)

**Adverse effects**

Anti-folate HINGE

H ➔ hemolysis

I ➔ Drug interactions (competition with plasma proteins)

N ➔ Nephrotic damage

G ➔ GIT distress

---

**Other Antimalarial Drugs**

**Doxycycline** ➔ Tetracycline ➔ chemoprophylactic

**Amodiaquine** ➔ used against chloroquine resistant p-falciparum (Low cost drug)

**Atovaquone** ➔ Quine derivative (Disrupt mitochondrial electron transport) ➔ Chemoprophylaxis and treatment of p-falciparum malaria

**Halofantrine** ➔ Halo > whole ➔ active against erythrocytic stages of all 4 forms of malaria

**Artemisinins** ➔ only drug reliably effective against Quinine resistant strains

---

**Travellers Malaria**

1) Chloroquine is used as prophylaxis

2) Chloroquine resistant ➔ Mefloquine
3) Multidrug resistant ➔ doxycycline and Malarone

4) Primaquine ➔ for terminal prophylaxis of p-ovale and p-vivax
43. Anti-Microbial Drugs

Metronidazole

Imidazole Derivative

- Active against Protozoa and Bacteria

Mechanism

Reducive bioactivation of nitro group by Ferredoxin $\rightarrow$ and form reactive cytotoxic products

Clinical Uses

ABCDEFGH

A $\rightarrow$ Amebiasis and Anaerobic streptococci infections

B $\rightarrow$ Bacteroids infection

C $\rightarrow$ Clostridium perferenges infection

D $\rightarrow$ D-medinensis infection

E $\rightarrow$ pseudomembranous enterocolitis and Entameba infection

F $\rightarrow$ Fusobacterium infection
**Pharmacology Mnemonics and Short Notes**  
**By Muhammad Ramzan Ul Rehman**

**Contents**

- Giardiasis and gardenerela infection
- H pylori ulcer

**For antiprotozoal use GET**
- G ➔ Giardia infection
- E ➔ Entameba infection
- T ➔ Trichomonas infection

**Side effects**

DAD loves sexy girl parveen

- D ➔ Dark colour faeces and dark urine and Dizziness
- A ➔ ataxia
- Drug interactions with other drugs by competing with plasma proteins
- Loves ➔ Leukopenia
- Sexy ➔ Sar dard and stomatitis
- Girl ➔ Gastrointestinal irritations
- Parveen ➔ p in start and n in end ➔ Pregnancy not used (contraindicated) ➔ if to be used then with caution

- One other side effect is Metallic taste
44. Anti-Helminthic Drugs

Drugs used in Nematodes infections

Nematode hate AMP

A: • Albendazole
M: • Mebendazole
P: • Pyrantel pamoate

Mechanisms

Albendazole ➔ inhibit microtubule assembly
Mebendazole ➔ inhibit microtubule assembly
Pyrantel pamoate ➔ Stimulation of nicotinic receptors ➔ Depolarization ➔ paralysis.

Uses

Worm infections

• Round worm infection
• Thread worm infection
• Hook worm infection
• Pin worm infection
Drugs used in Cestode infection

Nikalo AMP

nikalo • Niclosamide

A • Albendazole

M • Mebendazole

P (change) • Pyraziquental

Mechanisms

Niclosamide ➔ uncoupling of oxidative phosphorylation or by activating ATPase

Pyraziquental ➔ increase permeability of Ca^{2+} ➔ contraction ➔ paralysis ➔ vacuolization ➔ death

Uses (CFTs)

- Cestodes infection
- Flukes and systomiasis
- Trematodes infections
- Schistosomiasis

Drugs used in trematode infections
Who put the trematode into the BOMP

- **B**: Bithinol
- **O**: Oxaminiquine
- **M**: Metrifonate
- **P**: Pyraziquental