PHARMACO KINETICS → Effect of body on Drug
PHARMACO DYNAMICS → Effect of Drug on Body

Drug:

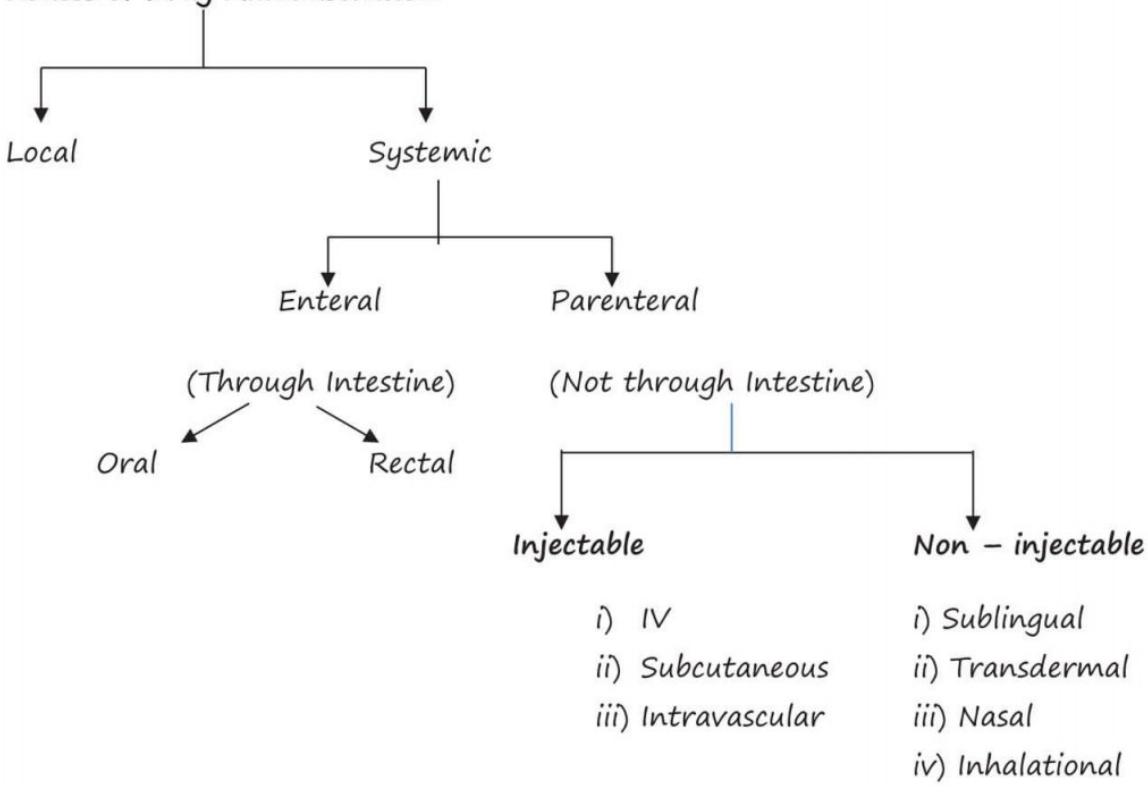
- Drug is substance which is intended to be used to modify or explore the physiological function or pathological state for the benefit of the recipient.

Risk benefit ratio –

Eg. Streptokinase: -

- Thrombolytic drugs like streptokinase are used in myocardial infarction in which coronary artery is blocked but sometimes also breaks normal physiological thrombus particularly in brain causing cerebral hemorrhage.
- Streptokinase cannot be used in peripheral vascular disease where risk is more than benefit

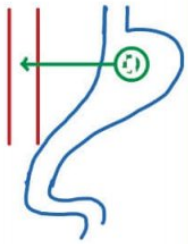
Routes of Drug Administration



PHARMACOKINETICS

→ aka ADME STUDY
- Absorption
- Distribution
- Metabolism
- Excretion

ORAL ROUTE



ABSORPTION

→ MOVEMENT OF DRUG FROM SITE OF ADMINISTRATION TO BLOOD

→ LIPID SOLUBILITY - Single most important factor in absorpt^{n}
- LIPID SOLUBLE DRUGS ARE ABSORBED

→ FORM OF DRUG

$$H_2O \rightleftharpoons H^+ + OH^-$$

$$HX \rightleftharpoons H^+ + X^-$$

- Ionized form of Drug is water Soluble
- Non Ionized form of Drug is Lipid soluble

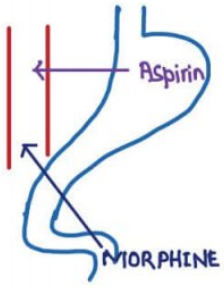
- DRUG IS ABSORBED IN NON-IONIZABLE FORM

→ MEDIUM

- WHEN THE MEDIUM IS SAME, THEN THE DRUG WILL CROSS

DRUG	MEDIUM	FORM	SOLUBILITY	CROSS
Acidic	Acidic	Non ionized	Lipid Soluble	✓
Basic	Basic	Non ionized	Lipid Soluble	✓
Acidic	Basic	ionized	Water Soluble	×
Basic	Acidic	ionized	Water Soluble	×

- Acidic Drug [ASPIRIN], mainly absorbed from stomach
- Basic Drug [MORPHINE] mainly absorbed from intestine



But practically all drugs (even acidic drugs like aspirin) are absorbed more from intestine as compared to stomach because:

- Large surface are of intestine
- Longer time drug stays in intestine

How much a drug will cross in different media?

Eg. Nature – Acidic

Pka = 6.0

PH	Lipid soluble	Water soluble
3.0	99.9%	0.1%
4.0	99%	1%
5.0	90%	10%
6.0	50%	50%
7.0	10%	90%
8.0	1%	99%
9.0	0.1%	99.9%
10.0	0.01%	99.99%

Henderson Hasselbach Equation

$$pH = pka + \log \frac{[Non - Ionised]}{[Ionised]}$$

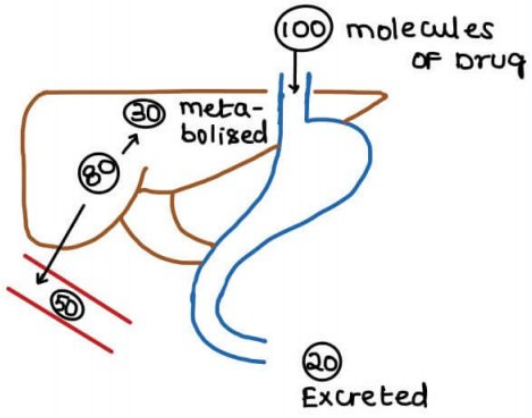
BIO AVAILABILITY

→ FRACTION OF GIVEN DOSE WHICH REACH SYSTEMIC CIRCULATION → Bio Availability

→ determines the DOSE

High bioavailability → Low dose

Low bioavailability → High close



Factors

① Absorption

↑ absorptⁿ → ↑ Bio availability

↓ absorptⁿ → ↓ Bio availability

Bio availability of drugs given by IV route is 100%.

② First Pass metabolism / Pre systemic metabolism

↑ First Pass metabolism → ↓ Bio availability

↓ First Pass metabolism → ↑ Bio availability

NTG [Nitro Glycerine]

- has high first pass metabolism
- SUB LINGUAL ROUTE is preferred

  Advantages of sublingual route

  - Fast acting → can be used in emergencies
  - No first pass metabolism
  - Self administratⁿ is possible
  - After desirable action, we can spit/ingest the extra dose

How to calculate bioavailability?

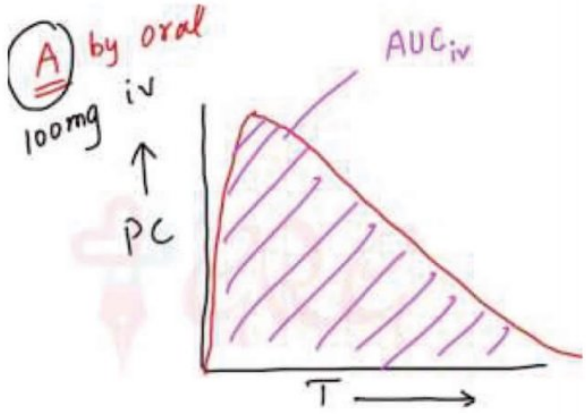
To know the bioavailability of Drug A by oral route

↓

Give drug A 100 mg by IV route

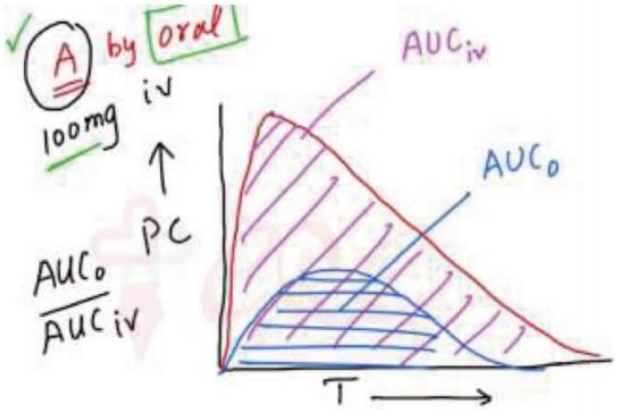
↓

Then plot a graph



- Measure plasma concentration every 30 min & plot it
- Now same dose (100 mg) given orally

  Plot the same graph



$$\text{Bioavailability} = \frac{AUCo}{AUCiv}$$

BIOEQUIVALENCE (biologically equivalent)

- 2 brands of same drug are compared

Eg. Aspirin 150 mg

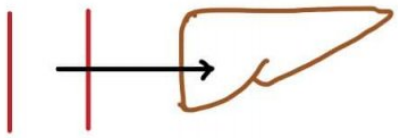
Ecosprin (Brands) Losprin

↓ ↓

100 µg/dl 90µg/dl or 95 or 99.999 µg/dl

- If two brands of same drug have almost similar bioavailability (±20%), these are called bioequivalent
- Most of the drugs are bioequivalent except phenytoin

DISTRIBUTION



DISTRIBUTION

FACTORS

① LIPID SOLUBILITY → most important factor

Lipid Soluble Drugs → Higher Distribution

Water Soluble Drugs → Lower Distribution

② PLASMA PROTEIN BINDING

↑ PPB → Low Distribution

→ Acidic drugs bind to → Albumin
→ Basic drugs bind to → α_1 ACID Glycoprotein
→ Different drugs have different percentage of binding

1. **Distribution:**
   - ➔ If PPB is ↑, its volume of distribution (Vd) → ↓↓
2. **Duration:**
   - ➔ If drug has ↑ P.P.B, Duration of action of drug ↑, bcoz plasma protein to which it is bound serves as storage site.
3. **Displacement interactions:**
   - ➔ PPB sites on albumin & α_1 – Acid glycoprotein are non – specific.
   - ➔ Suppose if we give 100 molecules of warfarin to a person & it has 99 % (↑) plasma protein binding, then 99 molecules are already bound to proteins & only 1 mol is free which is producing the action.
   - ➔ Now if this person develops infection (unrelated to warfarin) & to treat that infection; we start sulfonamides.
   - ➔ Sulfonamides also have high PPB & have tendency to bind at the same place where warfarin binds. So, there would be competition b/w warfarin & sulfonamides for binding to same place.
   - ➔ This may ↑ free molecules of warfarin → resulting in warfarin toxicity
   - ➔ This type of interaction is called as displacement interaction.
4. **Dialysis:**
   - ➔ If a drug has ↑ P.P.B; dialysis of that drug cannot be done.
   - ➔ Bcoz proteins are not filtered during dialysis; thus the drug with ↑ P.P.B. is retained along with plasma proteins.
5. If, drug has ↑ P.P.B. its filtration would be lesser.

Dialysis & drug poisoning:

- First A.B.C should be done (i.e maintenance of Airway patency, Breathing & Circulation)
- In poisons, D → Decontamination can also be done. (by giving activated charcoal etc.)
- For some drugs antidote can be given.
- Many drugs don't have antidote, so dialysis is the option in those poisoning.
- Dialysis is effective only if the drug is staying in the plasma (bcoz plasma is filtered in dialysis)
- So, for the dialysis to be effective, the drug should have
  → ↓ volume of distribution (Vd)
  → ↓ plasma protein binding (PDB)
  (↓ P.P.B doesn't always cause ↑ Vd; sometimes there can be ↓Vd due to other factors like ↓ tissue affinity of that drug etc)

*** Drugs in which dialysis is done:**

M → Methanol
L → Lithium
A → Aspirin

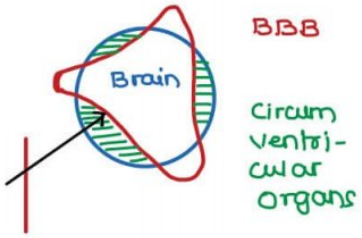
*** Drugs in which dialysis is not effective**

A → Amphetamines
V → Verapamil
O → Opioids & organophosphates
I → Imipramine
D → Digoxin
Dialysis → Diazepam (Most of benzodiazepines)

☺ BARRIERS

CIRCUMVENTRICULAR ORGANS [No Blood Brain Barrier]

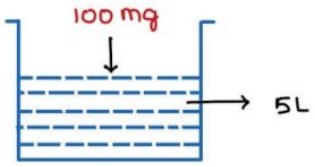
CTZ [Chemoreceptor Trigger Zone]
vomiting not caused by → Anti emetics
Anti Psychotics also has anti emetic property



VOLUME OF DISTRIBUTION V_d

→ $V_d = \frac{\text{Amount given by IV}}{\text{Plasma Concentration}}$

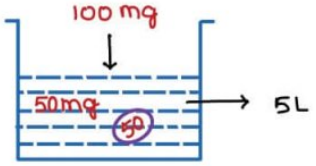
→ CASE 1



$PC = \frac{100}{5} = 20\ mg/L$

$V_d = \frac{100}{20} = 5\ L$

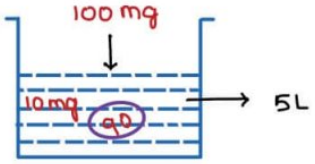
→ CASE 2



$PC = \frac{50}{5} = 10\ mg/L$

$V_d = \frac{100}{10} = 10\ L$

→ CASE 3



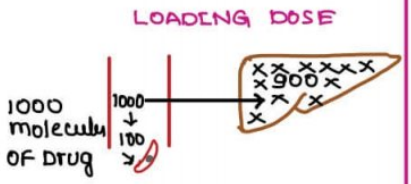
$PC = \frac{10}{5} = 2\ mg/L$

$V_d = \frac{100}{2} = 50\ L$

→ VOLUME OF DISTRIBUTION $V_d \propto$ AMOUNT OF DRUG IN TISSUES
more V_d → more distribution

CHLOROQUINE

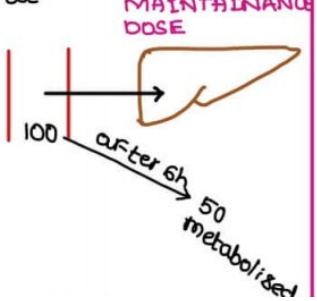
Drug ∴ maximum V_d [>13000 L]
mostly distributed in Liver
But site of preferred action is RBC



LOADING DOSE [LD]

- Initial high dose given to start the preferred action
- LD = V_d x Target Plasma concentration
- LD depends on V_d x Target Plasma Concentrat^n

MAINTAINANCE DOSE



- MD = Clearance x Target Plasma conc
- MD depends on clearance & Target plasma conc.

ELIMINATION

→ Termination of action of Drug → ELIMINATION
→ Includes Metabolism & Excretion

Metabolism

FATE OF METABOLISM

① Active ⟶ Inactive
② Active ⟶ Active
DIAZEPAM ⟶ OXAZEPAM (Brain depressant induced sleep)

③ Inactive [PRODRUG] ⟶ Active
LEVODOPA ⟶ DA [↓ of Parkinsonism]

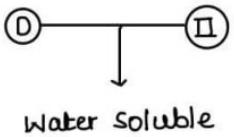
Prodrugs:

All – ACE inhibitors (PRIL) except Captopril and Lisinopril (ACL)
Prefer – PPI's (prazole) (Proton pump inhibitors),Prednisone , proguanil
Doing – Dipivefrine (Converted to epinephrine)
M – Methyldopa, Minoxidil, 6-MP (Marcaptopurin)
(Anti hypertenive drug)
D – levoDopa
In – Irinotecan (Anticancer drug)
Clinical – Clopidogrel, Carbimazole ,Cyclophosphamide(Anticacer drug)
(Anti platelets drug) (Anti thyroid drug)
Subjects – Sulfasalazine ,Sulindec (An acid)
(Ulcerative colitis)

AIM of METABOLISM → TO MAKE A DRUG WATER SOLUBLE

PHASE I REACTIONS	PHASE II REACTIONS
→ mostly catabolic Reactions	→ mostly anabolic reactions
→ includes	→ includes
– oxidation (Most common phase 1 reaction)	– Glucuronide [mc Phase Reaction]
– Reduction	– Glutathione conjugation
– Hydrolysis	– Acetylation
– Cyclization	– Methylation
– Deamination	– Sulfate

→ Purpose of PHASE II → makes the drug water soluble
→ Purpose of PHASE I → Expose functional Group on the drug



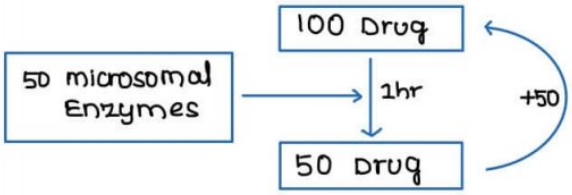
ENZYMES

→ Divided into
- Microsomal Enzymes → inside the microsomes (Smooth endoplasmic reticulum)
- Non Microsomal → Out side the microsomes

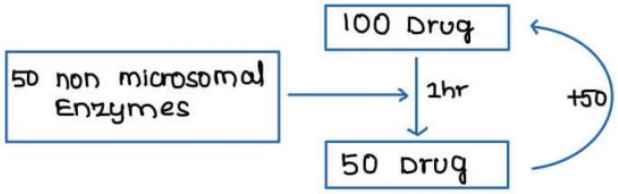
→ Microsome (Endoplasmic reticulum)
→ only Microsomal enzymes can be induced or inhibited

CASE 1

WARFARIN

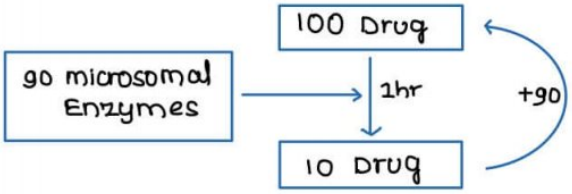


HEPARIN



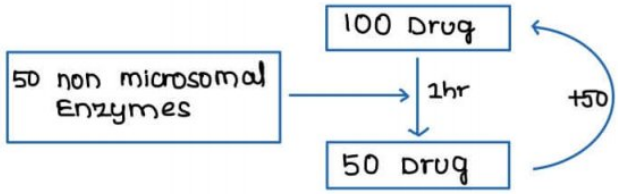
CASE 2 → Along ↓ RIFAMPICIN [enzyme inducer]

- 50 ME ⟶ 90 ME



- Drug dose ↑ to be increased

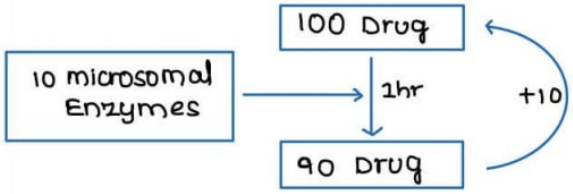
- 50 NME ⟶ 50 NME



- No change required

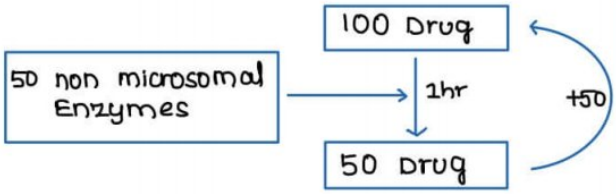
CASE 3 → Along ↓ CIMETIDINE [enzyme inhibitor]

- 50 ME ⟶ 10 ME



- Drug dose ↓ to be decreased

- 50 NME ⟶ 50 NME

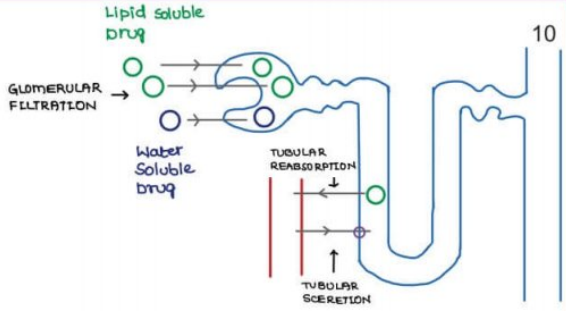


- No change required

ENZYME INDUCERS		ENZYME INHIBITORS	
G	GRISEOFULVIN (Antifungal)	Vit	VALPROATE
P	PHENYTOIN (Anti epileptic)	K	KETOCONAZOLE
R	RIFAMPICIN (Anti tuberculosis)	Can't	CIMETIDINE
S	SMOKING	Cause	CIPROFLOXACIN, Chloramphenicol
Cell	CARBAMAZAPINE	Enzyme	ERYTHROMYCIN
Phone	PHENO BARBITONE	Inhibitⁿ	ISONIAZIDE

most of anti epileptics → ENZYME INDUCERS
most of anti biotics → ENZYME INHIBITORS

EXCRETION



GLOMERULAR FILTRATION

→ Lipid soluble drugs filtered easily
Water soluble drugs also filtered

→ Filtration $\frac{1}{\alpha}$ Plasma Protein binding

→ Ⓝ GFR = 125 ml/min
= 7.5 ltr/hr
= ~180 Ltr/Day

→ Ⓝ Output of urine → 2L/Day

TUBULAR REABSORPION

→ 99% of GFR is reabsorbed
- Lipid soluble drugs reabsorbed
- Water soluble drugs excreted

→ If drug & media are same → drug absorbed
drug & media are different → drug not absorbed

→ Acidic drug poisoning [Aspirin], R_t by $NaHCO_3$ [Forced Alkaline Diuresis]
Alkaline drug poisoning [Amphetamine, R_t by NH_4Cl [Forced acid Diuresis]

TUBULAR SECRETION

→ d/t pumps / transporters in proximal tubules

→ These transporters are SATURABLE
- Penicillin is short acting
- Penicillin + Probenecid → Long acting
  - Probenecid has higher affinity for transporters & prevents Penicillin secretion

→Drugs enter urine via
- Glomerular filtration
- Tubular secretion

→Some of the drug can be reabsorbed by tubular reabsorption.

→Remaining part of drug is expelled in clearance.

Scenario 1:

→If 100 molecules of a drug is filtered through glomerular filtration and 150 molecules are expelled out in clearance

→If clearance is more than glomerular filtration which is due to,
- Tubular secretion

→Tubular reabsorption may or may not be present.

Scenario 2:

→If 100 molecules of a drug are filtered through glomerular filtration and only 50 molecules are expelled out in clearance.

→If the clearance is less than the glomerular filtration which is due to,

- Tubular reabsorption

→Tubular secretion may or may not be present.

SOME MORE FORMULAS

RATE OF ELIMINATION [R]

→ incomplete parameter

$$R \rightarrow \frac{\text{Amount of Drug Eliminated}}{\text{Time}}$$

CLEARANCE [CL]

→ complete parameter

$$CL \rightarrow \frac{R}{PC}$$

PC = Plasma concentration

Extraction Ratio

Hepatic extraction ratio in relation to clearance

Suppose

100 molecules of drug enter the liver through the arteries, 80 molecules of drug go out to other organs from liver through veins which means 20 molecules have been extracted by liver.

Formula

$$\text{Extraction ratio} = \frac{\text{Concentration of drug in arteries} - \text{Concentration of drug in veins}}{\text{Concentration of drug in the arteries}}$$

i.e. $$\frac{\text{Amount of drug extracted by the organ}}{\text{Amount of drug entering the organ}}$$

If a drug has high hepatic extraction ratio, on oral administration, liver can extract large amount of drug before it reaches the systemic circulation, leading to poor oral bio-availability which is known as First Pass Metabolism.

The drugs with high First pass metabolism/ High hepatic extraction ratio

L- Lignocaine

P- Propranolol

G- GTN (Glyceryl tri nitrate/ Nitroglycerine)

Hepatic Clearance = Hepatic Extraction Ratio × Blood flow to liver.

Renal Clearance = Renal Extraction ratio × blood flow to kidney

Total body clearance= Sum of all the clearances of individual organs.

HALF LIFE [$t_{1/2}$]

100

↓ $t_{1/2}$

50

↓ $t_{1/2}$

25

↓ $t_{1/2}$

12.5

↓ $t_{1/2}$

6.25

→ $t_{1/2}$ for most drugs is constant

$t_{1/2}$ = 6 hrs , after 1 day
→ How much drug remains in body → 6.25%
→ How much drug eliminated from body → 93.75%

→ Dose can't be calculated
DOSING INTERVAL / FREQUENCY can be known

→ $t_{1/2}$ $\propto$ volume of distribution [V_d]
$t_{1/2}$ $\frac{1}{\alpha}$ clearance

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

ORDER OF KINETICS

Rate of elimination $\propto = (Plasma\ concentration)^{order}$

First order kinetics- Rate of elimination $\propto$ plasma concentration

Zero order kinetics- Rate of elimination is constant.

Likewise,

Second order kinetics- Rate of elimination $\propto$ (plasma concentration)^2

Third order kinetics- Rate of elimination $\propto$ (plasma concentration)^3

FIRST ORDER KINETICS	ZERO ORDER KINETICS
→ Fraction is constant	→ Amount is constant
FIRST ORDER: 100 ↓1hr 50 ↓1hr 25 ↓1hr 12.5 ↓1hr 6.25	ZERO ORDER: 100 ↓1hr 80 ↓1hr 60 ↓1hr 40 ↓1hr 20
R: 50/hr ↓ 25/hr ↓ 12.5/hr ↓ 6.25/hr	R: 20/hr ↓ 20/hr ↓ 20/hr ↓ 20/hr
CL: ½ ↓ ½ ↓ ½ ↓ ½	CL: 0.20 ↓ 0.25 ↓ 0.33 ↓ 0.50
$t_{1/2}$: 1hr ↓ 1hr ↓ 1hr ↓ 1hr	$t_{1/2}$: 2.5 hr ↓ 2 hr ↓ 1.5 hr ↓ 1 hr
R α PC	R = constant
CL = constant	CL $\frac{1}{\alpha}$ PC
$t_{1/2}$ = constant	$t_{1/2}$ α PC

→ Majority drugs follow First order kinetics

DRUGS FOLLOWING ZERO ORDER KINETICS are

- ZERO → ZERO ORDER KINETICS
- W → WARFARIN
- A → ALCOHOL | ASPIRIN
- T → THEOPHYLLINE
- T → TOLBUTAMIDE
- Power → PHENYTOIN

Dose dependent actions of Aspirin

1. Antiplatelet action (Low dose is required)
2. Fever
3. Pain
4. Inflammation (Highest dose is required)

If aspirin is used for Anti-inflammatory action- it follows zero order kinetics and when concentration decreases, it will follow First order kinetics.

So, zero order kinetics are also known as Pseudo- Zero order kinetics/ Non- Linear kinetics.

REASON

→ Order of kinetics depends on Enzyme Saturation
- → If enzymes are abundant → follow 1st Order Kinetics
- → If enzymes are limiting factor → follow ZERO ORDER KINETICS [SATURATION KINETICS]

PHARMACODYNAMICS

→ D —AFFINITY→ 🜪 —INTRINSIC ACTIVITY→ ⚡

DRUG — RECEPTOR — ACTION

AFFINITY → ability of a drug to bind to a receptor

INTRINSIC ACTIVITY → ability to produce action after binding to receptor

→ **CLASSIFICATION OF DRUGS BASED ON INTRINSIC ACTIVITY**

- AGONIST → Maximum intrinsic activity [+1]
- PARTIAL AGONIST → Submaximum intrinsic activity [0 to +1]
- INVERSE AGONIST → Opposite action to agonist [−ve]
- ANTAGONIST → NO action [0] but interferes action of other drugs

→ D —AFFINITY→ 🜪 —INTRINSIC ACTIVITY→ ⚡

DRUG — RECEPTOR — ACTION

↑ Signal tranduction Mechanism

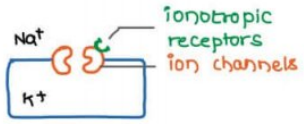
CLASSIFICATION OF DRUGS BASED ON SIGNAL TRANSDUCTN MECHANISM

① **INOTROPIC RECEPTORS**

→ Fastest acting receptors

→ Examples

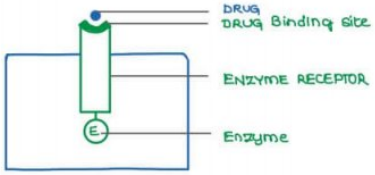
→ $GABA_A$ receptors	→ N_N receptors
→ NMDA receptors	→ N_M receptors
→ AMPA receptors	→ $5HT_3$ receptors



② **ENZYMATIC RECEPTORS**

→ aka TYROSINE KINASE RECEPTORS

[mostly associated enzyme is Tyrosine kinase]



→ Examples

cytokines

P Prolactin

I Insulin

G Growth hormone

PrepLadder

3 Types

1. **Intrinsic tyrosine kinase activity**
- Whenever drug bind outside
  - Tyrosine kinase enzyme gets activated inside
- E.g. Insulin receptor

2. **No Intrinsic activity**
- Some proteins present on Enzyme, which recruit tyrosine kinase from the cytoplasm
- Enzyme itself does not possess enzyme activity

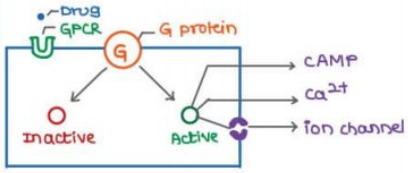
Eg:
1. JAK – STAT (JAK recruits STAT that will result in enzymatic activity)
2. Prolactin, Growth hormone
3. Cytokines

3. **Guanylate Cyclase**
- Whenever drug binds outside, guanylate cyclase gets activated inside and generates cGMP.
- Substances which act through Gyanylate cyclase are ANP, BNP, CNP

③ G – PROTEIN COUPLED RECEPTORS [GPCR]

Adrenaline
↓
acts on β receptor
↓
Stimulates G protein
↓
Active component
↑ cAMP
– ↑ HR
– Bronchodilatⁿ

Adrenaline
↓
acts on α receptor
↓
Stimulates G protein
↓
Active component
↑ Ca^{2+}
– vasoconstrictⁿ



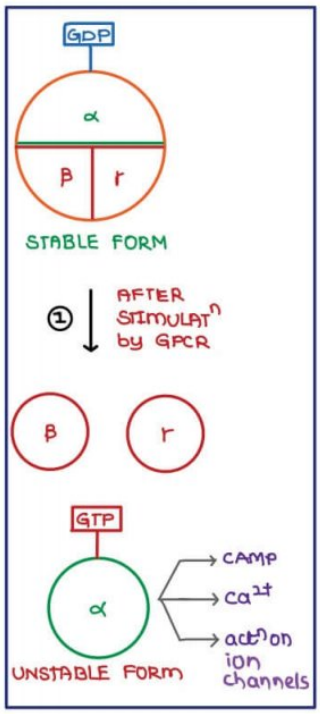
G PROTEIN

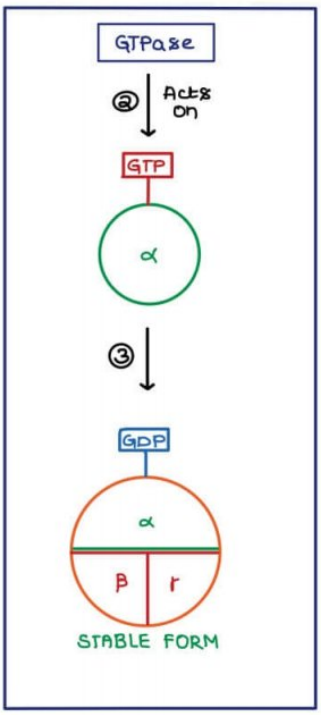
G stands for GDP/GTP binding protein

Components
- α → GDP binds here in resting state
- β
- γ

When G protein stimulated, phosphorylatⁿ occurs, GDP converted to GTP
↓
components seperates
β & γ components are inactive
α ī GTP is active
Produce one of following actⁿ on
→ cAMP
→ Ca^{2+}
→ actⁿ on ion channels

α component also has GTPase activity
→ converts GTP to GDP
→ G protein Stabilizatⁿ occurs
→ Recyling of G protein





PrepLadder

Types of G proteins

Gs → Adenyl cyclase (+) → ↑ CAMP
Gi → Adenyl cyclase (-) → ↓ CAMP
Gq → ↑ Ca^{2+} via PIP2 pathway

[Phosphatidyl inositol bisphosphate (PIP_2)

↓

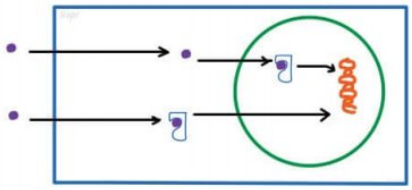
IP_3 + DAG

↓

↑ Ca^{2+} [IP_3, DAG, Ca^{2+} are second messenger]
In some books Ca^{2+} → 3rd messenger

④ INTRACELLULAR RECEPTORS

a. CYTOPLASMIC RECEPTORS
b. NUCLEAR RECEPTOR



→ only lipid soluble drugs acts through these receptors
→ slowest acting receptors
→ commony named as NUCLEAR RECEPTOR SUPERFAMILY

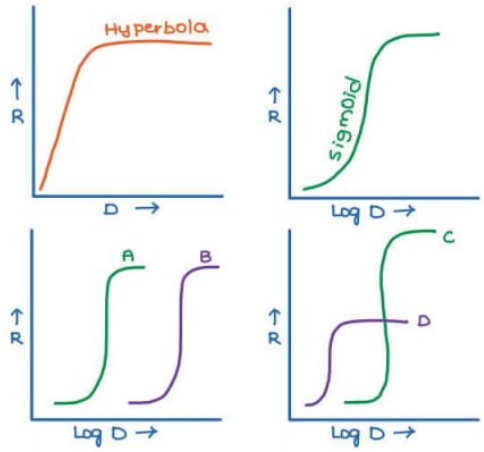
Cytoplasmic Receptors	Nuclear Receptors
C → Corticosteroids	P → PPAR
Gluco	S → Sex Hormones (E, P, T)
Mineralo	V → Vit A
D → Vit D	T → T_3, T_4

DOSE RESPONSE CURVE [DRC]

→ HYPERBOLA SHAPE

Log DOSE RESPONSE CURVE [log DRC]

→ S shaped curve [SIGMOID CURVE]
→ Clinically more useful than DRC



POTENCY

→ relates to POWER
→ left sided curve is more potent (A)
→ Right Sided curve is less potent (B)

EFFICACY

→ relates to effect regardless of dose
→ C is more efficaceous
D is less efficaceous

Q
BP
160
↓ -40
120

DOSE	A	B
5mg	10	0
10 mg	20	10
20 mg	25	20
40 mg	25	30
80 mg	25	40
	more potent	more efficacious

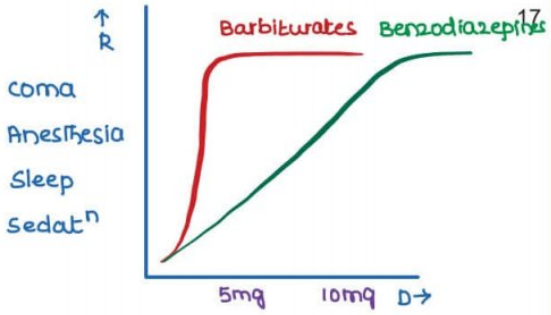
→ Efficacy is more important than potency ∵ respect to R↑

SLOPE

→ slope related to SAFETY

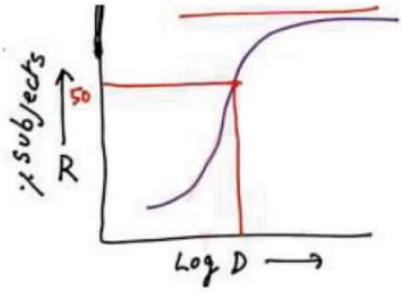
→ Drug ↑ less slope is more safer

Drug ↑ deep slope is less safer



QUANTAL DRC

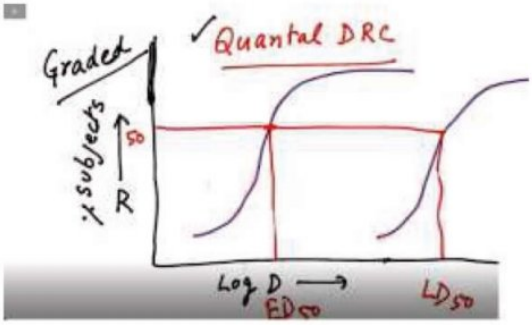
- For All or none phenomenon → On Y axis grade of response cannot be plotted.
- Percentage of subjects responding are kept on Y-axis.



If 50% respond to a particular dose → Then it is called ED_{50} (Median Effective dose)

ii)

If 50% of animals die after receiving a particular dose → it is called LD50 (Median Lethal dose)



- If
- If

- LD_{50}/ED_{50} = Therapeutic Index
- Therapeutic Index tells about the Safety of drug.

↑ Therapeutic Index – drug is safe

↓ Therapeutic Index – drug is unsafe

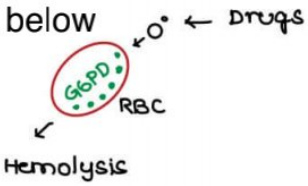
PHARMACO GENETICS

① G-6 PD DEFICIENCY

→ G-6 PD protects RBC from free radical injury

Drugs which leads to the hemolysis of RBCs when G-6PD is absent are mentioned below

- PRIMAQUINE
- SULFONAMIDES
- NITROFURANTOIN
- FURAZOLIDONE



② ACETYLATION

→ enzyme → NAT [N Acetyl Transferase]

→ FAST acetylator of INH → no response

SLOW acetylator of INH → Peripheral neuropathy

→ S → SULFONAMIDE [DAPSONE]

H → HYDRALAZINE

I → INH

P → PROCAINAMIDE

→ SHIP Drugs can cause SLE also

③ Sch INDUCED APNEA

Sch [SUCCINYL CHOLINE]

→ Muscle relaxant

→ Shortest acting [< 5 min]

– d/t Pseudocholinesterase

→ used for Endotracheal intubation

ATYPICAL PSEUDOCHOLINESTERASE

→ metabolizes Sch in 30 minutes or longer

→ causes prolonged Apnea

THERAPEUTIC DRUG MONITORING [TDM]

CASE 1 → AIM → reduce BP from 160 → 120 mm Hg,
Prescribed drug Ⓐ @ 10 mg for 1 week,
check BP after 1 week, change the dose accordingly

CASE 2 → Epilepsy Patient,
Prescribed DRUG Ⓑ @ 100 mg, then

→ required plasma concentrat^{n} → 10–20 µg/L
check plasma concentrat^{n} & change the dose accordingly

→ not used commonly

→ CRITERIA TO USE TDM

1. RESPONSE CAN'T MEASURABLE
2. LOW THERAPEUTIC INDEX DRUGS
3. INCONSISTENT PHARMACOKINETICS OF DRUGS

IMPORTANT POINTS ABOUT TDM

→ *The dose and plasma concentration graph need not be linear because if the plasma concentration is increasing, the dose can be reduced and therapeutic Drug monitoring is not essential.*

→ *The graph between Response and Plasma concentration should be Linear, because response does not increase in correspondence to increasing plasma concentration then there is no effect in measuring plasma concentration.*

→ *In therapeutic drug monitoring (TDM), the drug response should be directly proportional/ linear to plasma concentration.*

→ *TDM is not indicated for drugs which are activated in the body like pro-drugs.*

→ *TDM is used for measuring the compliance in case of long-term medications like epileptic drugs.*

→ TDM done for

A	→	Antibiotics
Drug	→	DIGOXIN
Possessing	→	PHENYTOIN [most antiepileptic drugs]
Low	→	LITHIUM
Therapeutic	→	TRICYCLIC ANTI DIPRESSANTS [TCA]
Index	→	IMMUNO SUPPRESANT DRUGS
		→ CYCLOSPORINE
		→ TACROLIMUS

PHARMACOLOGICAL ANTAGONISTS

→ acts on same receptors to produce opposite effects

→

ADRENALINE	Propranolol
↓	↓
β_2 R ⊕	β_2 R ⊖
↓	↓
Broncho dilation	Broncho constriction

→ Propranolol is pharmacological antagonist of adrenaline

CLINICAL TRAILS → Testing of drug in humans

PHASE I

→ done in HEALTHY PEOPLE

→ We can't do EFFICACY TESTING

→ MTD [maximum tolerable dose] can be found

→ Phase I can also be done in Patients for Toxic drugs

PHASE II

→ done in patients [20-200 number]

→ Indicator of EFFICACY [1st time efficacy is known]

PHASE III

→ done in patients [upto 5000]

→ Multicentric trails done [covers different genetic make up]

→ EFFICACY CONFIRMATION can be known

PHASE IV

→ Post marketing study done [max. no. of patients tested]

→ RARE SIDE EFFECTS can be studied

→ CHRONIC SIDE EFFECTS can be studied

FDA APPLICATIONS Food drug authority applications

INDA	→	Investigational New Drug Application
	→	Applied before starting clinical trails
NDA	→	New Drug Application
	→	Applied before marketing the drug

DETAILED INFORMATION ABOUT CLINICAL TRIALS

Licensing authority

→ *Authority to give approval for a new drug in USA =* **US – FDA**

→ *Authority to give approval for a new drug in India =* **CDSCO (Central Drug Standard Control Organization)**, *headed by* **DCGI (Drug controller General of India)**

FDA Applications

→ **INDA (Investigational New Drug Application)** – *Applied to start Clinical trials for a given drug*

→ **NDA (New Drug Application)** – *Applied to get permission for Marketing the drug*

Ethical guidelines

→ *Controlling authority for Animal studies / Pre-clinical studies –* **CPCSEA (Committee for the Purpose of Control & Supervision of Experiments on Animals)**

→ *Guidelines for Clinical trials on Humans –* **GCP (Good Clinical Practice) Guidelines**

Phase 1 studies are known as open labeled studies i.e both the subject and the investigator is aware of the drug given

Phases of Clinical trials

→ **Phase I** – Maximum tolerable dose can be found

→ **Phase II**

- II_A = Proof of Concept study
- II_B = Dose – Ranging study

→ **Phase III** – Pivotal clinical trials

→ **Phase IV** – Post Marketing studies

→ **Phase O**

- Micro-dosing study
- Maximum amount of drug given is **100µg or (1/100)th of Human Equivalent Dose**
- Radiolabeled substances are added with this sub-therapeutic dose to know the Pharmacokinetics of the drug
- It is not mandatory

Control & Blinding

→ **Drug group** – Newly developed drug will be given

→ **Control group**

- Placebo given
- For Life-threatening diseases – Standard drug given
- Placebo effect is mostly due to release of endorphins

→ **Blinding** - To keep drug or control group or both, unaware of the treatment

- **Single blind study**
  - Only the subject (Patient) is unaware of the treatment
  - Done in Phase II
- **Double blind study**
  - Both the Investigator & the subject are unaware of the treatment
  - Eliminate Investigator bias (considered as the best study)
  - Done in Phase III

PHARMACOVIGILANCE

→ It is the study of Detection, Assessment, Understanding & Prevention of Adverse effects of drugs

→ Adverse event (AE) – Includes anything adverse happening to the person while on drug therapy

→ Adverse drug reaction (ADR) – Out of Adverse events, adverse reactions caused by drugs are included

Detection

→ Detect all the adverse events happened

Assessment

→ Assess adverse reactions caused by drugs out of all adverse events

→ All ADR are AE but all AE are not ADRs

→ Dechallenge & Rechallenge method can be used

→ Severity of ADR is also assessed

Understanding

→ Postulate a mechanism for the cause of Adverse reaction by the given drug

Prevention

→ Proper advice to avoid the Adverse event from happening

NATIONAL PHARMACOVIGILANCE PROGRAM OF INDIA (NPVPI)

ADR monitoring centers (AMC)

→ Uses a software known as Vigiflow

→ It collects all the Adverse drug reactions reported and send them to National Coordinating center

National Coordinating center (NCC)

→ It is Indian Pharmacopoeia Commission (IPC)

→ Located in Ghaziabad (UP)

→ From here the data is sent to Uppsala Monitoring Center

Uppsala Monitoring Center (UMC)

→ Located in Uppsala, Sweden

→ Collects data from all over the world & analyses it - Report it to FDA

Food & Drug Administration (FDA)

→ May issue Black box warning or even withdrawal of drug from market

Note

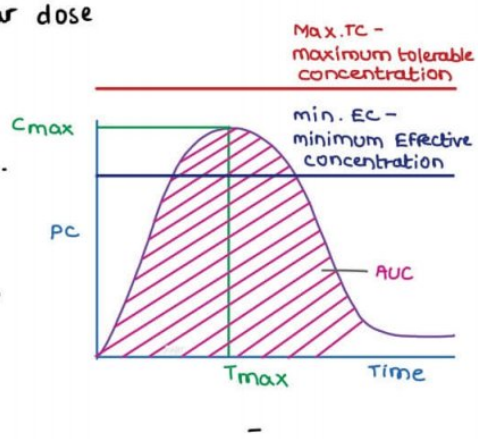
→ Materiovigilance – Program for Medical devices

PLASMA CONCENTRATION & TIME GRAPH

C_{max} → max plasma conc. obtained by a particular dose
depends on dosage
→ should lie b/w Min EC & Max TC

T_{max} → time in which concentrat^n becomes max
tells the RATE OF ABSORPTION

AUC → Area under the curve
→ tells the EXTENT OF ABSORPTION



TYPES OF DRUG ANTAGONISM

PHYSICAL → physical presence of drug stops the act^n of other [charcoal]
CHEMICAL → chemical react^n stops the action [ANTACIDS]
PHYSIOLOGICAL
PHARMACOLOGICAL

Act on the same receptors but producing different effects e.g propanolol and adrenaline acting on B2 receptors in the lungs one causing constriction of bronchioles and the other causing dilation

PHYSIOLOGICAL ANTAGONISTS

→ acts on different receptors produces opposite effects

→

Histamine	Adrenaline
↓	↓
H_1 ®	β_2 ®
↓	↓
Broncho constriction	Bronchodilation

→ Histamine is physiological antagonist of Adrenaline

ENZYME INHIBITION

COMPETITIVE → Drug can not bind to enzyme substrate complex

NON COMPETITIVE → Drug can bind to enzyme / enzyme substrate complex

UN COMPETITIVE → Drug mainly binds to enzyme substrate complex

	K_m	V_{max}
COMPETITIVE	↑	—
NON COMPETITIVE	—	↓
UN COMPETITIVE	↓	↓

Km means =How much substrates are required so half of the enzymes saturated or work i.e km inversely related to affinity and vm is the max reaction velocity or in simple word how fast the enzyme work

CYP [CYP → Cytochrome P_{450}]

SUBSTRATES FOR

CYP3A4

C → CYCLOSPORINE , CALCIUM CHANNEL BLOCKER

T → TACROLIMUS

S → STATINS

C → CAT DRUGS

A → AMIADARONE

N → NAVIRS [Protease inhibitors]

C → CISAPRIDE

A → ASTEMIZOLE

T → TERFENADINE

withdrawn d/t QT Prolongation

CYP 2D6

2 → B → β BLOCKERS

D → Depression → ANTI DEPRESSANTT DRUGS

- TCA
- SSRI
- SNRI

6 → ↑ HR → ANTI ARRYTHMICS Except AMIODARONE [by CYP3A4]

CYP 2C19

→ CLOPIDOGREL —CYP2C19→ ACTIVE

→ PPI

- PPI acts as competitive inhibitor
- clopidogrel should not be given ī PPIs

CYP 2C9

C → Clotting → WARFARIN

9 → P → PHENYTOIN

COMBINED EFFECT OF DRUGS

1. ADDITION / SUMMATION → 2 + 2 = 4
2. SYNERGISM → 2 + 2 ≅ 10
3. POTENTIATION → 2 + 0 ≅ 5
4. ANTAGONISM → 2 + 2 < 4

PrepLadder

ADDITION / SUMMATION → Individual effects of 2 drugs, simply added

SYNERGISM

→ COTRIMAXOZOLE → SULPHAMETHOXAZOLE + TRIMETHOPRIM
[Bacteriocidal] [Bacteriostatic] [Bacteriostatic]

POTENTIATION

→ LEVODOPA + CARBIDOPA [Inactive] → Efficacy of Levodopa ↑ses

ANTAGONISM → Combined effect of two drugs will be lesser

DIFFERENT TYPE OF DRUGS

Orphan drugs –

- These are drugs for which the expenditure done for the development of the drug is unlikely to be recovered from sale of the drug
- Includes drugs which are used for rare diseases
- Also includes drugs for relatively common diseases in third world countries with less paying capacity

Essential drugs

→ These are drugs that cater to Priority health care needs of a population

→ These drugs should be

- Always available
- In Adequate quantity
- With Assured quality

→ Mostly available as single compound

Me-too drugs

→ Includes drugs that has similar Mechanism of action (similar Pharmacodynamics) & minor Pharmacokinetics differences

→ Examples

- Enalapril
- Ramipril
- Captopril
- Lisinopril

Spurious drugs –

Include drugs that are manufactured, concealing the true identity of the product and made to resemble another drug (especially some popular brand)

Misbranded drugs –

Includes drugs that have false or misleading information on the drug label

Contaminated drugs –

Includes drugs that contain unhygienic or filthy mater

Spare Receptors

➢ At particular number of receptors stimulation, the response become maximum and those receptors which are present in body beyond these, are known as spare receptors

RECEPTOR REGULATION

Continuous stimulation of receptor can decrease the action. Following mechanisms are involved:

→ **Masking of receptors**
- Receptors present on surface of cell membrane mask themselves by going inside of cell membrane immediately.

→ **Down-regulation of receptors**
- Decrease in number of receptors either by stopping of receptor synthesis or by degradation of already present receptors.

→ **Uncoupling of signal transduction pathway**
- For example, constant agonistic action on G- protein coupled receptor results in decreased activation of G proteins. This Uncoupling happens due to presence of enzyme G- protein coupled Receptor kinase (GRK).
- Constant agonistic action will cause GRK to phosphorylate the receptor. The phosphorylated receptors is not able to interact with G protein
- In cases of Beta-adrenergic receptors, GRK is known as BARK (Beta adreno receptor kinase). This phosphorylated receptor binds to protein called arrestin to block interaction with G-proteins.

Constant antagonistic activity on receptors causes the activity of receptor to increase by the following methods:

→ **Unmasking of receptors**
- Receptors present near/ down /sideways of membrane moves up to increase activity.

→ **Up-regulation of receptors**
- Increase in synthesis and decrease in degradation of receptors

→ **Increase in signal transduction**

PRACTICALS IN GENERAL PHARMACOLOGY

→ **Drug label**

→ **Drug advertisement**

1. DRUG LABEL

Name

→ Generic name (Aspirin) – Must be present on drug label

→ Brand name (Ecosprin)

→ Chemical name (Acetylsalicylic acid)

Abbreviations

→ IP – Indian Pharmacopoeia

→ BP – British Pharmacopoeia

→ USP – United States Pharmacopoeia

→ BNF – British National Formulary

OTC (Over the Counter) drugs- Do not require prescription.

→ Schedule H drugs require prescription from a registered medical practitioner to be given to patients. Red line is seen on the drug label which indicates that it should be given on prescription only.

Expiry date (EXD) – MAY 2020

→ Expiry date indicates that the drug can be used until last day of the month.

→ Expiry date does not mean that the drug will become ineffective or toxic. It is the time till which the drug is expected to behave similar to, as written in Pharmacopoeia

→ Shelf life – The time between manufacturing date and expiry date.

Storage temperature

→ Keep frozen (freezer) at -20°c

→ Keep cold (Refrigerator) at 2 to 8°c

→ Keep cool (Room temperature) at 8 to 15°c in US (8 to 25°c in India)

2. PROMOTIONAL DRUG LITERATURE

1. Name
   - Brand name
   - Generic name (must be written compulsory)
   - Chemical name

   The ratio of brand name to generic name should be within a ratio of 3:1 and should not exceed it
2. Details
   - Indications of drug
   - Route of administration
   - Frequency of dosing
   - Duration of treatment
3. Cost of therapy
4. Adverse effects of the drug
   - Serious effects
   - Common effects

   Both should be mentioned in the drug advertisement leaflet
5. If some claims are made, these should be supported by appropriate reference
6. Address of manufacturing company
7. Expiry date is not required in the advertisement leaflet

ANTIMICROBIAL DRUGS

CELL WALL SYNTHESIS INHIBITORS

CLASSIFICATION OF AMA BASED ON

1 CIDAL DRUGS [kills]
STATIC DRUGS [inhibits growth]

→ Static and cidal drugs both can be used in normal immunocompetent persons.
→ In Immune-suppressed persons only cidal drugs are used, static drugs should not be used.
→ Major cidal drugs are, (BEVAFA)

- BE – BEta lactams
- VA – VAncomycin
- F – Fluoroquinolones
- A – Aminoglycosides

2 TYPE OF ORGANISMS
3 CHEMICAL STRUCTURE
4. SOURCE → ANTIBIOTICS & NON-ANTIBIOTICS
5. MECHANISM OF ACTION
   a. Cell wall synthesis Inhibitors
   b Protein synthesis Inhibitors
   c. Metabolism
   d. DNA
   c. Membranes

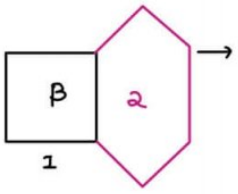
CELL WALL SYNTHESIS INHIBITORS

→ DRUGS

Firmly	→	FOSFOMYCIN	→ used for UTI
Bind to	→	BETA LACTAMS	
Bacterial	→	BACITRACIN	→ Local use only
cell	→	CYCLOSERINE	→ used in TB
vall	→	VANCOMYCIN	

BETA LACTAMS

1. PENICILLINS
2 CEPHALOSPORINS
3 CARBAPENEMS
4 MONOBACTAMS



→ 2nd ring is different in different β lactams & absent in monobactams

PENICILLINS

PENICILLIN G / BENZYL PENICILLIN

LIMITATIONS

1 not effective orally [Acid labile]
2 short acting [dlt rapid tubular secretion]
3 Narrow Spectrum
4 Resistance
5. Allergy

1. ACID RESISTANT / ORAL PENICILLINS

- V → PENICILLIN V
- O → OXACILLIN
- D → DICLOXACILLIN
- C → CLOXACILLIN
- A → AMPICILLIN
  AMOXYCILLIN

2. ↑ DURATION OF ACTION OF PENICILLIN G

→ PROBENECID compete ī Penicillin at tubular pumps → ↑ duration of action of Penecillin

→ DEPOT PREPARATIONS

- B → BENZATHINE PENICILLIN G → Longest acting Penicillin
- P → PROCAINE PENICILLIN G

→ Depot preparations are given by im only

3. SPECTRUM OF PENICILLIN G

GRAM +ive		Gram −ive	
cocci	Bacillus	cocci	Bacilli
↓	↓	↓	↓
Strepto	Bacillus	Neisseria	not effective
Staphylo	clostridium		
Pneumococcus	Diphtheria		
	Listeria		

S
S
P

EXTENDED / WIDE SPECTRUM PENICILLINS

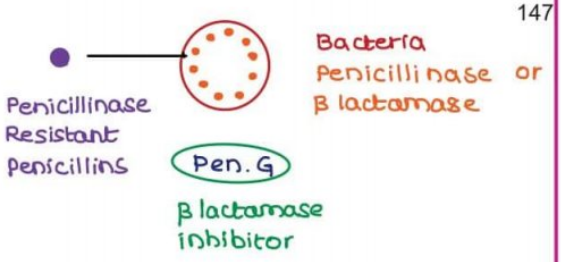
- A → AMPICILLIN, AMOXYCILLIN
- Ci → CARBENICILLIN
- Ty → TICARCILLIN
- M → MEZLOCILLIN
- A → AZLOCILLIN
- P → PIPERACILLIN

} ANTI PSEUDOMONAL DRUGS

VANCOMYCIN IS NOT EFFECTIVE AGAINST PSEUDOMONAS

4. β LACTAMASE INHIBITORS

CLAVULINIC ACID + AMOXYCILLIN
SULBACTAM + AMPICILLIN
TAZOBACTAM + PIPERACILLIN
Avibactam (Newly discovered)



PENICILLINASE RESISTANT PENICILLINS

C → CLOXACILLIN
O → OXACILLIN
N → NAFCILLIN
D → DICLOXACILLIN
O
M → METHICILLIN [most resistant]

→ MRSA [Methicillin Resistant Staph. aureus]
→ resistance is dlt alterat^{n} in Penicillin Binding Protein
→ β lactams are ineffective except 5 th gen. Cephalosporins

5. ALLERGY

→ SKIN TESTING done by Intradermal inject^{n} of drug
→ CROSS ALLERGY → allergic to one penicillins, all β lactams are allergic except MONOBACTAMS

PENICILLIN G INDICATIONS

FIRST LINE DRUGS IN

L → LISTERIA
A → ACTINOMYCOSIS
S → SYPHILIS
T → TETANUS
M → MENINGOCOCCUS
A } ANTHRAX
N }
GO - gonococeus

LISTERIA:

→ Drug of choice for listeria is Ampicillin.

SYPHILIS:

SYPHILIS TYPES		TREATMENT
Primary syphilis		single injection of Benzathine Penicillin G
Secondary syphilis	Early	IM route, Dose of 2.4 MU
Latent		
	Late	3 injections (1 injection a week) of
Tertiary syphilis (except neuro)		Benzathine Penicillin G, IM with 2.4 MU

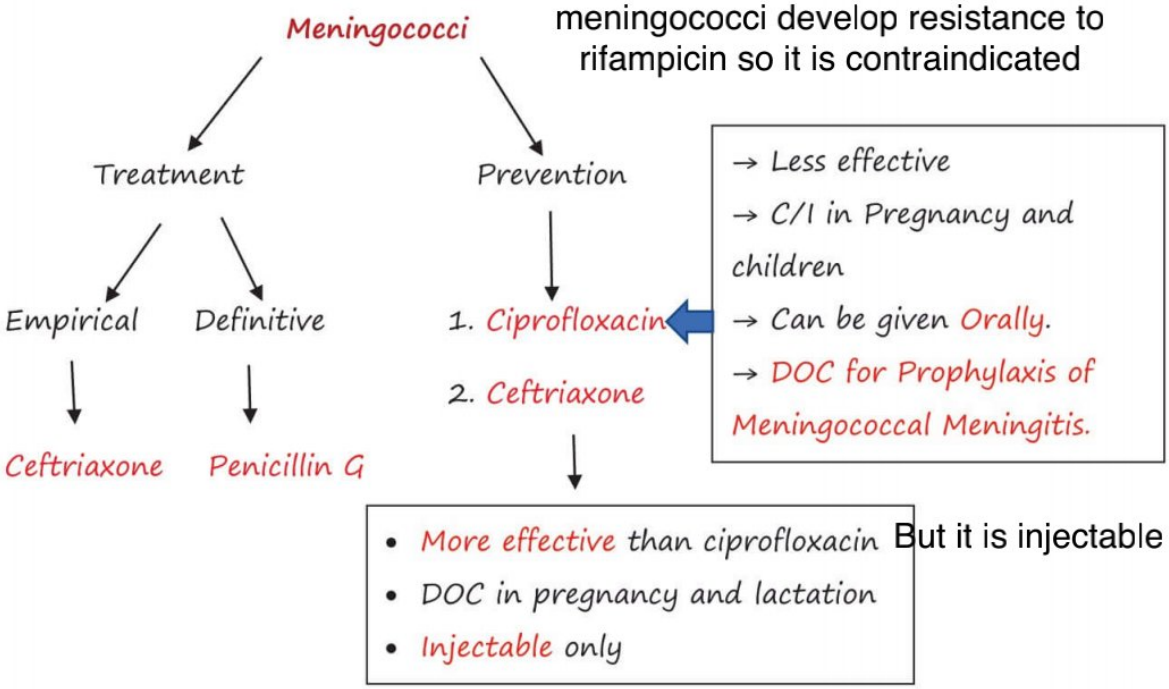
Neurosyphilis – Penicillin G (Aqueous/Crystalline) is the Drug of Choice of Neurosyphilis, Procaine Penicillin G Can also be used for the treatment.

TETANUS:

→ Drug of choice and First line drug for Tetanus is Penicillin G ≫ Metronidazole.

MENINGOCOCCI:

Rifampicin can also be used as a drug of choice in large population but now it is notes that most of meningococci develop resistance to rifampicin so it is contraindicated



But it is injectable

ANTHRAX:

→ Drug of choice and first line treatment is Penicillin G ≫ Ciprofloxacin.

GONOCOCCI:

Penicillin G was early used but now it is contraindicated because most of the gonococci developed resistance

→ Drug of choice for Gonococcal Urethritis is Ceftriaxone.
→ Drug of choice for Non-Gonococcal Urethritis is Azithromycin.
→ Drug of choice for Mixed (Gonococcal and Non gonococcal) urethritis is Azithromycin.

CEPHALOSPORINS

1st GEN.	2nd GEN.	3rd GEN.	4th GEN	5th GEN
EFFECTIVE AGAINST				
Gm +ive	Gm +ive Gm -ive Anaerobic	Gram +ve Gram -ive Widest Spectrum	Gram -ive	MRSA

1st GEN.	2nd GEN.	3rd GEN.	4ℸ GEN	5ℸ GEN
CEFAZOLIN	CEFUROXIME	CEFOPERAZONE	CEFEPIME	CEFTIBIPROLE
CEFALEXIN	CEFOXITIN	CEFTRIAXONE	CEFPIROME	CEFTAROLINE
CEFALOTHIN	CEFMETAZOLE	CEFOTAXIME		
CEFALORIDINE	CEFOMANDOLE	CEFTIZOXIME		
CEFADROXIL	CEFACLOR	CEFPODOXIME		
		CEFTAZIDIME		
		CEFTIBUTEN		
		MOXALACTAM		
		CEFIXIME		

1 BILE SECRETED CEPHALOSPORINES
- → safe in renal failure
- → includes
  - CEFOPERAZONE
  - CEFTRIAXONE

Can cause Biliary sludge syndrome if seftriaxone secreted in very large amounts

BILE SECRETED ANTIMICROBIAL AGENTS		
Cef in	→	CEFOPERAZONE, CEFTRIAXONE
R	→	RIFAMPICIN
E	→	ERYTHROMYCIN
N	→	NAFCILLIN
A	→	AMPICILLIN
L	→	LINCOSAMIDES [CLINDAMYCIN]
Disease	→	DOXYCYCLINE

The Tigecycline

2 ANTI PSEUDOMONAL CEPHALOSPORINS
- → includes
  - CEFEPIME
  - CEFPIROME
  - CEFOPERAZONE
  - CEFTAZIDIME [most effective antipseudomonal cephalosporin]

3 DISULFIRAM LIKE REACTION
- → not to be given ± alcohol
- → includes
  - CEFOPERAZONE
  - MOXALACTAM
  - CEFOTETAN
  - CEFOMANDOLE

4 ↓ PROTHROMBIN
- → includes
  - CEFOPERAZONE
  - MOXALACTAM
  - CEFOTETAN
  - CEFOMANDOLE

CARBAPENEMS

Imipenem:

- Effective against Gram (+), Gram (-) and Anaerobes
- Always given with Cilastatin because if given alone it is broken down by Dehydropeptidase enzyme in the kidney
- Imipenem is a broad spectrum antibiotic, it is also effective against Pseudomonas.

Side effect of imipenem: Seizures

Contraindication: Epileptic patients

Other Carbapenems:

- Meropenem
- Ertapenem
- Doripenem
- Faropenem

} cilastatin not required, lesser risk of seizures

→ All carbapenem's are injectable except Faropenem which can be given Orally.

→ Any bacteria (mostly Klebsiella) which has Extended Spectrum Beta Lactamase (ESBL) enzyme is resistant to most of the antibiotics (except carbapenems)

Limitations of ESBL:

→ Cannot break carbapenems and hence carbapenems are the drug of choice for ESBL producing bacteria.

→ Can be inhibited by Beta lactamase inhibitors like Piperacilllin + Tazobactam combination.

New Delhi metallo-beta lactamase (NDM):

→ NDM can break most of the antibiotics (just like ESBL) and it

- Can break even Carbapenems
- It cannot be inhibited by Beta lactamase inhibitors

→ This infection is also known as **Superbug.**

→ **Colistin** can kill the bacteria that produces NDM beta lactamase

→ Colistin is the drug of choice for **NDM producing bacterial infections**

MONOBACTAM

AZTREONAM

→ do not show cross allergy

→ effective only against Gm -ive bacteria including Pseudomonas

VANCOMYCIN

→ Not effective orally [NOT ABSORBED]

→ given by iv → releases HISTAMINE → RED MAN SYNDROME

→ SIE

→ nephrotoxic

→ ototoxic

→ not effective against Pseudomonas

→ USE
- → MRSA [DOC]
- → PSEUDO MEMBRANOUS COLITIS
  - → commensal bacteria protect the GIT from infection
    - → by competing ↑ nutrition & producing BACTERIOCIN
  - → Broad spectrum antibiotics kills commensals, which Predisposed to SUPER INFECTION
  - → WBC forms a membrane → PSEUDO MEMBRANE

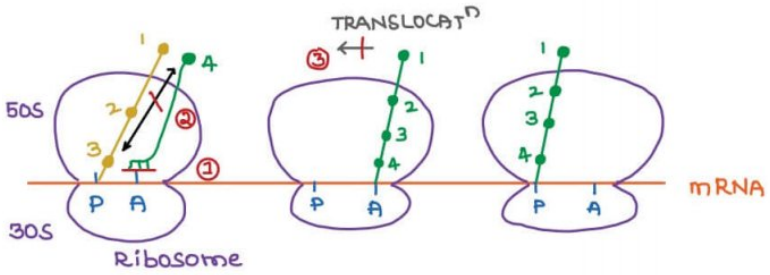
PSEUDOMEMBRANE COLITIS

1. mc organism responsible → Clostridium difficile
2. mc cause → 3rd gen. cephalosporins > Clindamycin
3. DOC → ORAL VANCOMYCIN [only oral indicatn of vancomycin]

GLYCOPEPTIDES	
VANCOMYCIN TEICOPLANIN ORITAVANCIN DALBAVANCIN TELAVANCIN	DO not cause RED MAN SYNDROME

PROTEIN SYNTHESIS INHIBITORS

PROTEIN SYNTHESIS INHIBITORS



1. TETRACYCLINES → inhibit the attachment of tRNA to A site
2. CHLORAMPHENICOL → inhibit the joining of 2 AA [peptide bond formatn]
3. M → MACROLIDS
   C → CLINDAMYCIN
   Q → QUINPRISTIN
   } Inhibit Translocation
4. AMINOGLYCOSIDES → acts by causing Misreading of mRNA codon
   → only cidal protein synthesis inhibitor

BINDING

Binding	
A	AMINOGLYCOSIDES
T	TETRACYCLINES
30S	bind @ 30S Ribosome

Rest all bind at 50S ribosome

1. TETRACYCLINES

DRUGS

- TETRACYCLINE
- OXYTETRACYCLINE
- CHLORTETRACYCLINE
- DEMECLOCYCLINE → most phototoxic, highest risk of DI
- DOXYCYCLINE
- MINOCYCLINE → highest vestibular dysfunction

ADVERSE EFFECTS

- K → Kidney failure → C/I except Doxycycline
- A → Antianabolic
- P → Phototoxic
- I → Insipidus diabetes
- L → Liver failure C/I
- D → Dentition & Bone (C/I in pregnancy & children)
- E → not be given after Expiry [risk of Fanconi syndrome]
- V → Vestibular dysfunctⁿ

USES

- S → SIADH [Demeclocycline]
- R → Rickettsia [DOC]
- I → Granuloma Inguinale [DOC]
- L → LGV
- A, N → Atypical pNeumonia [DOC → MACROLIDES]
- K → Cholera [DOC]
- A → Luminal Amoebiasis [DOC for amoebiasis → METRONIDAZOLE]

RESISTANCE:

→ Resistance to tetracyclines → Due to development of efflux pumps in bacteria.

TIGECYCLINE

→ Resistant to efflux pump
→ Mechanism of action is similar to tetracycline but chemical structure belongs to Glycylcycline.
→ Tigecycline is a broad-spectrum antibiotic but it is not effective against pseudomonas
→ It is secreted in bile and so it is safe in case of renal disease.

2. CHLORAMPHENICOL

→ It is a protein synthesis inhibitor
→ It binds to 50 s ribosomes and inhibits the joining of amino acids.
→ Bacteriostatic drug (like most of the protein synthesis inhibitors).
→ Rarely used now a days → bcoz, Not effective and toxic.
→ Initially, chloramphenicol was the DOC for enteric fever.

→ But now most of salmonella has become resistant to Chloramphenicol by developing inactivating enzymes.

→ It has high risk of causing **BONE MARROW SUPPRESSION**

→ It is contraindicated in newborn babies due to risk of development of cyanosis in babies → **Grey Baby Syndrome.**

→ Now-a-days, it is mainly used in Meningitis (for bacteria resistant to ceftriaxone).

→ It is effective against anaerobic bacteria.

→ Rarely if chloramphenicol is sensitive to Salmonella, it is used in typhoid fever/ enteric fever

3 MACROLIDES

DRUGS

- ERYTHROMYCIN
- CLARITHROMYCIN
- ROXITHROMYCIN
- AZITHROMYCIN

} 2nd Line drugs to Penicillins
DOC for
C → Chancroid
L → Legionella
A → Atypical pneumonia
P → Pertussis

- FIDAXOMICIN → used in mild to moderate Pseudo Membrane colitis

→ causes stimulation of Motilin ® in GIT
  → Diarrhea is SIE
  → used in Diabetic gastroparesis

AZITHROMYCIN	OTHER 'THROMYCINS'
→ very long acting	→ Relatively short acting
→ non microsomal enzyme ⊖	→ microsomal enzyme inhibitors
→ Fewer drug interactions	→ more drug interactions

→ Major adverse effects of Macrolides: (MACRO)

- M: Stimulate Motilin receptor (used in diabetic gastroparesis and paralytic ileus)
- A: Allergy
- C: Cholestasis: Erythromycin estolate (higher risk in pregnancy therefore CI in pregnancy but it is not teratogenic)
- R: Reversible
- O: Ototoxicity

→ Drugs which are safe in pregnancy: PCM

- Penicillin
- Cephalosporin
- Macrolide

→ Irreversible ototoxicity is seen in:

- Cisplatin
- Vancomycin
- Aminoglycoside

→ Macrolides: have both antimicrobial and immunosuppressant activity.

→ Macrolide with stronger immunosuppressant activity: Tacrolimus

→ Spiramycin is used to treat Toxoplasmosis in pregnancy.

CLINDAMYCIN

→ Secreted in Bile

→ causes Pseudo membranous colitis

→ used in anaerobic bacterial Infections

MAJOR USES OF CLINDAMYCIN:

→ C – Cocci

→ A – Anaerobes

→ P – Parasites

- Pneumocystis
- Malaria
- Toxoplasma

QUINPRISTIN + DALFOPRISTIN

→ Both are Streptogramins

→ indicated in VRSA [DOC → DAPTOMYCIN]

Vencomysin resistance staph areus infections

4. AMINOGLYCOSIDES

DRUGS

STREPTOMYCIN
GENTAMICIN
TOBRAMYCIN
NETILMYCIN
NEOMYCIN
CAPREOMYCIN
KANAMYCIN
AMIKACIN

- Not effective orally [not absorbed]
- active mainly on Gm –ive [incl. Pseudomonas]
- not effective on anaerobic bacteria
- cidal drugs
- nephrotoxic [max. by Neomycin]
- ototoxic
  - Auditory [max. by Amikacin]
  - vestibular [max. by Streptomycin]
- cause neuromuscular blockade [max by Neomycin]

→ CAPREOMYCIN is chemically not aminoglycoside

STREPTOMYCIN – TB, PLAGUE

CAPREOMYCIN
KANAMYCIN
AMIKACIN
– 2ND LINE DRUGS FOR T.B

NEOMYCIN – HEPATIC COMA [GIVEN ORALLY]

Hepatic coma:

→In our GIT, urea is present which is converted into ammonia (NH_3) by the enzyme urease.

→Ammonia is absorbed and goes to brain causing hepatic coma.

Neomycin:

→ It is effective against gram negative organisms and kills urease producing organisms in GIT.

→ It is given orally for Hepatic coma and this use of neomycin is known as Gut sterilization.

LEPROSY

MULTIBACILLARY LEPROSY

RCIN	600 mg	Once monthly	Supervised	X 12 MONTHS
CLOFAZIMINE	300 mg	Once monthly	Supervised	
CLOFAZIMINE	50 mg	Once daily for 28 days	Unsupervised	
DAPSONE	100 mg	Once daily for 28 days	Unsupervised	

PAUCIBACILLARY LEPROSY

RCIN	600 mg	Once monthly	Supervised	X 6 MONTHS
CLOFAZIMINE	300 mg	Once monthly	Supervised	
CLOFAZIMINE	50 mg	Once daily for 28 days	Unsupervised	
DAPSONE	100 mg	Once daily for 28 days	Unsupervised	

→ **In case of resistance, the drugs used are**

- Ofloxacin
- Minocycline
- Clarithromycin

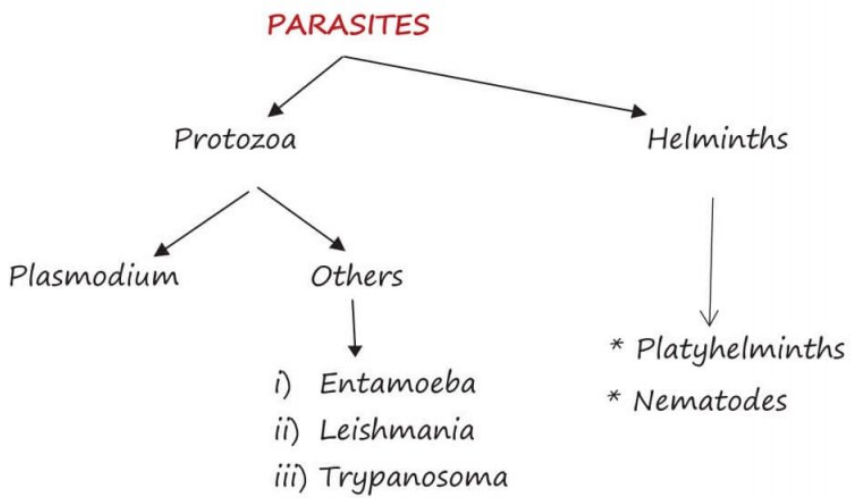
MAC (MYCOBACTERIUM AVIUM COMPLEX)

→ **Associated with immunocompromised patient (HIV)**

→ **Treatment**: Rifabutin + Ethambutol + Clarithromycin

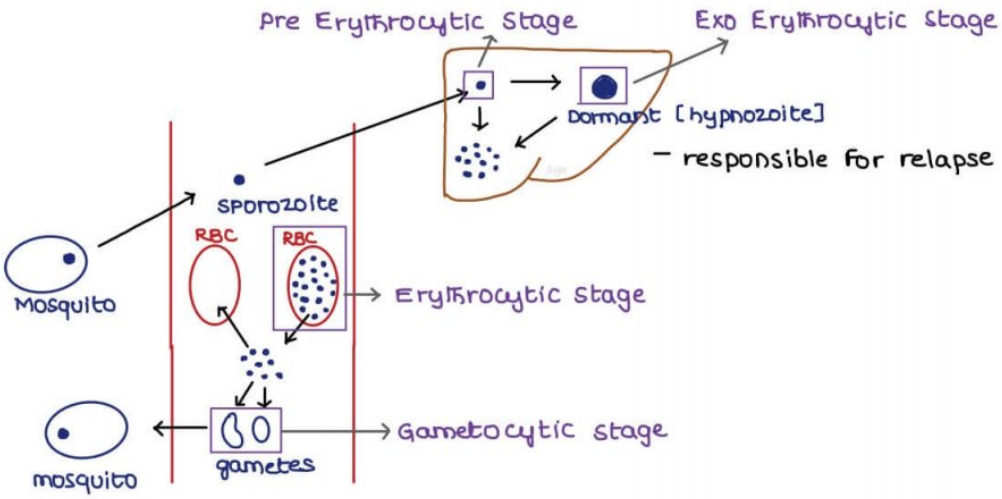
→ **Prophylaxis**: Azithromycin (weekly) OR Clarithromycin (daily)

ANTIPARASITIC DRUGS

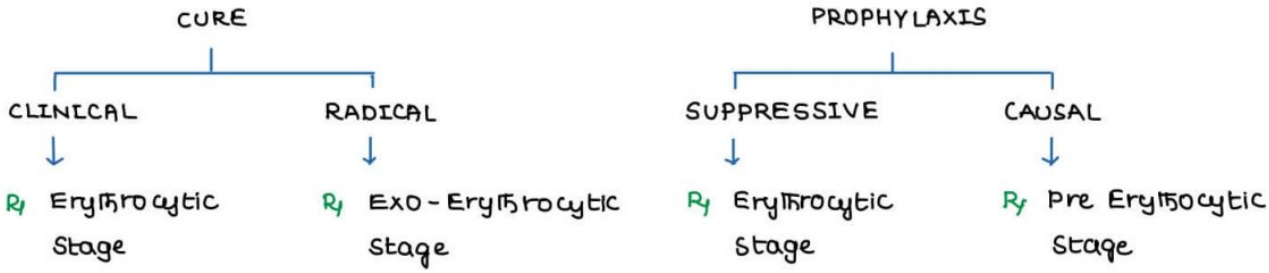


ANTI MALARIAL DRUGS

→ Plasmodium Knowlesi can also cause malaria



TREATMENT MODALITIES



PRIMAQUINE

→ ACTS ON

- PRE ERYTHROCYTIC STAGE → used for causal Prophylaxis
- EXO ERYTHROCYTIC STAGE → used for Radical cure
- GAMETOGENIC STAGE → used to prevent transmission

→ can't act on ERYTHROCYTIC STAGE → not useful to Rf or prevent malaria

→ can cause HEMOLYSIS in G6PD Deficiency

→ CI in Pregnancy & infants

→ Can kill the gametes of all species of plasmodium (vivax, falciparum, ovale, malariae) in a single dose whereas chlorquine and quinine can kill gametes of plasmodium vivax only.

→ Can kill the exoerythrocytic stage (hypnozooites) when given for 14 days.

→ In plasmodium falciparum there is no exoerythrocytic stage and hence there is no relapse in plasmodium falciparum.

→So in ,

- Plasmodium falciparum, single dose of primaquine is given (to kill gametes).
- Plasmodium vivax, it is given for 14 days to kill the hypnozoites.

CONTRAINDICATIONS OF PRIMAQUINE :

→ G6PD deficiency patients
→ Pregnancy
→ In infants (< 1 year of age)

TAFENOQUINE

→ Can kill the hypnozoites in single dose
→ Like Primaquine, it can also cause hemolysis and hence it is also contraindicated in G6PD deficient patients, pregnancy and infants.

DRUGS ACTING ON ERYTHROCYTIC STAGE

FAST ACTING

M → MEFLOQUINE
A → ATOVAQUONE
C → CHLOROQUINE
H → HALOFANTRINE
A → ARTEMISININS
R → RES - Q [QUININE]

SLOW ACTING

PROGUANIL
PYRIMETHAMINE
SULFADOXINE
DOXYCYCLINE
CLINDAMYCIN

CHLOROQUINE

→ causes BULL'S EYE MACULOPATHY [on prolonged usage for 2-3 yrs]

USES

R → Rheumatoid Arthritis
E → Extra intestinal Amoebiasis
D → DLE
L → Lepra reaction
I → Infectious mononucleosis
P → Photogenic Reactions
Mahatma → Malaria
Gandhi → Giardiasis

MEFLOQUINE:

- Long acting drug
- Neuropsychiatric side effects

QUININE:

- Safe in 1st trimester of pregnancy
- Derivatives of cinchona plant: excess will lead to development of Cinchonism (headache, blurred vision, tinnitus, deafness)
- If only quinine has to be given, it is given for 7 days for treatment for malaria.
- Therefore, we add doxycycline or clindamycin to quinine, so that we decrease duration of treatment to 3 days.

ARTEMISININS

DRUGS

ARTESUNATE
ARTETHER
ARTEMETHER
DIHYDRO ARTEMISININ

→ Fastest acting antimalarials
→ effective against MDR parasites
→ short acting
→ CI in 1st trimester

ARTEMISININ COMBINATION THERAPY [ACT]

→ Artimisinin + Long acting drug
→ DOC for Chloroquine resistance
→ COMBINATIONS
  LUMEFANTRENE + ARTEMETHER → DOC in North Eastern States
  ARTESUNATE + SULFADOXINE-PYRIMETHAMINE → DOC for rest of India

TREATMENT OF MALARIA UNDER NVBDCP

		1st Trimester
P. Vivax malaria	Chloroquine	Chloroquine
P. falciparam malaria	ACT	Quinine
mixed infection	ACT	Quinine
complicated or severe or cerebral Malaria	iv Artesunate + ACT	iv Artesunate

MALARIA PROPHYLAXIS

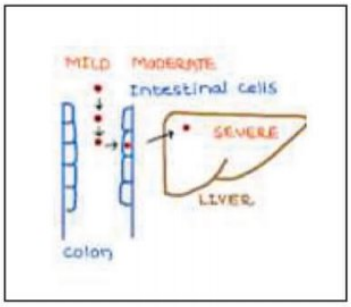
- Given to traveler going from non-endemic area to endemic area.
- Drugs are given before the journey.
- Prophylaxis depends on duration of stay:

Short term (<6 weeks)	Long term (>6 weeks)
• Doxycycline • Given daily • Start 2 days before journey to • 4 weeks after journey	• Mefloquine • Given weekly • Start 2 weeks before journey to • 4 weeks after journey

OTHER PROTOZOAL DISEASES

1. AMOEBIASIS

- Entamoeba histolytica comes through feco-oral route
- Through mouth it can penetrate cells of intestine → reach liver



1. Luminal amoebiasis – Enters mouth to lumen
2. Intestinal amoebiasis – when it penetrates intestinal cells
3. Extra intestinal amoebiasis – when it penetrates tissue

DRUG OF CHOICE

- Luminal amoebiasis & carrier state – Diloxanide Furoate (or) Paromomycin
- Intestinal & Hepatic amoebiasis – Nitroimidazole (Nidazole)

  Eg. Metronidazole, Tinidazole, Secnidazole, Ornidazole, Satranidazole

  ↓

  Cause disulfiram like reaction

  C/I in alcoholics (except satranidazole)

  → Other uses of Metronidazole

  G – Giardiasis, Gardnerella vaginalis

  U – Ulcer (Peptic ulcer)

  P – Pseudomembranous colitis

  T – Trichomoniasis

  A – Amoebiasis, Anaerobic bacterial infection

2. LEISHMANIASIS

Leishmania

Visceral	Mucocutaneous	Dermal
(KALA AZAR)		(PKDL)
DOC – Liposomal AMB	Liposomal AMB	Miltefosine
(IV Single dose)		(Only oral drug)
Other drug – Antimony (Stibogluconate)		

3. TRYPANOSOMIASIS

AFRICAN TRYPANOSOMIASIS / SLEEPING SICKNESS	SOUTH AMERICAN TRYPANOSOMIASIS/ CHAGA'S DISEASE
EARLY STAGES – SURAMIN (DOC) LATE STAGES – MELARSOPROL (DOC)	BENZNIDAZOLE (DOC)

ANTI HELMINTHIC DRUGS

PLATYHELMINTHS

Tapeworms

→ DOC → PRAZIQUANTAL
except Echinococcus granulosus [DOG Tapeworm]

→ DOC for Echinococcus granulosus
→ ALBENDAZOLE

Flukes

→ DOC → PRAZIQUANTAL
except for Liver fluke [Fasciola hepatica]

→ DOC for Liver fluke → TRICLABENDAZOLE

NEMATODES

→ DOC for all nematode incl. larvae → ALBENDAZOLE
→ Except
Filaria → DEC [Di Ethyl carbamazine]
Strongyloides, Onchocerca } IVERMECTIN

→ Ivermectin is the only oral drug approved for scabies
→ DOC for Scabies – Permethrin
→ Treatment of **Neurocysticercosis** : ALBENDAZOLE (DOC)
PRAZIQUANTAL

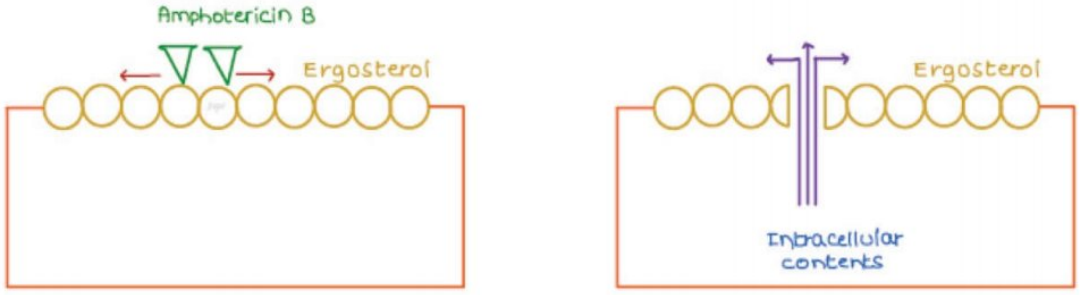
ANTIFUNGAL DRUGS

1. POLYENES:

→ Amphotericin B
→ Nystatin
→ Hamycin

Mechanism of action

Bind to Ergosterol, creates pores leading to death of fungus, which makes them fungicidal.



AMPHOTERICIN B

→ Used for serious fungal infections (DOC for cryptococcal meningitis, mucormycosis)

→ Given IV

→ Very toxic (side effect):

- Infusion related reaction (MC side effect): chills, fever
- Nephrotoxic (RTA with hypokalemia): MC dose dependent side effect.
- BM suppression

→ Liposomal amphotericin B:

- Less nephrotoxic as compared to conventional amphotericin B
- But cost is higher
- DOC for KALA AZAR

NYSTATIN: Used topically for oropharyngeal candidiasis

HAMYCIN: Used topically

2. ALLYL-AMINES

→ Allyl-amines inhibit Sq epoxidase and lead to accumulation of squalene which is toxic to fungal cell (fungicidal drugs). Azoles inhibit 14 alpha demethylase and are fungistatic.

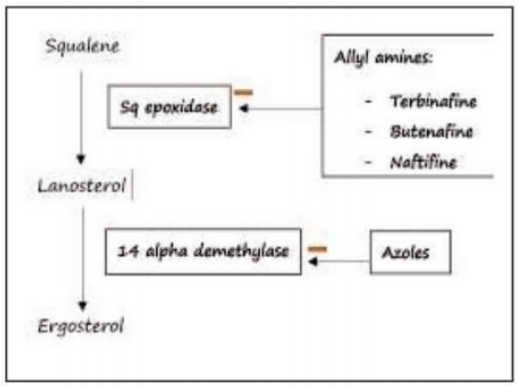
→ Allyl-amine: are fungicidal and available in oral form as well as topical preparations.

A. TERBINAFINE

B. BUTENAFINE

C. NAFTIFINE

- After absorption, these drugs accumulate in Keratin rich areas like skin, hair and nails.
- Therefore, these drugs are used in fungal infection of skin, nail and hair, i.e. dermatophytosis (tinea infection).



3. AZOLES

→ Azoles are fungistatic drugs:

A. KETOCONAZOLE
B. FLUCONAZOLE
C. ITRACONAZOLE
D. VORICONAZOLE
E. POSACONAZOLE

- Ketoconazole: not much in use these days due to:
  - Microsomal enzyme inhibition
  - Cause Gynaecomastia
  - Cause Adrenal suppression
  - Hepatotoxic
- Fluconazole:
  - max oral bioavailability
  - max CNS penetration
  - DOC for candida and Cryptococcus (maintenance phase)
  - DOC for cryptococcal meningitis is Ampho B (Acute phase)
- Itraconazole: DOC
  - Histoplasma
  - Sporothrix
  - Blastomyces
- Voriconazole: DOC
  - Aspergillosis
- Posaconazole: can be use in
  - Mucormycosis (DOC is Ampho B)

Drugs causing gynaecomastia

DI: Digitalis

S: Spironolactone

C: Cisplatin

K: Ketoconazole

O: Oestrogen

4. HETEROCYCLIC BENZOFURAN: GRISEOFULVIN

- Act on mitotic spindle
- Oral, static drug
- High affinity for keratin
- Used for dermatophytosis
- Avoided in patient taking Disulfiram.

5. 5-FLUCYTOSINE:

- Inhibit DNA polymerase

6. ECHINOCANDINS:

- CASPOFUNGIN (use for Candida and aspergillosis)
- Act on beta 1,3 – glycan of cell wall

- New drugs are:
    - Micafungin
    - Anidulafungin

7. TAVABOROLE

- Topical antifungal drug for dermatophytosis
- Acts by inhibiting fungal tRNA synthase (protein synthesis)

ANTIVIRAL DRUGS

Virus multiplication:

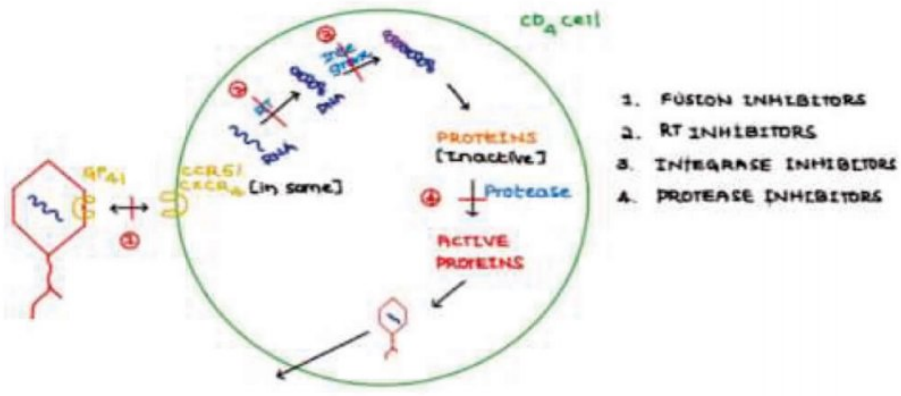
→Virus fuse with human cell and sends the genetic material inside human cell; uncoating occurs genetic material is set free and then it multiplies, replication occurs and forms inactive proteins.

→Inactive proteins are activated and then assembly and maturation occurs, virus matures and is released outside the cell.

DRUGS:

1. **Fusion inhibitors**
    - Enfuvirtide (inhibits the fusion of virus and human cell)
2. **Uncoating inhibitors**
    - Amantadine
3. **Virus nucleic acid inhibitors** - Acyclovir
4. **Protease inhibitors** – inhibits activation of proteins
5. **Virus maturation inhibitors** - Tecovirimat
6. **Virus release inhibitors**
    - Oseltamivir

ANTI-HIV DRUGS



1. FUSION INHIBITOR

ENFUVIRTIDE	MARAVIROC	IBALIZUMAB
• Binds with GP 41 of Envelope & Fusion of VIRus with T cell is Inhibited • Given subcutaneously	• Binds with CCR-5 • Given orally • Can't bind with CD4 cells with CxCR4	• Monoclonal antibody against CD4 receptors • Given intravenously

2. REVERSE TRANSCRIPTASE INHIBITORS

→ Inhibit reverse transcriptase (RNA dependent DNA polymerase)

→ May be competitive (NRTI) or non-competitive (NNRTI)

COMPETITIVE		NON COMPETITIVE	
NRTI (nucleotide or side RT inhibitors)		NNRTI (Non NRTI)	
Nucleoside RTI	Nucleotide RTI	1st Gen	2nd Gen
Zidovudine Lamivudine Stavudine Didanosine Zalcitabine Emtricitabine Abacavir	Tenofovir	Efavirenz Nevirapine Delavirdine	Etravirine Rilpivirine Doravirine

NUCLEOSIDE OR NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI)

Most cause peripheral neuropathy & pancreatitis

→ Max risk of peripheral neuropathy – Stavudine

→ Max. risk of pancreatitis – Didanosine

→ Min. risk of peripheral neuropathy – Lamivudine (safest NRTI)

→ Min. risk of pancreatitis - Lamivudine

Bone marrow suppression by – Zidovudine

MI predisposition by – Abacavir

NRTIs used for hepatitis B.

L – Lamivudine

E – Emtricitabine

T – Tenofovir

NON- NUCLEOSIDE/TIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI)

→ Prone to develop Resistance (hence not given alone)

→ Effective against HIV -1 only

→ Metabolized by CYP (microsomal) enzymes and are prone to drug interactions.

Nevirapine:

→ Prevents vertical transmission from HIV infected mothers

→ Hepatotoxic (should not be given with other hepatotoxic drugs)

→ Examples of hepatotoxic drugs include TB drugs like Isoniazid, Rifampicin.

3. INTEGRASE INHIBITORS

→ Can be given orally and according to latest 2018 guidelines they are one of the first line drugs of HIV

→ First line HAART therapy – 2 NRTI'S AND 1 NNRTI (or) Integrase inhibitor

→Elvitegravir is combined with cobicistat which is a CYP3A4 inhibitor to boost the effect of elvitegravir.

4. PROTEASE INHIBITORS

RITONAVIR

LOPINAVIR

AMPRENAVIR

FOSAMPRENAVIR

ATAZANAVIR

SAQUINAVIR

NELFINAVIR

INDINAVIR

→ Metabolized by CYP3A4

→ CYP3A4 inhibitors themselves

- Strongest – Ritonavir
- Ritonavir boosting – boost the other inhibitors

→ Cause lipodystrophy syndrome (also caused by atypical antipsychotics)

- ↑ Glucose
- ↑ Lipids
  - Insulin resistance

•Wt. gain

RITONAVIR

→Strongest microsomal enzyme inhibitor

→It is not used as a protease inhibitor

→ In low doses, it is used to inhibit microsomal enzymes and to boost the effect of other protease inhibitors except nelfinavir.

NELFINAVIR: Effect not boosted by ritonavir

INDINAVIR

→Causes Renal stones, hyperbilirubinemia, Kidney stones

ATAZANAVIR

→Among all the protease inhibitors it has the minimum risk of causing LIPODYSTROPHY SYNDROME, but it can result in hyperbilirubinemia.

HAART – HIGHLY ACTIVE ANTI RETRO VIRAL THERAPY

1. When to start Rx – All patients irrespective of CD4 count
2. How long – Life long
3. WHAT – minimum 3 drugs from minimum 2 groups

- 2 NRTI + 1 NNRTI /Integrase Inhibitor
- T +L+E (preferred)

POST EXPOSURE PROPHYLAXIS:

→ To prevent development of HIV after exposure

→ Used commonly in health care workers

→ Should be started as early as possible after exposure (within maximum limit of 72 hours)

→ Should be given for 28days (4 weeks)

→ All the drugs are given orally

→ Drugs: TENOFOVIR + LAMIVUDINE + PROTEASE INHIBITOR

- If protease inhibitor is contraindicated, prefer EFAVIRENZ

PREVENTION OF VERTICAL TRANSMISSION:

- Transfer of HIV from mother to baby through vertical transmission
- Prevented by giving
  - → Mother should be given full HAART therapy (TLE)
  - → After delivery, Baby is given Nevirapine for 6 weeks
- If mother is already exposed to Nevirapine alone, then zidovudine is given

ANTI-INFLUENZA DRUGS

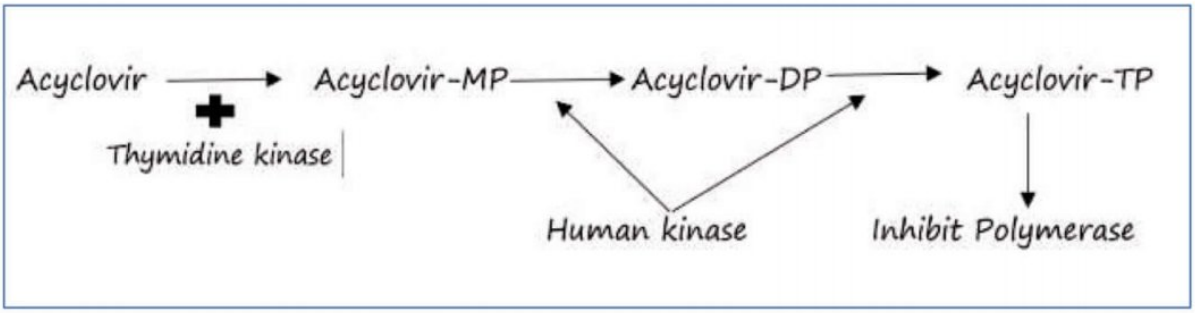
- 3 types of drugs

Uncoating inhibitors	Neuraminidase inhibitors	Polymerase inhibitors
Genetic material cannot become free	- Virus after maturation ↓	Baloxavir ↓ inhibit

as uncoating is inhibited **Drugs:** **AMANTADINE** *Anti-Parkinson drug * used only for influenza -A **RIMANTADINE**	Has to leave that cell & infect other cells - Its connection with that cell should be removed to infect other cells ↓ Done by Neuraminidase - If this enzyme is inhibited, the virus remains clumped to that human cell only & its infection is limited - Drugs: o Oseltamivir – oral o Zanamivir – inhalational o Peramivir – Parenteral These are D.O.C for o Bird flu – H5N1 o Swine flu – H1N1	multiplication of influenza virus -It is single dose treatment for influenza

ANTI-HERPES VIRUS DRUGS

- HSV-1: Mucocutaneous Herpes and Herpes Encephalitis
- HSV-2: Genital Herpes
- VZV: Chicken pox
- DOC for all of them is **ACYCLOVIR**



- Acyclovir will be activated in only those cells which are being infected by virus, As this drug require viral thymidine kinase for activation

↓

If mutation occurs in this enzyme

↓

Virus becomes resistant to this drug

- Acyclovir – short acting
  - Nephrotoxic
- Other drugs which belongs to acyclovir group are:
  - Valacyclovir
  - Penciclovir
  - Famciclovir
- Ganciclovir is a DOC for CMV. Ganciclovir also cause BM suppression therefore it shouldn't be combined with Zidovudine.

ANTI-HEPATITIS VIRUS DRUGS

- HEPATITIS A & E → self-limiting → no anti-viral drug is recommended.
  - Only symptomatic treatment is enough
- HEPATITIS D – causes infection only with hepatitis -B .So if we treat hepatitis -B; hepatitis – D will not occur
- HEPATITIS B – D.O.C – Tenofovir (1st priority) / Entecavir
  - Alternate to this, drugs which can be given orally that are effective against H.I.V also are
    - L- Lamivudine
    - E – Emtricitabine
    - T- Tenofovir
  - If oral drugs are not effective, injection should be given – interferon(IFN) – non-specific & very toxic
- HEPATITIS C
  - Previously treated with Interferons and ribavirin
  - Treatment was very toxic
  - Now all oral treatment is used

NEW ORAL DRUGS FOR HEPATITIS C

PROTEASE INHIBITORS	NS5A INHIBITORS	NS5B INHIBITORS
PREVIRS	ASVIRS	BUVIRS
Telaprevir	Elbasvir	Sofosbuvir
Simprevir	Ledipasvir	Dasabuvir
Boceprevir	Daclatasvir	Beclabuvir
Grazoprevir	Ombitasvir	
Paritaprevir	Pimbrentasvir	

ANTIMETABOLITES & QUINOLONES

PTERIDINE + PABA + GLUTAMATE
SULFONAMIDES ⊣ FOLIC ACID SYNTHASE
Dfet ⟶ FOLIC ACID
TRIMETHOPRIM PYRIMETHAMINE ⊣ DIHYDRO FA REDUCTASE
TETRA HYDRDFOLIC ACID [FOLINIC ACID]
↓
DNA

Ship - sulfonamide hydralazine isoniazid and procainamide causes sle

SULFONAMIDES / SULFA DRUGS

DRUGS		ADVERSE EFFECTS
SULFADOXINE	A →	Aplastic anemia
SULFACYTINE	B →	Bilirubin displacement → cause Kernicterus in newborns
SULFASOXAZOLE	C →	Crystalluria
SULFAMETHOXAZOLE	R →	Rash
SULFASALAZINE	A →	Acetylation
SULFADIAZINE	S →	SLE
DAPSONE	H →	Hemolysis in G6PD deficiency

- *Sulfonamides are structural analogs of PABA, which is essential for synthesis of folic acid. Therefore, sulfonamides are competitive inhibitor of FA synthase enzyme.*
- *In any infection, where pus is present, which usually contains PABA, Sulfonamides are unlikely to be effective.*

Sulfa- soxasole has Most soluble so min risk of crystalluria

→ Sulfonamide ↓ minimum risk of crystalluria → Sulfasoxazole
→ Sulfadoxine → longest acting
→ Sulfacytine → shortest acting
→ Sulfasalazine
  → prodrug
  → uses → Ulcerative colitis [DOC]
  → Rheumatoid Arthritis
→ Ag Sulfadiazine → used for Burn dressing
→ Dapsone → used for leprosy
  Dermatitis Herpetiformis [DOC]

COMBINATIONS

1 COTRIMOXAZOLE

TRIMETHOPRIM + SULFAMETHOXAZOLE

→ ratio for best bactericidal activity → 1 : 20
ratio in tablet to attain this ratio → 1 : 5
→ DOC for
  P → Pneumocystis jiroveci
  N → Nocardia
  B → Burkholderia cepacia

2. SULFADOXINE + PYRIMETHAMINE
   → Indicated in Parasitic infections → Malaria
   → Toxoplasmosis

DNA GYRASE INHIBITORS
- → DNA GYRASE → introduces negative coils & helps in replication
- → DNA gyrase Inhibitors
  - → Inhibit replication
  - → Chemically these are QUINOLONES

QUINOLONES
1. NALIDIXIC ACID → Used in UTI
2. FLUORO QUINOLONES

FLUOROQUINOLONES

DRUGS
- NORFLOXACIN → Used in UTI
- CIPROFLOXACIN → Oral drug for Typhoid & DOC for Anthrax
- OFLOXACIN
- PEFLOXACIN
- SPARFLOXACIN
- LEVOFLOXACIN
- MOXIFLOXACIN → Long acting, also active against anaerobes
- GATIFLOXACIN → Withdrawn [causes dysglycemia]
- TROVAFLOXACIN

- → Oral cidal drugs
- → Wide spectrum [Gm +ive & Gm -ive]
- → CI in pregnancy & children (<18yrs) [cause cartilage & tendon damage]
- → Induce seizures [avoided in Epilepsy]
- → CI in Renal Failure
  - EXCEPTION
    - P → PEFLOXACIN
    - M → MOXIFLOXACIN
    - T → TROVAFLOXACIN
- → Phototoxicity [max. : Sparfloxacin]
- → RESPIRATORY FQ
  - O → OFLOXACIN
  - M → MOXIFLOXACIN
  - G → GATIFLOXACIN
    LEVOFLOXACIN [isomer of ofloxacin, Long acting]
  - → active against respiratory infections caused by
    - Gm +ive bacteria
    - Gm -ive bacteria
    - Atypical bacteria
    - Mycobacterium TB

→ Recently FDA issued a black box warning which says that they cause neurological side effects.

→ Neurological side effects are of two types,
- CNS
- Peripheral Neuropathy (PN)

Norfloxacin:

→ Mainly excreted by kidney and it is used for Urinary tract infection

→ Among all the fluoroquinolones
- Minimum oral bioavailability - Norfloxacin.
- Maximum oral bioavailability – Levofloxacin.

Ciprofloxacin:

→ Drug of choice for prophylaxis of Meningococcal meningitis

→ Contraindicated in pregnancy and children.

→ Ciprofloxacin is co – drug of choice in Anthrax. (Penicillin G is DOC)

→ Used in enteric fever.

Sparfloxacin :

→ Most phototoxic and longest acting fluoroquinolone.

→ Second longest acting fluoroquinolone is Moxifloxacin.

Gatifloxacin :

→ Gatifloxacin can affect blood glucose level causing Dysglycemia leading to hyperglycemia or hypoglycemia.

→ Due to these side effects it has been withdrawn from india.

Moxifloxacin :

→ Second longest acting fluoroquinolone.

→ Safe in renal failure like (Pefloxacin and Trovafloxacin).

→ Respiratory fluoroquinolones with widest spectrum used for treating many infections.

→ Effective against anaerobes.

DRUGS AFFECTING CELL MEMBRANES

→ DAPTOMYCIN (Drug of choice for VRSA but not in case of VRSA causing Pneumonia; as it is inactivated by pulmonary surfactant)

→ POLYMYXIN B

→ POLYMYXIN E also called as Colistin

→ Drug of choice for VRSA causing Pneumonia – Linezolid.

→ Major side effect of Daptomycin - Myopathy.

→ Polymyxins are effect against Gram negative organisms including Pseudomonas.

→ Colistin is effective against Metallo B lactamase and not effective against serratia and proteus.

ANTIMICROBIAL AGENTS PHARMACOKINETICS

BACTERICIDAL drugs may follow

- Concentration dependent killing (CDK)
- Time dependent killing (TDK)
- Area under curve (AUC) dependent killing (AUC-DK)

CIDAL Drugs

BE – BEta lactams

VA – VAncomycin

F – Fluroquinolones (FQ)

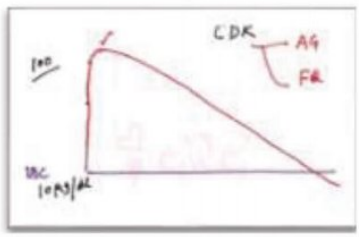
A – Aminoglycosides (AG)

CDK

→ More the conc. of drug more is the killing ie. At higher concentration more killing activity

→ Given as a single high dose

→ Followed by AG and FQ



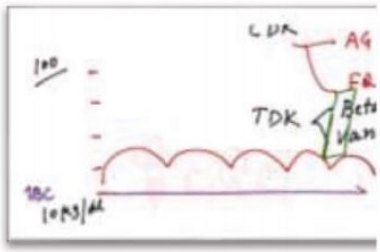
TDK

→ Killing activity depends on time for which concentration of drugs remains above MBC

→ Killing activity does not depend on concentration

→ Given as multiple dose but small doses

→ Followed by Beta lactams and vancomycin

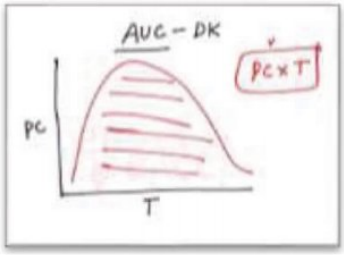


Mnemonic **BV** ko **Time** nahi doge to **kill** kar degi

AUC-DK

→ Killing activity depends on the area of PC-time curve

→ Followed by daptomycin and newer FQ like moxifloxacin



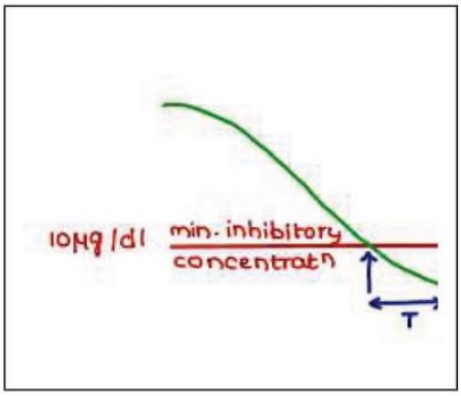
POST ANTIBIOTIC AFFECT (PAE)

- Applies to both CIDAL and STATIC drugs

  - Time for which antibiotic bacteria is not able to show bacterial growth even when its concentration is below MIC
  - Bacteria prepare for growing
  - Almost all drugs have long PAE for gram +ve bacteria
  - Drugs with short PAE (<90 min) against gram negative bacteria are:
    i) β - lactams except carbapenems

    ii) Vancomycin

  - Drugs with long PAE (>90 min) are:
    - DNA inhibitors – eg FQ
    - Proteins synthesis inhibitors e.g.
      - Tetracyclines
      - Macrolides
      - Clindamycin
      - AG
    - Carbapenems



DRUGS NOT AFFECTIVE AGAINST PARTICULAR BACTERIA

Bacteria	Resistant to	DOC
1. Mycoplasma	Cell wall inhibitors	Macrolides
2. MRSA	Beta lactams	Vancomycin (for treatment) For Nasal Carriers - Mupirocin, Bactracin
3. Pseudomonas	Vancomycin	Aminoglycoside + Ceftazidime
4. Enteric fever	Aminoglycosides	Ceftriaxone
5. Anaerobes	Aminoglycosides	Metronidazole

Enteric fever Amino glycosides Ceftriaxone

AUTACOIDS

→ have autocrine effects [local effects]

→ Based on chemical structure

a. PEPTIDE AUTACOIDS → ANGIOTENSIN
→ BRADYKININ

b. AMINE AUTACOIDS → HISTAMINE
→ 5 - HT

c. LIPID AUTACOIDS → PROSTAGLANDINS
→ LEUKOTRIENES
→ THROMBOXANE

HISTAMINE

RECEPTORS

	LOCATION	ACTION	BLOCKERS
H_1		1. Allergy Inflammation 2. Stimulates RAS Promote wakefulness	
H_2	Stomach		
H_3	Pre synaptic	BRAKE	H_3 # or INVERSE AGONIST TIPROLISANT [PITOLISANT] used for NARCOLEPSY
H_4	WBC		

H_1 BLOCKERS

1st GENERATION	2nd GENERATION
cross BBB, cause sedatⁿ	do not cross BBB, no sedatⁿ
Ach # → Anticholinergic SIE occur	no Ach #
useful for motion sickness Drug induced Parkinsonism muscular dystonias allergy	useful only for allergy
PROMETHAZINE [max. actⁿ] DIPHENHYDRAMINE DIMENHYDRINATE PHENIRAMINE CHLORPHENIRAMINE CYCLIZINE CINNARIZINE	TERFENADINE → not used [TDP] FEXOFENADINE → Terfinadine metabolite ASTEMIZOLE → not used [TDP] LORATIDINE DES - LORATIDINE CETIRIZINE, LEVO CETIRIZINE AZELASTINE, OLOPATADINE → Topical

WITHDRAWN DRUGS

Cisapride
Astemizole
Terfenadine

'CAT drugs' (cat is cute 'QT' prolongation) withdrawn because of QT prolongation.

- These drugs were metabolized by CYP 3A4
- Enzyme inhibitors
  - Ciprofloxacin
  - Ketoconazole
  - Erythromycin
- If any of these drugs are combined with (cisapride, astemizole, Terfenadine) result in QT prolongation

5 - HT

SEROTONIN RECEPTORS

→ 7 Receptors, $5\text{-}HT_1$ - $5\,HT_7$

→ $5\text{-}HT_{5,6,7}$ → Present in Brain

	LOCATION	ACTION	AGONIST/ANTAG.	DRUG	USES	S/E
$5HT_1$						
1A			Agonist	BUSPIRONE	Anxiety	
1B/1D	BV of Brain	VC	Agonist	SUMATRIPTAN NARATRIPTAN ELETRIPTAN RIZATRIPTAN	Acute Severe migraine [DOC]	
5HT 2A/2C			Blockers	CLOZAPINE OLANZAPINE	Atypical antipsychotics	LDS
			$5HT_{2C}$ Agonist	LORCASERIN	Obesity	
$5HT_3$	CT2	Emesis	Blockers	ONDANSETRON GRANISETRON TROPISETRON PALONOSETRON	DOC for chemotherapy / Radiotherapy induced vomiting Post op vomiting	
$5HT_4$	GIT	↑Peri-stali-sis	Agonists / prokinetics	CISAPRIDE MOSAPRIDE	GERD [DOC - PPIs]	

LDS → Lipodystrophy Syndrome

Gastroesophageal reflex disease

MIGRAINE :

→It is unilateral and pulsatile headache and the major reason of migraine is assumed to be inflammation and dilation of blood vessels in the brain.

→Latest theory states that migraine occurs due to release of Calcitonin Gene Related Peptide (CGRP) and its major functions are inflammation and vasodilation.

Treatment of acute attack:

→ Drug of choice – NSAIDs (paracetamol , diclofenac)

→ Drug of choice for **acute severe attack – Triptans** (sumatriptan, naratriptan, rizatriptan, eletriptan, frovatriptan)

Mechanism of action of drugs:

→ Triptans act by stimulating 5HT 1B/1D receptor which
- Acts on Blood vessels causing vasoconstriction
- Inhibit CGRP release that inhibits vasodilation and inflammation.

→ Ergotamine also stimulates 5HT 1B/1D receptor and can also be used in acute severe attack of migraine but because of side effects (ncreased vomiting and gangrene); Triptans are preferred over ergotamine.

→ Both triptans and ergotamine together should never be given because they can cause vasoconstriction which causes coronary artery spasm and so they are also avoided in patients with coronary artery disease.

Prophylaxis of migraine :

A	B	C	of Migraine
ANTIDEPRESSANTS • Imipramine ANTIEPILEPTICS • Valproate • topiramate	BETA BLOCKERS • Propranolol (DOC) BOTULINUM TOXIN	CCBs • Flunarizine CGRP # • Erenumab • Fremanezumab • Galcanezumab	METHYSERGIDE • Ergot derivative • Risk of pulmonary fibrosis (so, not preferred)

NEW DRUGS FOR MIGRAINE:

1. **LASMIDITAN**

→stimulates **5HT1F receptor** which stimulates F receptor and decrease CGRP and prevents vasodilation and inflammation.

→It is recently approved for **Acute attacks of migraine.**

2. MONOCLONAL ANTIBODIES AGAINST CGRP

→Approved for **prophylaxis of migraine.**

a. Erenumab

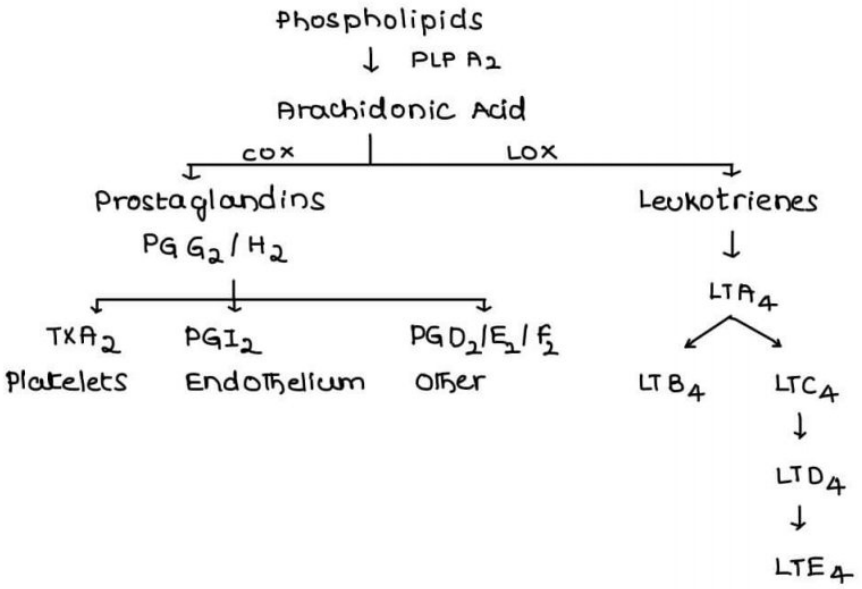
b. Framanezumab

c. Galcanezumab

3. CGRP ANTAGONIST:

→ OLCEGEPANT

LIPID AUTACOIDS



LTB_4 major funct^n → Chemotaxis

LTC_4, LTD_4, LTE_4 → Bronchoconstrictors → Bronchial Asthma

→ Subscript 2 (in PG) and 4 (in LT) represents number of double bonds

→ Arachidonic acid is a 20 Carbon fatty acid with 4 double bonds.

→ All 4 double bonds are intact in Leukotrienes as they are straight chain fatty acids

→ Cyclooxygenase enzyme converts the straight chain fatty acid to cycle in which 2 double bonds break and form Prostaglandins with 2 double bonds.

→ Endogenous prostaglandins contain 2 double bonds.

→ Exogenous Prostaglandins (that are synthesized in laboratory) like **Misoprostol and Alprostadil** (PGE_1) have single bonds but are functionally similar to PGE_2

PROSTAGLANDINS

EFFECTS

1 Fever
Pain
Inflammation

2 PLATELETS
- TxA_2 → Aggregation
- PGI_2 → Inhibition of aggregation

3 HEART

DUCTUS ARTERIOSUS
- → Connects pulmonary trunk to aorta
- → Present in IUL
- → it is kept open by PGE_2

PDA [Patent ductus Arteriosus]

TREATMENT
- ASPIRIN
- INDOMETHACIN
- IBUPROFEN

TRANSPOSIT^{n} OF GREAT VESSELS
ALPROSTADIL [PGE_1 analogue] indicated to keep open the DA

4 BLOOD VESSELS
- → PGE_2, PGI_2 } cause vasodilation
- → ILOPROST [PGI_2] → Used for Pulmonary HTN

5 UTERUS
- → PGE_2, $PGF_{2\alpha}$ } Contracts upper segment of uterus
- → PGE_2 → Relaxes Lower segment of uterus

→ MISOPROSTOL [PGE_1 analogue]

USES
- → Abortion
- → cervical ripening in induction of labour

→ CARBOPROST used for PPH [DOC – OXYTOCIN]

Post partum hemorrhage

6 STOMACH

PGE_2

→ Inhibit Proton Pump
→ ↑ mucous & bicarbonate
→ Vasodilation

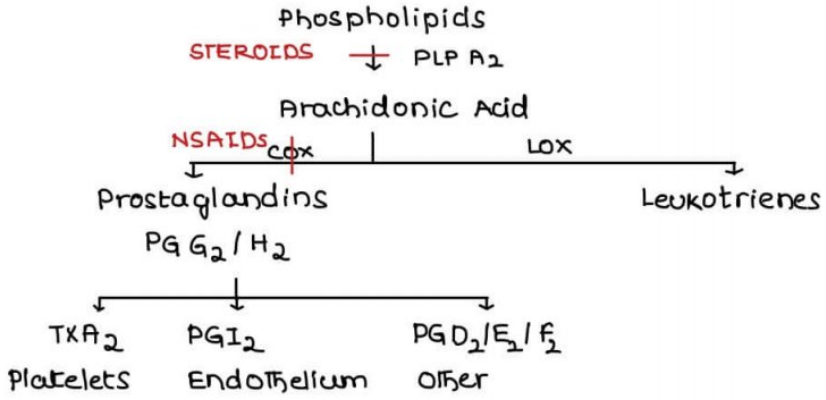
} Protects for PUD

→ COX Inhibitors [NSAIDs] cause PUD → NSAID INDUCED PEPTIC ULCER
Rx by MISOPROSTOL [DOC → PPIs]

7 EYE

$PGF_{2\alpha}$ → ↑ Uveo Scleral outflow
→ LATANOPROST → DOC for Primary Open Angle Glaucoma
→ SIE
P Pigmentation of Iris [Heterochromia iridis]
G Growth of eyelashes [Hypertrichosis]
$F_{2\alpha}$ Fluid in macula [macular edema]

NSAIDS



COX 1	COX - 2
Constitutive Enzyme Inducible at site of inflammatn	Inducible enzyme Ⓝ sites → Kidney Endothelium CNS

NSAIDs

NON SELECTIVE COX INHIBITORS
↑ risk of PUD

SELECTIVE COX-2 INHIBITORS
less risk of PUD

NON SELECTIVE COX INHIBITORS

DRUGS
ASPIRIN
PARACETAMOL [ACETAMINOPHEN]
IBUPROFEN → NSAID of choice in children

DICLOFENAC
INDOMETHACIN → Sedative
MEFENAMIC ACID
PIROXICAM → Long acting
PHENYL BUTAZONE

USES
- Fever
- Pain
- inflammatⁿ

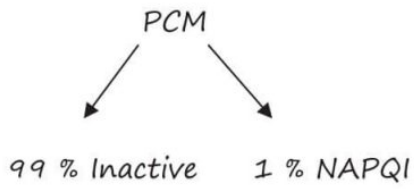
SIE
- PUD

PARACETAMOL / ACETAMINOPHEN

→ Only NSAID with no anti-inflammatory activity
→ Less risk of PUD

- Peroxide Theory → PCM is inactive in presence of H_2O_2
- COX 3 Inhibition Theory → PCM inhibits COX – 3 in CNS
- Analgesic action may be mediated by a metabolite which acts on vanilloid receptors (TRPV)

→ Approved in children for fever & pain
→ **NAPQI (N-Acetyl) Para – amino benzo quinone Imine**



→ NAPQI has high affinity for → SH group
→ Glutathione produced by liver binds with NAPQI & neutralizes it

PCM TOXICITY
→ Occurs d/t
1. Overdosage
2. Liver disease
3. Chronic Alcoholism

→ ANTIDOTE → N-ACETYL CYSTEINE (DOC)

ASPIRIN

→ only Irreversible cox inhibitor
→ antiplatlet drug
→ CI in child ↑ viral infect^{n} [Risk of Reye's syndrome]
→ can cause Hyperuricemia at therapeutic closes → avoid in gout

SALICYLISM

Respiratory centre ⊕
↓
Hyperventilation
↓
↓ CO_2
↓
Respiratory Alkalosis → Reversible

↓ HCO_3^-
↑ Lactic acid
Aspirin
↓
Metabolic Acidosis → Irreversible

→ TREATMENT
$NaHCO_3$
→ reverses metabolic acidosis
→ helps in aspirin Excretion

SELECTIVE COX 2 INHIBITORS

DRUGS

CELECOXIB
ROFECOXIB
VALDECOXIB
ETORICOXIB
PARECOXIB
LUMIRACOXIB

↓ GI Toxicity
↑ MI
↑ Stroke
} not 1st line drugs

→ Etoricoxib → Longest acting
→ Rofecoxib & valdecoxib → Withdrawn because of MI and stroke
→ Parecoxib is given by → Parenteral route
→ Lumiracoxib is withdrawn → Due to Liver toxicity.

PREFERENTIAL SELECTIVE COX-2 INHIBITORS

→ Inhibit cox2 > cox 1
→ Intermediate between non-selective and selective cox-2 inhibitors.
→ D- Diclofenac
→ M- Meloxicam
→ E- Etodolac
→ N- Nabumetone

GOUT

ACUTE GOUT

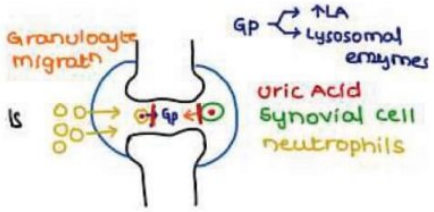
1. NSAIDS [DOC]
2. STEROIDS
3. *COLCHICINE* Can cause Myopathies and severe diarrhea

Mechanism of Colchicine

→ *Inhibit granulocyte migration*

→ *Inhibit the release of glycoprotein from neutrophils*

→ *Inhibit mitotic spindle in neutrophils*



CHRONIC GOUT

URIC ACID PRODUCTION

Proteins / Purines
↓
xanthine
① ↓ xanthine oxidase
Uric Acid → Excretion ②
in birds { ↓ uricase ③
ALLANTOIN

↓ Formatⁿ of Uric Acid	↑ Excretⁿ of Uric Acid [URICOSURIC DRUGS]
ALLOPURINOL → inhibit xanthine oxidase → DOC for chronic gout FEBUXOSTAT → inhibit xanthine oxidase	PROBENECID SULFINPYRAZONE BENZBROMARONE LESINURAD → Plenty of fluids should be taken
↑ Uric Acid Metabolism	
(R)AS(B)URICASE → Recombinant uricase PEGLOTICASE → Long acting	

RHEUMATOID ARTHRITIS

NSAIDS STEROIDS	DMARDS or SAARDS Slow acting anti rheumatoid drugs
↓ Pain & inflammation no effect on disease progression fast acting	Slows down the disease progression Slow acting

DMARDs → Disease Modifying Anti Rheumatoid Drugs
SAARDs → Slow Acting Anti Rheumatoid Drugs

DMARDS CLASSIFICATION	
Conventional DMARDS	**Biological DMARDS**
→ Available since long time	→ Formed by Biological methods like recombinant DNA technology against some particular target.

I. CONVENTIONAL DMARDS:

Cute &	→	Chloroquine	DMARD of choice in pregnancy
P	→	Penicillamine	→ Chelating agent → Used for Cu poisoning / Wilson's disease
A	→	Azathioprine	
G	→	Gold salts	
L	→	Leflunomide	Inhibit formation of pyrimidines by ⊖ Dihydroorotate dehydrogenase
I	→	Inhibitors of JAK	
Malika	→	Methotrexate	M.C. used (D.O.C for R.A]
Sherawat	→	Sulfasalazine	→ Used in R.A. & U.C → Only DMART used as dis modifying agent in ankylosing spondylitis

METHOTREXATE:

Used for

Cancer	R.A
- High dose 25mg/day - ⊖ DHFRase (↓folic acid) - Cause megaloblastic anemia	-Low dose → 7.5 mg weekly - ↑ Extracellular adenosine ↓ Anti – Inflammatory property

→ Can cause Hepatotoxicity (L.F.T monitoring is recommended)

JAK INHIBITORS:

→ Given orally for R.A
→ ↑ risk of Infections
* TOFACITINIB
* BARICITINIB

2. BIOLOGICAL DMARDS:

i. By ⊖ TNF – α

ii. By ⊖ I.L – 1

iii. By ⊖ I.L. – 6

iv. Co stimulation inhibitor

i. DRUGS ⊖ TNF–ALPHA:

- All are injectable

A	– Adalimumab –Subcutaneous route [S.C]
C	– Certolizumab – S.C
E	– Etanercept – S.C
Inhibitor	– Infliximab – I.V
GoLI	– Golimumab – S.C

→ ↑ risk of infections like T.B. & Hep-B (So C/I in these pts; even if subclinical infection is present)

→ Apart from R.A., these drugs can be used for Crohn's disease as well as psoriasis

ii. I.L – 1 RECEPTOR ANTAGONISTS:

- ANAKINRA
  - A – 1st letter
  - KIN – Interleukin
  - R – Receptor
  - A – Antagonist

iii. I.L – 6 ANTAGONISTS:

- Tocilizumab → 1st I.L – 6 targeted monoclonal Antibody.
  → Approved for treatment of cytokine release syndrome also
- SARILUMAB → Used for rheumatoid arthritis
  - S – Six
  - AR – R.A.
  - MAB – Monoclonal antibody

iv. COSTIMULATION INHIBITORS

→ ABATACEPT Work like a gear lock