Pharmacology
Handwritten Note

Name: _______________________________________

Subject: __________________________ Pharmacology

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PHARMACOLOGY

- Sympathetic System Neurotransmitter - Nor-Epinephrine
  → Thoraco-lumbar outflow (T1 to L3)
- Parasympathetic System Neurotransmitter - Acetyl choline
  → Cranio-sacral outflow (III, IV, IX, X, S2, S3, S4)

Cholinergic drug:

Choline uptake → Na⁺-Choline Symport
  → 1st step → Rate limiting step in synthesis of Ach.
  # Source of choline → Serine.

\[ \text{Cholin} \xrightarrow{\text{Sodium}} \text{Choline} \xrightarrow{\text{Acetyl CoA}} \text{Ach} \]

Ca²⁺ channel
# with the help of Ca²⁺ Ach Release.

 Vesicular uptake of Ach
  \[ \text{Ach} \xrightarrow{\text{Vesicle}} \]
  \[ \text{Choline esterase} \xrightarrow{\text{Ach}} \]

Muscarnic Nicotinic

# True cholinesterase → +nt at synapse:

Pseudocholinesterase → +nt in plasma.

Cholinergic drug metabolised by Pseudocholinesterase.

Choline uptake inhibited by → Hemicholinium.

Vesicular uptake up of Ach blocked by → Vesamicol.

Release of Ach modulated by < blocked by - Botulinum toxin
  Stimulated by - Spider Venom.

Defect in Ca²⁺ Channel - Lambert Eaton Syndrome.
Lambert-Eaton Syndrome:
Defect is Ca\(^{2+}\) channel Presynaptically.
For t/t we need Ca\(^{2+}\) channel actuator → 3,4-diaminopyridine
(Dalfampridine)

Also useful for t/t of
- Multiple Sclerosis
  to improve walking capacity.
- It is K\(^{+}\) channel blocker & Ca\(^{2+}\) channel activator.

Sites of Release of Ach Neurotransmitter:
- at the 1) Ganglion
  - Preganglionic fibre of sympathetic & parasympathetic Release Ach at ganglion.
  2) Adrenal Medulla.
  3) Neuromuscular junction.
  4) Postganglionic Parasympathetic fibre.

# Postganglionic sympathetic fibre normally releases
  - Nor-epinephrine (NE)

Exception:
a) Sweat gland - Release Ach (Sympathetic cholinergic)
  # Hyperhydrosis (Excessive Sweating)

  t/t < Sympathectomy
  Botulinum toxin injection.

b) Renal blood flow - Release Dopamine by Sympathetic postganglionic fibre.
Extra point:

1. Conversion of NA into Adrenaline by Methylation
   - Eg. of Phase II reaction

2. Conversion of Histamine into methyl histamine by Methylation
   - Mast cell secretes histamine
     - Mastocytosis (Histamine releasing tumour)

   Urinary estimation of Methyl histamine - Useful for diagnosis of Mastocytosis

   * Urinary estimation of VMA (Vanillyl Mandelic Acid) - Useful for diagnosis of Pheochromocytoma

Toxins in ANS:

**Botulinum Toxin** — A to G Subtype

**Clinical uses of Botulinum A toxin:**

1. Blepharospasm
2. Strabismus
3. Wrinkle (in forehead corrected)
4. Cosmetic

**Clinical uses of Botulinum B toxin:**

- Used as muscle relaxant.
  - Cervical dystonia (Painful muscle spasm)

Onabotulinum Toxin

- Derivative of Botulinum A toxin

  Useful for —
  1. Prophylaxis of Chronic Migraine
  2. Relaxation of Detrusor muscle - Given intravesically

  Causing Retention of urine

  So useful for t/t of overactive bladder
Alpha Bungaroloxin:
- Component of venom of Banded Krait
- Nature of toxin - Antagonistic action at Nm receptor

Saxitoxin 
-> Both released by Dinoflagellates (Algae)

Tetradotoxin 
-> This toxin infect a fish (shell fish)

Ingested by human - cause Na+ channel blockage, causing Muscle Paralysis.
So, called Paralytic shell fish poisoning.

T/t of α-Bungaroloxin:
- Neostigmine & Atropine

↑ Ach in synapse
- We need only nicotinic action,
we don't need muscarinic action.
- So, muscarinic blocker given.

Muscarinic
- M1, M2, M3, M4, M5
- All muscarinic are
  G-coupled protein receptor
  gated.

Nicotinic
- NM, NN
- All nicotinic are ligand
  gated.

Cholinceptors:

Muscarnic

Nicotinic

Adenylyl cyclase pathway
- Gs → Stimulatory
- Gi → Inhibitory

Phospholipase pathway
- 2 improv. And Messenger
- IP3
- DAG.
Adenylyl cyclase Pathway:

2nd Messenger — CAMP.

M1, M3 & M5 follow Gq pathway
M2 & M4 follow Gi pathway.

Muscarinic Receptors:

M1: Location — Gomach
Action: Releasing Hcl

Overstimulation of M1 — Gastritis

Selective M1 agonist — Oxotremorine.

⇒ GE — Gastritis

For Gastric ulcer — Block M1.

Selective M1 antagonist (PIRENZEPINE) — For ty of

TELENZEPINE — gastric ulcer.

M2: Located on Myocardium

⇒ Maximally in AV node.

Action: Stimulation of M2 causes reduction in conduction

Causing Bradycardia
as Vagus (X) fibre is Parasympathetic fibre

⇒ act on M2 receptor — Causes Bradycardia.

# Athleteic person — High Vagal tone

# Vagomimetic drug — Causing Bradycardia

Use of M2 agonist — SVT (Supraventricular Tachycardia).

Selective M2 agonist — METHACHOLINE (< 98-99% — M2

1-2% — M1, M3

Selective M2 antagonist — METHOTRAMINE

TRIPITRAMINE

# Methacholine challenge test — Δ of Asthma.

⇒ Cause bronchoconstriction.
Digoxin = Vagomimetic property
  - Anti-arrhythmic
  
  Atrial Fibrillation
  Atrial Flutter
  - Inhibit Na⁺ - K⁺ ATPase test.
  - Accumulate intracellular Ca²⁺ (↑ Ca²⁺)
  - ↑ Force of contraction
  - Useful for t/t of low output CCF.

Muscarnic Receptors:
  M₃ Receptor - Location:

  Smooth muscle - Blood vessel (endothelium)
  Eye
  Endocrine glands.

Smooth muscle

Vascular Visceral
  - Endothelium - M₃ antagonist (COPD/BA)
     ↓
  Vasodilation - Edrophonium bromide
  Hypotension - We don't use Atropine 6oz
  - Selectivity
  - Don't interfere mucociliary muscle.

  - Intestine & Bladder
  - Prokinetic action

M₃ agonist: Uses
  - Constipation
  - Post op paralytic ileus, urinary retention.
Selective M3 agonist acting on Intestine & Bladder
→ BETHANECHOL

Selective M3 agonist acting on GIT & Bladder
- DARifenacin
- SOLifenacin
- Useful for the treatment of diarrhea &
diarrheal dominant IBS.
Overacting bladder.

Selective M3 agonist acting only on Bladder
- Vesico Selective M3 agonist
  - Oxybutynin
  - Tolterodine
  - Solifenacin (Prodrug)
  - Trospium Chloride

Extra information on bladder:
- Nn. Action - Relax detrusor - causing urinary retention
  ↓
  - MIRABEGRON (M3 agonist)
  → Use - Overactive bladder.

Location of M3 mostly in adipose tissue
- SUBUTRAMINE (M3 agonist)
  - Adipolysis (wt. loss)
  - At is withdrawn - Cause Cardiotoxicity.

# Nocturnal enuresis
- Opiopramine (TCA)
  - Anti cholinergic
DOC: Desmopressin
V₂ analogue - Vasopressin

Stress incontinence:

\[ t/t \rightarrow \text{Duloxetine} \]

- ↑ urethral tone
- Also useful for t/t
  - Chronic neuropathy pain
  - Fibromyalgia.
- It is SNRI (Anti-depressant)

\[ \downarrow \]

eg: Duloxetine

Venlafaxine (S/E - Sustained H:\N)
Mirtazapine
Leva-mirtazapine
Vilazodone
Vortioxetine \( \text{Newer drug} \).

M₃ on Eye:

- Sphincter muscle: Stimulation of M₃
- Constrictor: Constriction of pupil \( \text{(Miōδīs)} \)
- Radial muscle: Stimulation of a₁:
  - Dilator
  - Mydriasis
  \( \rightarrow \text{On Radial muscle} \)

\( \text{M₃ agonist acting on eyes} \)
- Pilocarpine
- Ecothiopate
  - Organophosphorus Comp₉
  - Irreversible cholinesterase inhibitor
α, agonist acting on eyes:
- Phenylephrine
  (Adrenergic agonist)

Adrenergic drugs - Only Mydriasis

Anticholinergic drugs - Mydriasis + Cycloplegia
  (loss of light reflex)

# β-blocker don't alter pupil size
  Timolol - Use in 4º of Glaucoma.

# Oculomotor Nerve supplies constrictor muscle.  
  (Circular muscle).

Causes Miosis.

Injury - Mydriasis
  Even after CN III nerve injury if we use pilocarpine
  we will get miosis, as receptors are intact.

# M3 receptor agonist - Useful for glaucoma.
  Pilocarpine - Useful for glaucoma by promoting
  drainage
  
  Ecothio phate - ¼º - Cataract.

Mydriatic anticholinergic:
  Atropine (longest acting = 10wk)
  Homatropine
  Cyclopentolate
  (M/C) Tropicamide (fastest but shortest acting = 5-6hr)

> GI - Glaucoma.
Only for fundus exam - Mydriasis enough

Phenylephrine preferred

Or

Tropicamide.

Error of Refraction:

- Mydriasis & Cycloplegia
- DC - Tropicamide

- In child < 5yr
  - Atropine ointment 1%

M3 on exocrine glands:

M3 location - Salivary gland

Lacrimal gland

Sweat gland

M3 agonist: Pilocarpine

Cevimeline

Sjogren syndrome - Pilocarpine used

Xerostomia

# Amifostine - Radio protective

Antidote for Cisplatin

[\text{\text{SE - Nephrotoxicity.}}]

# Radio sensitizer - Gemcitabine, Methotrexate

Radiation Recall - Dactinomycin, Doxorubicin

Anti cancer antibodies
Gemcitabine:

Pyrimidine anti-metabolite

DOC - Pancreatic Cancer.

# Atropine - C/I in hyper/hernia

Nicotinic Receptors:

Nm & Nn

Nm:

N = Nicotinic, m = Skeletal muscle

1. Activation of Nm causes opening of Na⁺ & Ca²⁺ channel.
2. Entry of Ca²⁺ causes contraction of muscle.
3. (Muscle depolarisation)

Ach - ↑ muscle power

So, Cholinergic drugs used for ↑ for Myasthenia gravis.

Skeletal muscle Relaxation (SMR):

Q₃-Tubocurarine = Competitive antagonist.

→ Non depolarizing SMR.

For reversal - Neostigmine & Atropine

Newer drug - Sugammadex

Useful for Reversal of Rocuronium & Vecuronium.

• Similar to Neostigmine
Non-depolarizing SMR

Steroidal   Non-Steroidal

Pancuronium Rocuronium Rapacuronium Vecuronium

Anticholinergic action
(OT) Anti-Vagal

# Glycopyrrolate: Anti-Cholinergic agent

Useful for preanaesthetic medication to control secretion.

It is quaternary amine - lipid insoluble.
So, no CNS side effect. So it is useful instead of Atropine.

Rocuronium:
- Fastest acting SMR
- Alternate to Succinyl choline (ScCh) for tracheal intubation
- Least histamine releasing property
- Severe pain during injection

Rapacuronium:
- Cause Severe Bronchospasm

Vecuronium:
- Preferred in cardiac pts.
Benzyl isoquinoline

Doxacurium  Mivacurium  Atrocurium  a-Tubocurarine
- longest acting (120 min)  - Shortest acting
- Most potent (15-20 min)  - Hoffman's Releasing
- Useful for drug degradation  - Adverse effect
- Care: SX.  - Self metabolism
- Hypotension

Gantacurium  metabolise out
(5-10 min)  - Liver & Kidney

Newer drug  - They do not need enzyme
- for degradation
- Safe in Hepatic
- Renal failure
- Produce by product

Laudanosine  (Causes - Seizure)

# Cis Atracurium  - Less Laudanosine
Less secreting histamine

SMR having less histamine releasing property
- Cis Atracurium
- Rocuronium
Depolarising SMR:

succinylcholine (SCh):

structurally & functionally - similar to ACh.

5-10 - Muscle fasciculation

post op: muscle pain

• shortest acting (3-5 min)

rapidly undergo metabolism by pseudocholinesterase.

Some people have atypical pseudocholinesterase

• action < 5 min

lead to SCh apnea

1/4 fresh blood transfusion bcz blood plasma

is rich in pseudocholinesterase.

Doxucaine number:

useful to assess whether the pt. have atypical

pseudocholinesterase or normal.

cause - local anesthetic agent.

80% - hydrolysis - normal pseudocholinesterase.

<20% - hydrolysis - atypical

Adverse drug effect of SCh:

- hyperkalemia (Burns, nerve injury, crush injury

- Malignant hyperthermia

- ↑ intra ocular/gastric pressure

those who are having genetic abnormality to

Ry anadine receptor.
Primaquine – Causes hemolysis only in G6PD deficiency.

Pharmacogenic/Idiosyncrasy – Renin Receptor

Occurs disease in only genetic abo person.

3/7 → Dantriolene

(Directly acting SMR)

DOC for: Malignant hypothermia
Neuroleptic malignant syndrome.

# SMR – causes pain on injection – Rocuronium.

GA causing pain → Propofol
Post- op muscle pain – Sux

Analgesic used during sx causing Post-op truncal rigidity – Fentanyl, Alfentanil

T/t – Wooden chest syndrome.

Antibiotics causing SMR:

- Aminoglycosides (Maxim) – Neomycin
- Macrolides
- Quinolone
- Tetracyclines

# Aminoglycosides – Inhibit Release of Acch

Similar to Botulism toxin.

T/t – Neostigmine + Calcium:
**Autonomic ganglia**

**Sympathetic:**

- Preganglionic (Ach, NN)
- Post-ganglionic (NE)

**Parasympathetic:**

- Preganglionic (Ach, NN)
- Post-ganglionic

**Ganglia**

<table>
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<tr>
<td>Hexamethonium</td>
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<tr>
<td>Trimethaphine</td>
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<tr>
<td>Mecamylamine (Smoking Control)</td>
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Useful to produce controlled hypotension.

**Antismoking drugs:**

**First line drug (therapy):**

- Varenicline ($\alpha_4\beta_2$ nicotinic agonist) - Suicidal thought
- Nicotine (patch, inhaler, lozenges, chewing gum)
- Bupropion - NBRI (Norepinephrine Dopamine Reuptake Inhibitor)
  - Antidepressant
  - Adverse drug reaction
  - Weight loss
  - Seizure
  - ADHD (off-label)

**Second line therapy:**

- Clonidine ($\alpha_2$ agonist)
- Nortriptyline (TCA)
ADR = Adverse Drug Reaction

Miscellaneous:

- Rimonabant
  - Topiramate - Antiepileptic
  - ADR - Weight loss, Nephrotic syndrome

Mecamylamine

Rimonabant: Inverse agonist/Agonist of Cannabinoid receptor.

- Weight loss
- Prevent craving of alcohol

ADR - Psychiatry problems (withdraw)

ADHD (Attention deficit hyperactivity disorder):

Drug used - Amphetamine

Causes - Cardioxic
- Addiction
- Appetite suppressant
  (Failure of growth)

First line drugs:
- Methylphenidate (First choice)
- Atomoxetine
  - Ritalinic acid (Metabolite)

Other drugs:
- PB: Pemoline (Hepatotoxic)
- Modafinil - Use: Narcolepsy
  - Shift worker
  - Obstructive sleep apnea
  - ADHD (FDA - Unapproved)
Newer drug under Narcolepsy:

H₃ inverse agonist

Pitolisant OR Tiprolisant

Narcolepsy (Orphan drug status)

Drug useful for tip of obesity:
- Selulimine (β₃ agonist) - Cardio toxic (Withdrawn)
- Orlistat (lipase inhibitor) - Steatorrhea
- Olestra (Sucrose polyester) - Cooking medium.
- Rimonabant (Cannabinoid 1 antagonist) - Withdrawn
- Leptin (Endogenous slimming peptide)

Combination therapy:
- Bupropion + Naltrexone (opioid antagonist)

- Bupropion + Zonisamide (Antiepileptic)

- Phenteramine + Topiramate (Antiepileptic)
  (Sympathetic Stimulant)
  (Causing Causing
  Appetite Suppressant)

Newer drug: SHTRC agonist - LORCASERIN

S/E - Serotonin Syndrome

GLP-1 → LIRAGlutide

FDA approved drug for obesity.

Extra point: Antiepileptic causing wt. loss
- Topiramate
- Zonisamide
- Felbamate
Antiepileptic causing Wt. gain:
  * Sodium Valporate
  * Gabapentin

# Felbamate < Hepatic failure (ye)  
  Aplastic Anemia

# Type 2 DM o obesity — 1st line drug — Metformin  
  Non-diabetic o obesity — NO Metformin.

# Antidiabetic Causing:
  Weight gain: — Insulin, Insulin secretagogues  
  — Sulfonyl ureas, meglitinides,  
  Thiazolidinediones.

  Weight loss — Pramlintide, GLP-1 agonist, SGLT2 inhibitors

  Weight neutral — Metformin, DPP4 inhibitors.
**ANTI CHOLINESTERASE**

**Reversible**
- Carbamalei
- Acridine
- **OPCs**
- Carbamalei

**Irreversible**
- Physoestigmine (Natural origin)
- Tacrine
- Pyrifos
- Carbaryl

- Alkaloid (plant)
- Hepatotoxic
- Parathion
- (Baygen)

- Highly lipid soluble
- So, not used
- Malathion
- Insecticide
- In Alzheimer
- Diazinon

**DOC**: Atropine
- Poisoning
- (Belladona)

- Neostigmine
- Malathion – Pediculosis (lice)
- Malathion – Lice infestations
- Echothiophate – Use in Glaucoma
- S/E Cataract

- Neo - direct action
- on NM receptor

- Pyri - long acting
- Rapid dissociation

- Eecho - Atrionic site binding

- Used for A of myasthenia gravis.

- (Benailou test
- or, Augliorative test)

- Provocative test
  (done by injecting
  1- Tubocurarine)
  
  # Aging of enzyme
  - Jabun (Slow)
  - Sarin (3-5hrs)
  - Soman (2hrs) - Fastest acting

  t/t - Atropine + Pralidoxime
  In convulsion – Diazepam
Rivastigmine useful for the
donapegol of Alzheimer’s
galantamine deficiency of Ach.

OPC’s poisoning:
Parathion, Malathion, Diazinon
Cholinesterase inhibitors
(Irreversible)

1st line DOC: Atropine (Muscarnic Blocker)

Dose & depends upon sign & symptoms of Atropenisation:
- HR > 100/min
- Pupil Size
- Pulmonary secretion
- Secretion

Max 280 mg

Oximes:
- Cholin Esterase inhibitor reactivation.
- Only used for the OPC’s poisoning not carbamate poisoning.

eg: Pralidoxime (1-2g; slow i.v. 15-30 min)
- Obidoxime (more potent)
- Diacetyl mono oxime (highly lipid soluble)
  → More CNS action

S/E - HTN
→ T/e - Phentolamine (Non-selective & blocker)
Myasthenia Gravis (MG):

- Ameliorative test
- Provocative test

Definitive test → Anti Ach Receptor Radioimmuno Assay.

Confirmatory → Single fibre Electromyography. (SF-EMG)

First line drug — Neostigmine

Pyridostigmine

Others — Corticosteroids

- Thymectomy
- Plasmapheresis
- Intravenous Immunoglobulin (IV Ig)

Other immunosuppressant — Azathioprine

Cyclosporine

Monoclonal antibody — Rituximab

Remission/Exacerbation

Rapid Recovery — Plasmapheresis

IV Ig.

Quinine

- Used in MG
- 3rd line in SMR
- Used in Nocturnal leg cramps.
- Avoid Aminoglycoside in MG.

# MEMANTINE - NMDA Blocker
useful for moderate to severe Alzheimer's.

# Drug useful in cervical ripening - VACATHAMATE

  Anti-cholinergic drug
  Smooth muscle relaxant.

# Diphenoxylate - Opioid
  Anti-diarrheal
  Addiction
  \rightarrow Atropine & addiction of Diphenoxylate

# Glycopyrrolate - Anticholinergic
  Preanaesthetic
  Quaternary amine.

# Scopolamine - Also K/A Hyoscine → CNS depressant (sedation)
  Used in motion sickness.
  DOC: Hyoscine → Narco Analysis

# 1st Gen. (H + M): Promethazine
  \rightarrow In treating nausea, motion sickness, treating EPS (extra pyramidal symptoms), allergic conditions, sickness

# For Sea Sickness - Same t/t.
  \rightarrow Meclizine - 1st gen long acting anti-histamine.
For Mountain Sickness: Acetazolamide  
(Carbonic Anhydrase Inhibitor)

Morning Sickness: Doxylamine & Vit B6

\[\text{antiemetic vitamin}\]

Vit B6 (in Pyridoxine):
- Anti-emetic
- Controls intracerebral seizure

Stimulant of dopa decarboxylase
C/I - Levodopa

Vit B6 should not be given with levodopa.

Vit B6 definitely given & Anti TB drug (isoniazid)

To correct peripheral neuropathy.

Antidote for Vit B6 - 4-deoxy pyridoxine

Folic acid -

Prophylactic - 500 µg daily in pregnancy.

Previous H/O Neural tube defect - 5 mg/day.
Drug having Anticholinergic activity:

- TCAs
  - Amitriptyline
  - Imipramine — Nocturnal enuresis
  - Doc: Desmopressin

- Anti Psychotics
  - Theoridazone
  - Clozapine

- SMR
  - Pancuronium
  - Gallamine

- Class 1a Anti arrhythmie drugs.
  - Quinidine
  - Procainamide
  - Disopyramide (Highest anti cholinergic property).

- 1st H1 Blocker
  - Promethazine

- Anaesthetic
  Meperidine (Pethidine)
  - opioid analgesics
  - Q1 in MI pain

  Morphine is Used.
ADRENERGIC DRUGS

Synthesis, Storage, Release, Metabolism of NE:

\[
\text{Tyrosine} \xrightarrow{\text{TYR}} \text{Tyrosine Hydroxylation} \xrightarrow{\text{DOPA Decarboxylase}} \text{DOPA} \xrightarrow{\text{DOPA Decarboxylase}} \text{Dopamine} \xrightarrow{\text{MAO}} \text{Dopamine} \xrightarrow{\beta \text{-Hydroxylase}} \text{NE} \leftarrow \text{COMT} \xrightarrow{\text{RE- UPTAKE}} \text{NE}
\]

# Synthesis of NE → Only in the vesicle.

Catecholamine → Dopamine

NE

Epinephrine

Monoamines → Dopamine

NE

Serotonın

For metabolism of NE – MAO

COMT
- Even though NE undergoes metabolism by MAO & COMT, enzymatic degradation is not involved in termination.

- NE action is terminated by Re-uptake.

- Rate limiting enzyme of Synthesis of NE — Tyrosine Hydroxylase.

- Drug inhibiting Tyrosine hydroxylase — Alpha methyl parathionine (METYROSINE)

- Dopa decarboxylase inhibitor — Carbidopa

- Reserpine — Anti HTN agent
  - Vascular uptake inhibitor.
  - NE — Succidal depression.

- β-hydroxylase blocker — Disulfiram
  (Used in alcoholism deaddiction)

Ethyl alcohol
  ↓ Alcohol dehydrogenase
  Acetaldehyde
  ↓ Acetaldehyde dehydrogenase + Disulfiram
  Acetic Acid
New drug - Droxidopa

- Prodrug of NE
- Used in Neurogenic Orthostatic Hypotension
- Hemodialysis-induced hypotension

Bretyllium: Class 3 drug

- K⁺ channel blocker
- Also called Chemical defibrillator

Release of NE is blocked by - Bretyllium, Guanethidine

NE Re-uptake inhibitor - SNRI, NDRI, TCA, Cocaine

Cocaine - One & only anesthetic causing HTN.
- Causes mydriasis by acting on α₁ on the radial muscle

Adrenergic Receptor: < α

( Henry Ahlquist)

α-Receptor: < α₁ - post-synaptically (location)
- α₂ - pre-synaptically

⇒ Inhibition of release of NE
⇒ auto receptor for NE

α₂ agonist:

eg: Clonidine - Centrally acting Anti HTN
Methyldopa
Guanafacine
Guanabenz
- Mononidine
- Rilmonidine
- Apraclonidine: Useful in Glaucoma.
- Dorzolamide: Inadequate aqueous secretion
- Pitrimidine: Decrease aqueous secretion
- Timolol: Decrease aqueous secretion
- Timolol Maleate: Used as a Sedation (100 units)
- Pre-anesthetic medication

Meldepal: DOC for HTN during pregnancy

Hyperensive Emergency:
- Labetalol (β+α blocker)
- Hydralazine (K⁺ channel opener)
- Arteriolar dilator

Eclampsia — MgSO₄

Meldepal may cause hemolytic anemia to mother
- Coomb's test +ve

Drug avoided in pregnancy: ACEi (Renal & pulm agenesis)
- ARBs
- Sodium nitroprusside (contain cyanide)

Apraclonidine: Specific S/E — Lid lag
- Pilocarpine: S/E — Anterior uveitis
**α₂ agonists:** Release NE

- **α₁ agonists:**
  - *localization: Post-synaptically*
  - 1. α₁ seen on vascular smooth muscle.

- **α₂ agonists:**
  - Based on vascular action
  - Useful in t/t of Hypotension

  - Nasal congestion

- **Selective α₂ agonists for t/t for Hypotension:**
  - Methoxamine
  - Naphazoline

- **Selective α₁ agonist for t/t for Nasal congestion:**

  - Cause Atrophic
  - Naphazoline
  - Rhinitis
  - Oxymetazoline
  - (Rhinitis medicamentosa)
  - Xylocaine

- **# α₁ Receptor - Radial muscle of iris → Mydriasis**
  - Phenylephrine

- **# α₁ Receptor seen in internal urethral sphincter**
  - Causes sphincter constriction
  - Retention of urine

- **# α₁ blocker used in BPH**
# Vesico ureteric junction & Receptor tons.

# \(\alpha\) blocker useful in urt of lower ureteric calculi

# As seen on Vas deferens of penis.
  Action → Ejaculation.

# \(\alpha\) of \(\alpha\) blocker → Impairment of Ejaculation.

# Directly acting Sympathomimetic
  \(\alpha,\beta\) agonist
  Adrenaline, NA.

Indirectly acting Sympathomimetic:
  
  Tyramine → Act on vesicle → Causes release of NE.

  Causes depletion of storage of NE.

  Hyperplasia → Rapid tolerance.

# MAO inhibitors taking \(\varepsilon\) Tyramine containing food (cheese, wine, bread) causes HTN, it is called Cheese effect.

  DOC for \(\text{t/f of HTN due to cheese effect: Phenolamine}\)

  (non-selective \(\beta\) blocker)

# Mixed action Sympathomimetic → Ephedrine

  causing Hypotension

  Safe in pregnancy.
Selective α1 blocker:

- eg: Prazosin (PDE inhibition property).
- Doxazosin → Apoptotic action on Prostate.
- Terazosin

α1A blocked]

Silodosin
Alfuzosin

mainly Tamsulosin

acting on bladder.

Indoramine → Useful in Hypertensive Emergency.

Urapidil.

PRAZOSIN:

- Vasodilatation → on smooth muscle.

Users - HTN

PVD

CCF

Scorpion Bite.

S/E - Postural hypotension

(1st dose hypotension)

- Impairment of ejaculation.

Selection of Prazosin as Anti-HTN:

1. HTN & dyslipidemia
2. HTN & elderly male with BPH.
3. Can be used in diabetics with HTN.

HTN & dyslipidemia:

Choice - Prazosin

Anti HTN avoided - Non-selective β-blockers

Thiazide diuretics
No problem if → CCB, ACEi, ARB, Clonidine.

HTN if diabetes:

Choice → ACEi = ARB > CCB

Unfavourable (avoid) → β-blocker

Diuretics.

Anti-HTN causing erectile dysfunction —

Highest risk → Diuretics (Thiazides)

High risk → β-blocker (Atenolol, Carvedilol,

# In BPH → Static obstruction is overcome by Finasteride + Tamsulosine.

\[ \sqrt{\text{Rapid Benefit}} \]

It takes 3-6 months for action.

Tamsulosine overcomes dynamic obstruction.

# Pt. on Tamsulosine may cause risk of floppy iris syndrome → going for cataract.
Non-selective α-blocker:

Irreversible - Phenoxybenzamine

Reversible - Tolazoline, Phentolamine.

Phenoxybenzamine:

# Definitive therapy for t/t of HTN in Pheochromocytoma
  - Phenoxybenzamine.

# For controlling intra-operative HTN during pheochromocytoma Sr
  - i.v. Phentolamine
  - i.v. Nitroprusside.

# Don’t use Propanolol as a 1st line drug for t/t HTN due to Pheochromocytoma.

# In Pheochromocytoma Sr
  - Drugs like Halothane is O.I.

  ↓

  Sensitize the myocardium for catecholamine

  ↓

  Causes MI.

Phentolamine:

Use – DOC for t/t of Clonidine withdrawal HTN

DOC for t/t of HTN due to cheese recha.

In intra-op HTN during Pheochromocytoma Sr

Oxime induced HTN.

Useful for t/t of Erectile dysfunction (injectable drug)
PIPE Therapy (Pharmacologically induced penile erection):

Injectable drugs used for t/ of erectile dysfunc-

- Alprostadil (PDE1 analogue)
- Phentolamine
- Papaverine (Non-selecting PDE inhibitor).

\[ \beta - \text{Receptors} \rightarrow \text{G-protein couple acting via Gs pathway.} \]

\[ \beta_1 \rightarrow \beta_2 \rightarrow \beta_3 \]

Location - Myocardium

Action (Heart) → ↑ HR

↑ Force of contraction

↑ CO.

In kidney → Renin release

Selective β agonist:

Dobutamine (Synthetic Catecholamine)

# eg of synthetic Catecholamine

1. Isoproterenol → acting on β₁, β₂, β₃
2. Dopexamine → D₁, β₂
3. Dobutamine → β₁ (t₁/₂ = 2min)
4. Fenoldopam → D₁

# Dobutamine Used in → Stress ECHO

# D₁ receptor seen in Renal blood vessel → Renal Vasodilation
ifenoldopam used iv → iv infusion
- HTN emergency & renal
  impairment.

β₂:
Location: Smooth muscle < Vascular
  Visceral.

Stimulation of β₂ → Vasodilation.

Visceral -
Bronchial muscle → Bronchodilation.

β₂ agonist useful for t/t of Bronchial Asthma:
- Salbutamol > short acting
  Terbutaline useful for Acute asthma.
- Salmeterol
  Formoterol > long acting
  Indacaterol useful for Chronic asthma

Salbutamol:
- M/C S/E - Tremors
  Palpitation.

Uterus → Action → Uterine muscle relaxation.
- Toxolytic – Ritonavir (FDA approved)
  Isoxuprine

# β₂ agonist having anabolic action – Clenbuterol.
Phospholipase-Gq $\rightarrow \alpha_1$ - G-Protein Couple receptor
Adenylyl cyclase-Gi $\rightarrow \alpha_2$

$\beta_2$ - Role on metabolism

- Carbohydrate
- Potassium
- Lipid
- Hyperglycemia
- Hypokalemia
- Reducing blood cholesterol

Hyperkalemia:
- Mild $\rightarrow$ 5.5 to 6.5 mEq/L
- Moderate $\rightarrow$ 6.5 to 8.0 mEq/L
- Severe $\rightarrow$ > 8.0 mEq/L

For Rapid control of potassium in Hyperkalemia (emergency) - Insulin + Glucose infusion

For Hyperkalemia + ECG abnormalities - Calcium Gluconate

$\beta_3$:
- Location: Adipose tissue

Selective $\beta_3$ agonist - SIBUTRAMINE
- Lipolysis
- Withdraw due to CardioToxic

MIRABEGRON:
- $\beta_2$ agonist
- Relax detrusor
- Used in - Overactive bladder

Which one of the following don't have significant dopaminergic activity:
- A) Dopamine ($D_1$, $D_2$, $D_3$)
- B) Fenoldopam ($D_1$)
- C) Dobutamine ($\beta_1$)
- D) Boperamine ($D_1$, $\beta_2$)
Dopamine: has $D_1$, $D_2$, $\alpha_1$ action.

\[ \downarrow \downarrow \downarrow \]

<2 µg/kg  2-5  5-10 µg/kg.

DOC for Cardiogenic Shock - Dopamine.

<table>
<thead>
<tr>
<th>Shock</th>
<th>T/t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiogenic</td>
<td>NE or Dopamine</td>
</tr>
<tr>
<td>Cardiogenic &amp; oliguria</td>
<td>Dopamine</td>
</tr>
<tr>
<td>Anaphylactic</td>
<td>Adrenaline</td>
</tr>
<tr>
<td>Secondary</td>
<td>$\alpha$-blocker</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>Steroids</td>
</tr>
</tbody>
</table>

Blood pressure:

\[ BP = CO \times \text{Peripheral resistance} \]

\[ \downarrow \downarrow \]

SBP  DBP

Effect of Isoprenaline on BP:

- $\beta_1$, $\beta_2$, $\beta_3$ action.
- No $\alpha$ action.
- ↑SBP; ↑DBP → Reflex Tachycardia
- Wide pulse pressure.

NA: $\alpha_1$, $\alpha_2$, $\beta_1$

No $\pi_2$ action

↑SBP; ↑DBP → Reflex Bradycardia

Adrenaline on BP: acting on $\alpha$, $\alpha_2$, $\beta_1$, $\beta_2$
Biphasic response of Adrenaline on BP.
- Adrenaline cause initial ↓BP & later ↑BP.

# Dalei Vasomotor reversal phenomenon:

\[ \alpha_1 \text{ Adrenaline} \sqrt{ } \]

If we give \( \alpha_1 \) blocker before adrenaline, adrenaline blocker \( \beta_1 \) act only on \( \beta_2 \) causing fall in BP.

9. All are lipid insoluble \( \beta \)-blocker except?
   A) Nadalol
   B) Propanolol
   C) Atenolol
   D) Sotalol

Lipid soluble \( \beta \)-blocker - Propanolol (Highly soluble)
- M/commenest drug used for prophylaxis of migraine.
- Performance anxiety
- Essential tremor
- Akathisia

Lipid insoluble \( \beta \)-blocker - Nadalol (Most longest acting >40h)
- Long duration of action
- No hepatic metabolism
- Unsafe in Renal failure - Dose adjustment required.
_β-blocker_

**Non-selective β-blocker**: 1st generation β-blocker
- Drug block both β₁ & β₂.

Cardioselective β-blocker: 2nd generation β-blocker
- (Predominantly blocks β₁ blocker)

- No selective β₂ blocker.

# 3rd generation β-blocker - β-blockers with additional properties

Cardioselective β-blocker:

- **Nebivolol** (Most Cardioselective; Releases NO)

  - Vasodilation

- Betaxol - Useful in Glaucoma; Safe in asthma?

- Bisoprolol - Useful in CCF

- Atenolol

- Esculolol - Most ultra short acting (9 min), i.v., Emergency

- Acebutolol

- Metoprolol - Useful in HTN, Angina, MI, CCF

- Celiprolol

3rd generation β-blocker:

1. β-blocker having α blocking property:

   - **Labetalol** - β & α blocker
     - Use → HTN emergency in pregnancy
     - S/E → Postural hypotension, hepatotoxic

   - Carvedilol - β & α blocker
     - Antioxidant
     - Use → in CCF → Bisoprolol → Metoprolol
(2) β-blocker having NO releasing property -
Nebivolol
Neprilide

(3) β-blocker having K⁺ channel opening action -
Tilisolol

(4) β-blocker having K⁺ channel blocking property -
Sotalol — Class III antiarrhythmic group.

# BUTOXAMINE:
- Only selective β₂ blocker
- Used for research purpose, not for therapeutic purpose.

β-blocker having highest myocardial stabilizing

Na⁺ channel blocking property
or local anaesthetic action:
→ Propranolol.

β-blocker having highest intrinsic sympathomimetic
→ Pindolol

β blocker having favourable effect on lipid profile
→ Pindolol.

Antidote for β-blocker poisoning — Glucagon.
Uses of β-blockers:

1. CNS - Performance, Anxiety
   - Prophylaxis - Migraine
   - Akathisia
   - Essential tremors.

2. Eye - Glaucoma
   - β blocker - Timolol
     - Betaxolol
     - Carteolol
     - Labetalol
     - Metipranolol

   Systemic side effect of Timolol - Bradycardia
   - Heart block
   - Bronchospasm

   # Betaxolol - Safe in asthma.

   Local side effect of Timolol - Blepharitis, conjunctivitis
   - Nasolacrimal duct obstruction

3. Thyroid - Hyperthyroidism
   - propranolol inhibits peripheral conversion of T4 → T3
   - Symptom relief.

4. CVS - HTN, Arrhythmia, Dissection of aorta
   - Angina
   - CCF
   - MI
   - HOCM
AFC Joint National Committee guidelines

First line drugs used in HTN:
- Thiazides
- ACEi
- ARB
- CCB

→ NO β blockers.

5) Useful for portal hypertension (Prophylaxis)

Propranolol

DOC for HT of bleeding due to esophageal varices
- OCTREOTIDE

Most potent vasoconstrictor
- Controls bleeding
  - Terlipressin – Vi agonist can be added.

DOC for prophylaxis – Propranolol, Nadalol.
Central acting drugs

**GABA:**

![GABA diagram](image)

Metabolism by - GABA transaminase.

**Action of GABA:** When GABA enters GABA A, Cl-channel enters causing hyperpolarization.

**Drugs acting via GABA A pathway**

- Benzodiazepines
- Barbiturates

**BZD binding to BZD receptor which is made up of d, y units of GABA A.**

**BZD - GABA facilitatory.**

\[ \text{frequency of Cl-channel opening.} \]
MOA of Barbiturates —
- Barbiturates binding α, β units of GABA A.

Barbiturate:
- Low dose → GABA facilitatory
- High dose → GABA mimetics
- Duration of Cl channel opening.

Benzodiazepine (BZD):
- Action (USE) → Sedation
  - Anti-convulsions
  - Anti-anxiety
  - SMR.

Diazepam — DOC for Acute febrile seizure (Rectal Diazepam)
- Status Epilepsy (currently DOC - i.v. lorazepam)
- Delirium tremors.

Lorazepam — DOC for Status Epilepsy.

Alcohol withdrawal: DOC: Chlordiazepoxide.
- (Delirium tremors)

Midazolam → short acting
Remimazolam → ultra short acting
- Anaesthetic properly.

Alprazolam — Insomnia, Anxiety disorder

Long term use of BZD — Addiction
- Tolerance
- Daytime sleeping.
BZD safe in liver failure pt:
- Temazepam
- Orazepam (Metabolite of Diazepam)
- Lorazepam

Sleep onset Insomnia:
- Z compounds - Zolpidem (Most common)
  - Zopiclone
- All are short acting - Zaleplon (Shortest)

**FLUNITRAZEPAM**: Date Rape drug.
Causes Anterograde amnesia.

**KETAMINE**: Also date rape drug.

BZD poisoning -

**Antagonist**:
- Competitive antagonist — FLUMAZENIL
  - Prevent binding of BZD against GABA-A at 
    - Specific antidote of BZD
    - Given i.v.
    - \( t_{1/2} = 60 \text{ min} \)

**BICUCULLINE**: Competitive antagonist of GABA
- Non-competitive inhibitor of BZD

**PICROTOXIN**: Direct Cl– channel blocker
Inverse agonist of BZD Receptor - β-Carboline

Flumazenil used for - BZD poisoning, β-carboline poisoning, γ-compound poisoning.

BARBITURATES:

Long acting
- Primidone
- Phenobarbitone

Short acting
- Secobarbitone
- Pentobarbitone

Ultrashort acting
- Theophenone Sodium
- Methohexital

Theophenone sodium - Indications
- IV induction GA
- Redistribution
- Cerebro protective

Other uses - Narco analysis, Status epilepsy

Methohexital - Causing convulsion
Used in Electroconvulsive therapy

Phenobarbitone - Metabolite of Primidone
- Useful in Anti-convulsion in pregnancy & pediatrics
- In children it causes hyperkinesia
General properties of Barbiturates:
- Algesic property (produce pain)
- Narrow therapeutic index (Hence - unsafe)
  
  Used in - Epilepsy
  Anaesthesia

Clinical manifestation of Barbiturates:
- Flabby muscle
- Coma
- Shallow & falling Resp
- Bullous eruption

T/I:
- No specific antidote.

- Poisoning → Forced alkaline diuresis
  Nephrodialysis.

# All barbiturates are microsomal enzyme inducer.

Since powerful enzyme inducer
:: C/I - acute intermittent porphyria.
**GABA analogues:**

- **GABA Reuptake inhibitor:** TIAGABINE
- **GABA Transaminase inhibitor:** VIGABATRINE
- SODIUM VALPROATE
- Glutamic acid decarboxylase activator: VALPROATE

**VIGABATRINE** - DOC for infantile spasm (Tuberous Sclerosis)

**YE** → Visual field defect → Psychosis

For Simple Infantile Spasm - ACTH

**LEVATIRACETAM**: ligand for SV2A protein

- Synaptic Vesicle
  - modify synaptic release of Glutamate/GABA

Controls Seizure

New drug - **GABAPENTIN** → Useful in DM neuropathy pain,

**PREGABALIN** → Post herpetic neuralgia.

**GANAXALONE**

- Neurosteroid
  - Direct Cl⁻ Channel opener

Useful in - Absence seizure

Catasternal seizure.
**GABA B (G-protein Coupled Receptor)**

- **Agonist:** BECLOFEN
- **Antagonist:** SACLOFEN

**BACLOFEN** - Centrally acting SMR

Useful in:
- Hiccough
- Craving of alcohol.

**MELATONIN**:

- Sleep inducing hormone
- Secreted from pineal gland.

Melatonin analogue - **REMELTEON**

\[ \begin{align*}
&\text{MT1} & & \text{MT2} \\
\downarrow & & \downarrow \\
& \text{Useful in sleep onset insomnia} & & \text{No risk of ABUSE/TOLERANCE.} \\
\end{align*} \]

**TASIMELTEON** - Useful in T/F sleep awake disorder in blind.

Melatonin analogue

**AGOMELATINE** - Agonist on MT1/MT2

- Antagonist on 5-HT2C
- Melatonin analogue

- Antidepressive property

**SUvorexant** → FDA approved drug for insomnia

**ALMOREXANT** → Non-selective OREXIN receptor antagonist

Another OREXIN receptor antagonist.
Glutamate

AMPA receptor
\[ \text{open Na}^+ \text{, Ca}^{2+} \]
Channel

NMDA receptor
\[ \text{open Na}^+ \text{, Ca}^{2+} \]
Channel

Both are ligand gated receptor.

# T/t of Epilepsy – Glutamate antagonist

AMPA blocker NMDA blocker

Topiramate Felbamate
Lamotrigine Valproate
Remacemide
Perampanel
Tolamipemal

Actions of Sodium Valproate:

- GABA agonism
- Anti glutamate
- Na\(^+\) Channel blocking action
- Ca\(^{2+}\) Channel blocking action
- Broad spectrum anti-epileptic

Lennox Gastroate Syndrome:

\[ R \rightarrow \text{FELBAMATE} - \text{Se - Hepatic failure} \]
\[ \text{Aplastic anemia} \]

Currently Used

Valproate
Rufinamide (Na\(^+\) Channel blocker)

**TOPIRAMATE:**

Use → Epilepsy

Prophylaxis of Migraine

Alcohol (Anti-craving)

Smoking ( )

GE → Renal Stone

Wt. loss

**LAMOTRIGINE:**

Useful in → Epilepsy

BPD Depressive

Rarely cause SJS (Steven Johnson Syndrome).

TEN (Toxic epidermal necrolysis)

**NMDA Blockers:**

Ketamine: → Dissociative anaesthesia

Anaesthetic: [Xenon

Action: $N_2 O$ (laughing gas) → GE → Megaloblastic Anemia

Memantine → Useful in Alzheimers

Acamprosate → GSHP agonist properly, Craving alcohol

Acamprosate → Useful in Parkinsonian

Methadone → Doc for opioid deaddiction

Reluzole → Useful for ALS

Phencyclidine → Angel dust
**Dopamine as a Neurotransmitter:**

**Dopaminergic pathway:**

1. Meso-limbic fibre - extend up to prefrontal lobe
   - secrete dopamine
   - dopamine - cause Psychosis

2. Nigro-striatal neuron - function is to synthesise & release dopamine in corpus striatum
   - helps in initiation of movement.

   In corpus striatum - amount of ACh & Dopamine balanced.

   At age - adequate amount of dopamine is not secreted & there is P in ACh activity.
   - Muscle rigidity occurs due to P ACh.
   - Hypokinesia, Tremor, Rigidity.

3. Tubero-infundibular fibre - extend from hypothalamus to anterior pituitary.
   - Dopamine analogue are used for t/t of galactorrhea.
   - Dopamine act on D2 receptor in the brain & causes psychosis.
   - Any drug blocking D2 & causing anti-psychotic effect is called ATYPICAL ANTI-PsychOTIC.

# Two most common side of anti-psychotic < EPS

   Galactorrhea.
# Levodopa & Carbidopa: long term S/E

1. Psychosis
2. Choreathetoid movement (Dyskinesia).

Psychosis:
- Overactivity of Dopamine.
- D<sub>2</sub> blockers → Conventional / Typical Antipsychotic.

Conventional / Typical Antipsychotic Drugs

- Phenothiazines
- Butyrophenones
- Thioxanthenes
- Chlorpromazine
- Haloperidol
- Thiothixene
- Trihexyphenidyl
- Haloperidol
- Flupenthixol
- Huperzine
- Pimozide

# Typical antipsychotic = Neuroleptic agents.

# Most potent D<sub>2</sub> blocker / Antipsychotic = Butyrophenone

Max. EPS produced

THIORIDAZINE S/E → Corneal pigmentation
- Cataract
- Retinal degeneration.
Most potent Antipsychotic — HALOPERIDOL

- Cause Max. EPS
- Less ANS side effect.

CHLORPROMAZINE — Causes Cholestasis jaundice.

Drug induced Parkinsonism:

TOC — Centrally acting Anticholinergic

Trihexyphenidyl (BENZHEXOL)

Other — Benzotropine
Reperiden
Procyclidine.

PROMETHAZINE — 1st gen. anti-histamine

have Anti-cholinergic action

So, used in EPS.

Extra pyramidal Syndrome:

1. Drug induced Parkinsonism
2. Acute muscular dystonia: PROMETHAZINE BENZOHAXAL
3. Tardive dyskinesia: No specific tse
   Symptomatic — Valproate, Vit E.

VALBENAZINE (Newer drug)

- Acts by vesicular monoamine transporter 2 inhibitor.
4. AKATHESIA - DOC: Propranolol

5. Malignant Neuroleptic Syndrome: DANTROLENE directly acting SMR.

Anti-Parkinson drug:

LEVODOPA:

- Protein meals reduce absorption of levodopa.
- Vit-B6 (Pyridoxine) should not be given as levodopa because it stimulates peripheral conversion.

Peripheral toxicity:

M/C S/E of levodopa - Nausea & Vomiting

- Alteration in taste sensation
- Due to stimulation of D2 receptor
  - wi CTZ:

D2 receptor blocker - Domperidone

- Metoclopramide

- Only domperidone is useful in t/t of vomiting due to levodopa.

- Metoclopramide is not used because it crosses BBB & reduces efficiency of levodopa.

- Causes - Cardiac arrhythmias
  - Exacerbation of angina
    - due to D1, β1, & α activation.
**LEVODOPA + CARBIDOPA**

→ Dopacarboxylase inhibitor

**long term &** → Abnormal choreo athetoid movement

→ Psychosis

**# Huntington’s Chorea** → Movement disorder due to

**# Tourette Syndrome** → Overaction of dopamine

↓

**T/t - Doc: Tetrabenzazine**

( Dopamine Depletor)

other - Chlorpromazine

Haloperidol


**# Levodopa is Precursor of melanin**

→ C/I in melanoma

**# Chronic therapy of levodopa may cause**

*On* & *off* phenomenon

Dyskinesia → Severe

Parkinsonism

↓

**Rescue therapy**

→ Apomorphine (Da)

given SC

**# Abrupt withdrawal of levodopa → Neuroleptic**

malignant Syndrome
AMANTIDINE:

Influenza

- Influenza A
  - Amantadine
  - Rimantadine
- Influenza A & B (Bird flu)
  - Oseltamivir
  - Zanamivir.

Oseltamivir - 75 mg / 1 BID / 5 days - Oral
  ↘ Prodrug - Causes Nausea & Vomiting.

Zanamivir - Intranasally - Bronchospasm

Vaccination:

PERAMIVIR (Neuraminidase Inhibitor)
  ↘ IV (Intravenous)

Amantadine:
- Anti cholénergic
- Dopaminergic agonist
- NMDA antagonist

- Useful in Parkinsonism

GE - Ankle edema
  Levido reticularis. (Net like skin rash).
# Ergot D₂ agonist: Bromocriptine
   Pergolide
   Cabergoline

Common SE of these 3 drugs - Erythromelalgia, Cardiac valve fibrosis.

# Pergolide - Causes max Cardiac valve fibrosis.

Other uses of Bromocriptine:
   - Prolactinoma.
   - Acromegaly
   - Type 2 DM

Non-Ergot D₂ agonist: Pramipexole / M/C Dementia / Psychosis.
   Ropinirole
   Rotigotine (Transdermal)

Advantage: No peripheral vasoconstriction.

Pramipexole → SE → Compulsive shopping
   Ropinirole
   Kleptomania
   Sexual desire

Useful for SE of Restless Leg Syndrome.
COMT inhibitors

**JALCAPONE**

**ENTACAPONE**

- **Dangerous toxicity**
  - Rhabdomyolysis
  - Severe diarrhoea
  - Hepatotoxicity

Urine - Yellowish Orange.

**SEROTONIN (5-HT)**

*Source* - Tyroptphan

*Func* of $5HT1A$ - Inhibition of release of Serotonin.

*Autoreceptor of Serotonin.*

Monoamine undergoes metabolism by Monoamminooxidase (MAO). They produce metabolite 5-hydroxyindole acetic acid.

- In Carcinoid tumour - ↑ 5-hydroxyindole acetic acid.
- Serotonin undergoes reuptake causing *central* serotonin.

**Action of Serotonin on 5HT1 B/D - Vasocostriction**

$\rightarrow$ **SUMATRIPTAN (use - Migraine)**

(mainly $1D$; min $1B$)

**Action of Serotonin on 5HT2 - Schizophrenia**

$\rightarrow$ **Clozapine**

*Risperidone* Olanzapine
Action of Serotonin on 5HT3: Nausea & Vomiting

5HT3 antagonist - Ondansetron
Granisetron

Action of serotonin on 5HT4: Diarrhoea.

Selective 5HT4 agonist - Cesapride
Mocapride
Tegaserod QT prolongation on ECG.

All serotonin receptors are G-protein coupled receptor except 5HT3 (ligand gated receptor)

# Acute Migraine:
Main issue - Vasodilation
For t/t of acute migraine - Vasocostriclor

Ergot Alkaloids - Ergotamine
5HT1B/D agonist - Sumatriptan (Doc)
Rizatriptan
Almotriptan
Frovatriptan
Zolmitriptan

Care is taken for HTN & IHD in these pts.

# St. Anthony’s fire → Chronic treatment of ergot alkaloid cause peripheral vasoconstriction (gangrene of foot)
Poisoning - Ergotism
# BUTOPHANOL - Opioid

Used intranasally for Headache.

# Drug useful for Prophylaxis of Chronic Migraine:

1. M/C drug - Propranolol (β-blocker)
2. CCB - Flunarizine
   (Not channel blocking & Antioxidant property)
3. Anti-convulsant - Valproate
   Gabapentin
   Topiramate
4. TCA - Amitriptyline

5. Clonidine

6. 5HT2 blocker
   - Pizotifen
   - Cyproheptadine
     Antihistamine + Antimuscarine
     + Antiserotonin.
   - Primary used as appetite
   - Used in Serotonin Syndrome.

   - Metyrapone (Not used)
   - Causes rhinobulbar & peritoneal fibrosis

   Newer drugs - Calcitonin gene related peptide (CGRP)
   - Vasodilation.

   CGRP antagonist → Telcagepant - i.v.
   → Telcagepant - Oral
   → Hepatotoxic
# LASMIDITAN - 5HT1E agonist

\[ \text{Undertrial} \]

**Atypical Antipsychotics**

(5HT2 Antagonists)

- **Clozapine**
  - Advantages:
  - Less EPS

- **Quetiapine**
  - Refractory cases

- **Olanzapine**
  - +ve & -ve symptoms of psychosis

- **Ziprasidone**
  - Not causes metabolic syndrome

- **Aripiprazole**
- **Asenapine**

**Clozapine** - s/e → Agranulocytosis 0.8 - 1% (dose independent)

- Seizure (10%)
- Ileus (Paralytic) → Constipation
- Salorrhoea
- Metabolic syndrome
  - Pillow syndrome
  - Wet
  - Anti-suicidal action

**Quetiapine** - s/e - Cataract, Priapism

**Olanzapine** - use → Mania in BPD

- Adverse effect → Max ++ wt gain
- Max ++ metabolic syndrome
RESPERIDONE: In addition to blocking 5HT2, it also blocks D2. May cause EPS.

LURASIDONE: Useful in BPD may also cause EPS.

ZIPRASIDONE: M/e S/E - QT Prolongation.

ARIPIPRAZOLE: Useful in BPD (mania) - Best drug among atypical antipsychotic.

ANXIETY DISORDER:
↑ GABA activity
↑ 5HT activity.

BUSPIRONE: 5HT1A agonist
Anti anxiety agent (Chronic Anxiety)
Advantage - Non sedative
Non habit forming.
Disadvantage - Delayed in onset (3 to 4 weeks)

For acute anxiety - Temporarily - BZD

# Performance anxiety = Res: Propranolol
Anxiety & panic attack = Res: SSRI
β1 blocker: Hydroxyzine (Anti anxiety property) → 1st gen. antihistamine.
Celebrex → Metabolite of Hydroxyzine → 2nd gen. antihistamine.
Female Sexual Stimulant: FLIBANSERIN useful in HSDD - Hypoactive Sexual Desire Disorder

# Deficiency of Serotonin & NE - Depression

# TCA, SNRI, NDRI → Inhibit reuptake of 5HT, NE

SSRI → Inhibit reuptake of 5HT.

MAO - inhibitors

MAO-A  MAO-B

- Involved in metabolism - Metabolism of Dopamine
  of NA & 5HT.

- Useful in depression

SELEGELINE
RASAGILINE
SAFINAMIDE

Selective [MECLOBAMIDE
MAO-A inhibitor] CLORGILINE

Non-selective MAO inhibitors:

PHENELZINE
TRANYLCPROMINE
ISOCARBOXAZID

# Cheese reaction = T/t : Phenolamine
SSRI:

Fluoxetine (longest acting \( \rightarrow \) 5 to 7 days)

Fluoxamine - Shortest acting

Paroxetine

Citalopram

Escitalopram - Highly selective SSRI

Sertraline - Least drug interaction.

Side effects of SSRI - May Cause HTN

- Insomnia, Anxiety, Sexual Side

\[ \rightarrow \text{delay in ejaculation.} \]

- It is taken in morning

\[ \rightarrow \text{Useful in t/f of premature ejaculation.} \]

M/c - Nausea & vomiting

- Diarrhea

Drug interaction:

Serotonin Syndrome - SSRI + MAO inhibitor

\[ \rightarrow \text{Primarily SHT2 antagonist} \]

\[ \text{Anti H1 + AcH} \]

# FLUOXETINE: Least discontinuation Syndrome

# PAROXETINE - Wt gain

Teratogenic tension

Used in Premenstrual Syndrome (PMS)

\[ \text{FDA approved.} \]
Drug interaction w/ Fluoxetine & Tamoxifen:

Tamoxifen - for anti-cancer activity needs activation.
- activated with help of CYP2D6 enzyme.

Fluoxetine - CYP2D6 enzyme inhibitor.

Tamoxifen failure occurs.

# SSRI Use:
1. Depression
   - juvenile depression - Fluoxetine
   - Sertraline
2. OCD
3. PTSD
4. Blumia nervosa
5. Anxiety & panic attack.
6. PMTS.

DOC: SSRI: ① OCD
② PTSD
③ Anxiety & panic attack.

TCA
- Inhibit reuptake of Serotonin & NE (Non-Selective)

Clomipramine - T/t of OCD
Doxepin - Strong antihistaminic property
  • Atopic dermatitis
  • Lichen Simplex

# All TCA have antihistaminic property.
IMIPRAMINE — Strong anticholinergic activity.
  * Nocturnal enuresis
  * DOC: Desmopressin

All TCA have anticholinergic activity.

AMITRYPTYLINE

Used in — Antidepressant
  * Prophylaxis of migraine
  * DM neuropathy pain
  * Gabapentin, Pregabalin

Other — Nortyline
  * Desipramine
  * Amoxapine — D2 blocking action
    * Anti-psychotic
    * EPS, Galactorrhea
  * Maprotiline
  * Reboxetine

Adverse effect of TCA:
  * All TCA having antihistaminic property
  * ” ” anticholinergic ” ”
  * ” ” D2 blocking ” ”

  - Sedation, wt gain, seizure
    * taken at bed time.
  - Dryness of mouth, constipation, tachycardia
    & Retention of urine
  - Postural hypotension
TCA poisoning & t/t:
- Cardiac arrhythmia → Lidocaine, Bretylium, Avoid clausa
- Convulsion → Diazepam
- Coma →
- Metabolic acidosis → i.v. Sodium bicarbonate
  - No role of dialysis in TCA poisoning
  - Often large Vd.

# Anti-cholinergic
1. Avoid TCA in elderly male → Aggravate Urinary Retention.
2. Alzheimer's de.

ST JOHN'S WORT:
- Natural antidepressant.
- Hyperforin
  - Monoamine reuptake inhibitor.
  - Very powerful enzyme inducer.
  - Lead to OOP failure.
  - Anti-retroviral failure.

# Mianserin: Presynaptic 52 inhibitor
- Useful in depression.

Mirtazapine: Presynaptic 52/5HT1 inhibitor
- Useful in depression
- NSA (Noradrenergic & specific serotoninergic antidepressant)
**TIANEPTIN**

5HT reuptake enhancer

Used as antidepressant

Mechanism of action not known.

**BPD (Bipolar Disorder):**

Prophylaxis - Lithium

Acute mania - Valproate

- Carbamazepine
- Olanzapine
- Aripiprazole
- Diazepam

Depressive phase - Lamotrigine

For Rapid Cycler: DOC - Sodium Valproate

> more than 4 episodes of mania & depression in a year.

**Lithium:** Monovalent cation

Useful for prophylaxis of BPD.

Narrow Therapeutic Index (TDM)

Therapeutic drug monitoring

Monitoring plasma lithium level.

T1/2 = 24 hrs.

Maintenance for BPD = 0.5 - 0.8 mg/L

Acute Mania = 0.8 - 1.2 mg/L

Toxic symptom > 1.5 mg/L

Toxicity → Hemolyisis → 4 mg/L

Website: http://mbbshelp.com

WhatsApp: http://mbbshelp.com/whatsapp
Adverse effect of Lithium:

L = Leucocyte count ↑ (leucocytosis)
T = Tremor (M/c 8-10 Hz)
H = Hypothyroidism (inhibit release of T3 & T4)
I = ↑ urinalysis (polyuria = DI) (K: Antiloride)
M = Mother (EBstein's anomaly) = Teratogen

In CNS → T wave changes
Dermatology → Exacerbation of psoriasis

C/I:
1. Pregnancy & lactation
2. Sick sinus syndrome

Drug interaction w/ lithium & SMR (Succinylcholine & Pancuronium):

→ Lithium aggravate the action of SMR.
→ Stop lithium 1 day before Sx.

# Hypernatremia will occur in lithium toxicity.

[Diuretics aggravate lithium toxicity.

NSAID]
Opioid Receptors:

3 types: endogenous opioid Receptor in body

μ (Mu)
δ (Delta)
κ (Kappa)

All opioid receptor are GPCR - via Gi pathway.

Endogenous opioid peptides:

Endorphine - more affinity toward μ
Enkephaline - " " δ
Dynorphin - " " κ

Action of opioid:

- Due to activation of μ & δ:
  P = Physical dependence, ↑ Prolactin secretion
  M = Miosis
  C = Constipation, Convulsion (M3G)
  A = Analgesic
  R = Respiratory depression
  E = Euphoria
  S = Sedation

# Opioid are useful in t/r of dull pain

Continuous pain
Localised pain
Visceral pain

# Opioid (Morphine) activating Edinger westphal nucleus (III CN) causing miosis.

Only systemic Morphine cause miosis.
Action of opioid due to kappa:

D = Dysphoria
M = Miosis
A = Analgesia
R = Respiratory depression
D = Diuresis
S = Sedation

# Morphine having Histamine Releasing action.

↓ Vasodilatation

↓ Shifting of plasma fluid in systemic circulation.

It is useful for the treatment of Pulmonary edema.

# All the action of morphine may develop tolerance on repeated administration except - Miosis

Constipation

Convulsion

# Enkephalins may undergo metabolism by Enkephalinase.

For the treatment of Diarrhea - Lactobacillus

Enkephalinase inhibitor.

Pure agonist: Codeine converted to morphine by CYP2D6

Natural opioid - Morphine, Codeine (CYP2D6)

Semi-synthetic - Diacetylmorphine (Heroin), Pholcodeine

Synthetic - Pethidine (Meperidine - Anti mucocaricine,

Nor - Pethidine) Metabolite of pethidine

GI in the MI pain. SE - Seizure (Convulsion)
# Pethidine & Morphine GI in Renal failure.

Methadone:
- Longest acting opioid
- NMDA blocking property & inhibiting reuptake of NE & 5HT.
- Useful for the treatment of neuropathic pain & Cancer pain
- Dose for opioid deaddiction.

Tramadol:
- Also having property of inhibiting reuptake of 5HT & NE.

# Be careful using Methadone & Tramadol in pt. using SSRI, MAO inhibitor causing Serotonin Syndrome.

Fentanyl: Fentanyl group.

<table>
<thead>
<tr>
<th>Fentanyl</th>
<th>Sufentanil</th>
<th>Alfentanil</th>
<th>Remifentanil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potency</td>
<td>x100</td>
<td>x1000</td>
<td>x5</td>
</tr>
<tr>
<td>Dose</td>
<td>30 min</td>
<td>30 min</td>
<td>5-10 min</td>
</tr>
<tr>
<td>Least potent: Pethidine &amp; propoxyphene (1/10)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Analgesia for day care SX: Remifentanil.

# Fentanyl + Droperidol = Neuroleptic Analgesia
# Fentanyl + Droperidol + N₂O = Neuroleptic anaesthesia.

# Fentanyl group cause Post op bruical rigidity (Max - Alfentanil)

# Thorax muscle rigidity = wooden chest Syndrome

Mixed agonist - antagonist:
- µ agonist / kappa agonist:
  - Nalorphine (more euphoria, not in use)
  - Pentazocine (sympathetic stimulant) yi in MI pain
  - Butorphanol (nasal formulation)

- µ agonist / kappa antagonist:
  - Buprenorphine
    - Useful for all type of pain
    - Useful for opioid withdrawal
    - Alternate to mehidone

Pure antagonist:
- Naltrexone
- Nalmefene (intravenous)
- Naltrexone (Oral, long acting, Hepatotoxic)

Acute morphine poisoning:
  - Specific antidote - Naloxone (0.4-0.8mg)
    - I.V., repeated every 2-3 min.
  - It blocks µ receptor at much lower doses than those needed to block κ or δ receptors.
  - It promptly antagonizes
Naltrexone → Useful to control craving for Morphine & craving for alcohol.

For the treatment of constipation due to morphine (opioid)

Peripheral opioid antagonist: METHYL NALTREXONE

Newer opioid:
Peripheral Kappa antagonist: ASIMADOLINE

for IBS
Peripheral μ & κ-agonist; delta antagonist:
ELUXADOLINE → for IBS.
Peripheral K-agonist:
NALFURAFINE → Anti-fungal → CKD

Codine
Dextromethorphan → Anti-tussive opioid.

Anti-diarrhoeal opioid:
Diphenoxylate (Atropine can be added to Loperamide prevent addiction).

C/1 of Morphine:
- Head injury pain (Respiratory insufficiency)
- Biliary colic pain (Causing constriction
- Severe constipation of sphincter of Oddi.)
Ethyl Alcohol/ Alcohol:

Deaddition - Disulfiram like reaction

(Aldehyde dehydrogenase inhibitor)

Drug causing Disulfiram like reaction:

C = Chlorpropamide (Sulfonylurea - DM)

Cefoperazone (3rd gen. Cephalosporin)

M = Metronidazole

Praised = Procarbazine (Anti Cancer) → Alkylated

G = Griseofulvin

T = Tinidazole

Naidu = Nitrofurantoin (Causes coffee colour urine)

# Chronic alcoholic generally suffer Thiamine deficiency

(Vit B1)

# Alcohol undergo Zero order Kinetic elimination:

Zero  WAT 7 Power

W = Warfarin

A = Alcohol

A = Aspirin

T = Tolbutamide

T = Theophylline

P = Phenytoin

# Excretion of Alcohol → Kidney

# In acute ethanol poisoning, pt. presenting c

hypoglycemia. T/t = Glucose + Thiamine
Methyl alcohol:
  \[ \text{Methyl alcohol} \]
  \[ \text{Formaldehyde} \]
  \[ \text{Formic acid (dangerous)} \]
  \[ \text{Ocular damage} \]
  \[ \text{Metabolic acidosis} \]

Specific antidote for Methanol poisoning:
  \[ \text{Fomivazole (4-Methyl pyrazole)} \]

Acting by inhibiting Alcohol dehydrogenase.

Alternative drug - Ethanol also given.

Hemodialysis.

Anti craving drugs for Alcohol:
- Disulfiram (doc)
- Naltrexone (1st line drug)
- Acamprosate (2nd, NMDA blocker + GABA agonist)
- SSRI (Citalapram)
- Ondaselor
- Topiramate, Beclafen (GABA agonist)
- Rimonabant, a CB1 receptor antagonist.
FAS (Fetal alcoholic syndrome):
- CF - Microcephaly
- Maxillofacial abnormalities
- Movement disorder - Hyperkinetic
- Mental retardation

Phenytoin:
- Na+ channel blocking antiepileptic

Fosphenytoin - Prodrug of phenytoin
- Water soluble (im/slow iv)
- Safe for

Salvage Kinetics - First order → Zero order

Adverse effect:
1. Acute toxicity
   - On high iv → Cardiac arrest
   - High oral → Nystagmus
     Ataxia
     Diplopia
     Vertigo

2. Chronic toxicity
   - Gum hypertrophy (M/c - 30%)
     → Due to collagen accumulation
   - Blood → Megaloblastic anemia (Folic acid deficiency)
     Interference Vit K activity (Hemorrhage)
   - Interference - Vit D & Calcium activity
     → Osteomalacia & rickets
- Hypersensitivity reaction → Pseudolymphoma.

- In female → Hirsutism

- Inhibits release of insulin from β-cell of pancreas → Hyperglycemia (DM)

- Teratogenicity → due to Aneuploidy
  - C → Cleft lip & palate
  - P → Hypoplastic phalanges
  - M → Microcephaly.

- Extravasation of phenytoin → Purple glove syndrome.

# Phenytoin — Microsomal Enzyme inductor.

Non-epileptic uses of Phenytoin:
- Trigeminal neuralgia
- Digoxin → induced VT
- Wound healing

Carbamazepine:
- DOC for Partial Seizure (Focal seizure)
- For 1/3 of Temporal lobe epilepsy.

Non-epileptic uses:
- DOC for Trigeminal neuralgia.
- Useful for 1/3 mania in BPD
- Carbamazepine having SSAH activity → Antidepressive
  → Use in DT
It is microsomal enzyme inducer.

It also undergoes auto induction.

- Phenobarbitone
- Carbamazepine
- Neurapine

Sodium Valproate:
- Broad spectrum anti-epileptic.

MOA = GABA agonism, property
- Anti-glutamate
- Na⁺ channel blocking
- T-type CCB

DOC for Myoclonic/Atonic/Clonic and Tonic Seizures
First line drug for Absence Seizure/ Lennox Gestaut Syndrome.

Non-epileptic uses:
- Migraine prophylaxis
- Manic in BPD (LITHIUM)
- Rapid cycle (> 4 cycles/year)
- Jardine dyskinesia

# It is microsomal enzyme inhibitor

GE: V = GIT, Wt. gain (Vomiting)
AL = Alopecia / Curling of hair
P = Pancreatitis, hyper ammonia
R = Rashes
Q = PCOD
A = Allergy

T = Teratogenic (Spina bifida / CVS problem / Orofacial)

E = Hepatotoxicity (<2yr children) digital

Carnitine (Antioxidant)

Others Antiepileptic:
- Levaliracetam (S32A)
- Magnesium Sulfate (DOC in eclampsia)
- Acetazolamide
- ACTH (Infantile Spasm)

Levaliracetam — Modify synaptic release of glutamate / GABA.

Acetazolamide:
- Carbonic anhydrase inhibitor.
- Useful for Glaucoma → Taken orally.
- Used as diuretic — acts on PCT

Use — Acute mountain sickness
- Periodic paralysis
- Absence seizures
  → GANAXALONE
- Catamenial epilepsy

Absence Seizure:
- Abnormal of T-type Ca²⁺ Channel (Malamute)

Rx: T-type cCB
- ETHOSUXIMIDE
- SODIUM VALPROATE (1st line drug)
- TRIMETHADIONE (Withdrawn — Nephrotoxic)
  → Hemorhaphia — Day Blindness
# Anti-epileptic having Carbonic anhydrase inhibiting property:
   - Topiramate [cause Nephrolithiasis]
   - Zonisamide

# Retigabine
   or Ezogabine [used for partial seizure]
   - New drug
   - causing blue colour pigmentation on lip & skin

**GENERAL PHARMACOLOGY**

Pharmacokinetics (PK):

**Drug absorption:**
   - Food interferes drug absorption
     - eg: Milk (Ca\(^{2+}\))—Tetracycline
     - Protein meal reduces—Absorption of levodopa

Food enhances drug absorption
   - Lithium
   - Haloperidol
   - Carisoprodol
   - Bedaquiline
   - Fibrates—lowering cholesterol
     - more absorbed & cholesterol diet

- Absorption of Iron—Vit C (Ascorbic acid)

# For a drug to absorb better—Lipid soluble & distributed
   - Non-ionised
Acidic drug non-ionised in Acid medium. Basic drug non-ionised in Basic medium.

Acidic drug - Absorbed in stomach.
Basic drug - Absorbed in Duodenum/Intestine.

Morphine

Strongest Acid/Alkali always seen in ionised form.

Heparin - Can't be used orally.
- Heparin ionised molecule, not cross the placenta, so not cause teratogenicity.
- DOC for anticoagulation.

Lignocaine - For rapid absorption/onset of action.
- Given & Sodium Carbonate.

Weak basic drug. For 4 duration given & Adrenaline.

Acidic drug poisoning -
For acidic drug poisoning if the pt is passing acidic urine, you should alkalise the urine.
Urine alkalised & Sodium bicarbonate.

Alkaline drug poisoning -
For the pt of alkaline drug poisoning if the pt. passing alkaline urine, you should acidify the urine.
Urine acidified & Ascorbic acid

By injection Ammonium Chloride.

Ion-trapping - Acidic drug (Aspirin) reached basic medium get ionised & trapped in the region.
Pglycoprotein: Permeable efflux pump.

Presence of P glycoprotein decreases the bioavailability of digoxin.

e.g. of P glycoprotein inhibitor: Quinidine
      Itraconazole
      Erythromycin
      Amiodarone
      (Verapamil)

Drug undergoing high first pass metabolism orally:

Propranolol
Salbutamol
Theophylline
Verapamil
Lignocaine
Nitroprusside
Tramipramine

* All nitrates go to extensive 1st pass metabolism except - Gooseride, nitroprusside.

* Rectally given drug absorbed via External hemorrhoidal vein - No 1st pass metabolism.
  If via Internal hemorrhoidal vein - 1st pass metabolism occurs.
  i.v. - 100% Bioavailability.
Henderson–Hasselbalch equation:
\[
pKa = pH + \log \left( \frac{\text{ionized} \ A}{\text{un-ionized} \ A} \right)
\]

If \( pKa = pH \)

means, 50% drugs is in ionized form & 50% unionized form

# \( pKa - pH = 1 \rightarrow 90\% \) drug in absorbed form.
\( pKa - pH = 2 \rightarrow 99\% \)
\( pKa - pH = 3 \rightarrow 99.9\% \)

Bioavailability curve:

![Graph showing bioavailability parameters: C_{max}, AUC, Tmax, MTC, MEC, duration of action, therapeutic range, onset time, and time with formulas and notes on bioequivalence.]

\( C_{\text{max}} = \text{Maximum plasma conc} \)
\( T_{\text{max}} = \text{Time to reach } C_{\text{max}} \)
\( \text{AUC} = \text{Area under curve} \)

# Same drug, same dose, same dosage form,
\(< 20\% \rightarrow \text{Bioequivalent} \).
Orphan drug:
- A drug useful for diagnosis/prevention & treatment of rare disease.
  - E.g.: Fumipizole (4-methyl pyrazole - Alcohol dehydrogenase inhibitor)
  - Procainamide Sulfate (Antidote of Heparin - Chemical antagonist)
  - Calcitonin 1mg = 100 U of Heparin
  - Digibind (Antidote for Digoxin)
  - Liothyronine (Active T3, Medullary C-cell)

Calcitonin: Useful in Hypercalcemia
Page 11 of
Osteoporosis
diagnosis for Medullary Carcinoma.

Pitolisant / Tiprolisant: Use in Narcolepsy
(Orphan drug status).

Essential drugs:
- Drug that meet health needs of the majority of population
- Affordable & Available in all area
- Always single compound

Schedule H - Drug only given on prescription written
by medical practitioner (Registered).
Drug distribution:

60% Water

70 kg → 42 L

4 L 10 L 28 L

plasma  interstitial  cellular

fluid  compartment

# If a drug only in the plasma compartment, it is called as low Vd.

lipid insoluble

if drug is ionised → stays in plasma compartment

highly protein bound

large size

- Role of Hemodyalisis

# If a drug goes to cellular compartment it has high or large Vd.

lipid soluble

non ionised

free form

large Vd → no role of dialysis.
Drug can't removed by dialysis:

A = Amphetamine

V = Verapamil

O = Opioids, OPC

I = Imipramine (TCA)

D = Diazepam

Dialysis = Diazepam (BZD)

BZD - Very strong binding capacity

Can't remove by dialysis.

# Loading dose depend upon Vd.

# For drug having large Vd - for rapid action give loading dose

Volume of distribution (Vd)

\[ V_d = \frac{\text{Total i.v. dose}}{\text{Plasma conc.} \times \text{L}} \]

Loading dose = Vd x Target plasma conc.

Clearance = Rate of elimination / Plasma conc.

Maintenance dose = CL x Target plasma conc.

\[ t_{1/2} = 0.693 \times \frac{\text{Vd}}{\text{CL}} \]
Plasma protein binding:

- Acidic drug in plasma bind to plasma albumin.
- In nephrotic syndrome or liver failure (hypalbuminemia) plasma albumin can be low.
  Use low dose of Acidic drug.

- Basic drugs are generally bind to Alpha1 Acid Glycoprotein.

Drug displacement type of drug interaction:

eg: Warfarin displacing tolbutamide from protein binding site.

Sulphonamide displacing bilirubin from protein binding site.

BBB:

BBB absent - Pituicytes
  Pineal gland
  Area Postrema CTX
  Medial Eminence.

Do not cross BBB - Streptomycin (Aminoglycosides)
  Neostigmine (Doc for Atropine poisoning)
  Glycopyrrolate (Pre anaesthetic medication)
  Dopamine

# All aminoglycosides are ionised molecular, so never absorbed orally, so not given orally.

Even though aminoglycosides not absorbed in GIT.
Neomycin & Paromomycin

Streptomycin - 95% in pregnancy because it crosses placental barrier & causes permanent deafness.

Redistribution:
- eg: Thiopentone Sodium (Ultra short acting)
  - Rapidly entering brain & rapidly comes out & distributes to liver, kidney etc.

Bio-transformation (Drug metabolism):
- Consequences of drug metabolism
  1. Inactivation (more water soluble)
     - excreted easily.
  2. Active metabolite formation from an active drug
  3. Activation of inactive drug.

Active metabolite from active drug:
- Phenacetin → Paracetamol
  - causes Analgesic nephropathy so withdraw.
- Codeine → Morphine
  - CYP2D6
  - in some people it is deficient.
- Diazepam → Oxazepam
- Spironolactone → Canrenone.
Activation of inactive drug

<table>
<thead>
<tr>
<th>Prodrug</th>
<th>Active metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa</td>
<td>Dopamine</td>
</tr>
<tr>
<td>Methyl dopa</td>
<td>Methyl norepinephrine</td>
</tr>
<tr>
<td>Endapril</td>
<td>Enalaprilat</td>
</tr>
<tr>
<td></td>
<td>(All ACE inhibitors are prodrugs except Captopril, Lisinopril)</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Epinephrine</td>
</tr>
<tr>
<td>Becamphenicillin</td>
<td>Ampicillin</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>Minoxidil Sulphate</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Phosphamide mustard</td>
</tr>
</tbody>
</table>

Drug metabolism:

1. Non synthetic reaction (Phase I reaction):
   - Oxidation (M/c Phase I reaction)
     - All Phase I reactions are taken care by microsomal enzyme - CYP450

2. Reduction
3. Hydrolysis
4. Cyclization
5. Decyclization

Phase II reaction:
1. Glucuronidation (M/c) - Morphine
2. Sulfate Conjugation
3. Glycine
4. Glutathione (Paracetamol metabolisin)
5. Acetylation
6. Methylation
**PARACETAMOL**

**PHASE I**  
CYP2E1

N-acetyl benzoquinone (hepatotoxic  
immuno amine (NAA)) metabolite

**PHASE II**  
Glutathione conjugation

Inactivation

For paracetamol poisoning  
\[ N\text{-acetyl cysteine} \]

\[ \text{Methionine} \]

Becomes glutathione  
generated.

Chronic alcoholic  
More prone for liver damage

Booz Alcohol  
CYP2E1 inducer

# End result of phase II reaction  
*Inactivation*.

Drug undergoes Acetylation:  
\[ S = \text{ Sulphonaluride / Dapsone} \]
\[ H = \text{ Hydralazine} \]
\[ I = \text{ Isoniazid} \]
\[ P = \text{ Procainamide} \]

Methylation:  
e.g.: Histamine  
Methylhistamine

Noradrenaline  
Adrenaline
Microsomal enzyme:

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4 (M/c)</td>
<td>&gt;50% of drugs</td>
</tr>
<tr>
<td>CYP2D6 (and)</td>
<td>Codeine → Morphine</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine inhibit CYP2D6</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen activated by CYP2D6</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Warfarin</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Omeprazole metabolism</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Paracetamol - NABQIA</td>
</tr>
</tbody>
</table>

**Clopidogrel**: Anti-platelet

Prodrug

Activated by help of CYP2C19.

Aspirin + Clopidogrel (prodrug) →

Aspirin → Causes gasbris

\( t/t \) → Omeprazole

Omeprazole shouldn’t be given with clopidogrel.

Preferred PPI given with clopidogrel

Pantoprazole

Rabeprazole
### Microsomal Enzyme

<table>
<thead>
<tr>
<th>Inducers</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>G = Griseofulvin</td>
<td>VitB = Valproate</td>
</tr>
<tr>
<td>P = Phenytoin</td>
<td>K = Ketacongazole</td>
</tr>
<tr>
<td>R = Rifampicin</td>
<td>Cao = Cimetidine</td>
</tr>
<tr>
<td>S = Smoking</td>
<td>Cause = Ciproflaxacin</td>
</tr>
<tr>
<td>Cell = Carbamazepine</td>
<td>Enzyme = Erythromycin</td>
</tr>
<tr>
<td>Phone = Phenobarbitone</td>
<td>Inhibition = Isoniazid (INH)</td>
</tr>
</tbody>
</table>

**Drug excretion:**
- Major source = Kidney.
- Net excretion of drug = GF + TS - Tubular reabsorption.

- PROBENICID - by inhibiting
  - prolong the action of penicillin.

### First order kinetics
- Constant fraction of drug excreted constant interval of time.
- T1/2 constant
- 97% drug eliminated after 5 half life.

\[
\begin{align*}
100 & \quad \frac{T_{1/2}}{1\text{hr}} \quad \rightarrow \quad 50 \quad \rightarrow \quad 25 \quad \rightarrow \quad 12.5 \quad \rightarrow \quad 6.25 \quad \rightarrow \quad 3.125. \\
\downarrow & \quad 50\% \text{ of drug excreted every 1 hr.}
\end{align*}
\]
Zero order kinetics:
- Constant amount of drug excreted constant interval of time.
- No fixed T½.

eg: 25 mg of drug, every 1 hr.

\[
100 \xrightarrow{1\text{ hr}} 75 \xrightarrow{1\text{ hr}} 50 \xrightarrow{1\text{ hr}} 25 \xrightarrow{1\text{ hr}} 0
\]
\[
t_{1/2} = 2\text{ hr} \quad t_{1/2} = 1\text{ hr}
\]

Common drug undergoing Zero kinetic
- W = Warfarin
- A = Alcohol
- A = Aspirin
- T = Tolbutamide
- T = Theophylline
- Power = Phenytoin

Pharmacodynamics:
- Receptor mediated MOA
- Cell memt' Receptors.
- Ligand gated \xrightarrow{G-protein Coupled} \xrightarrow{Enzyme linked}
- Fastest acting receptor Serpenline Shape
- most active unit
- of GPCR is d-unit
Enzyme linked receptor:
- **Example:** Tyrosine kinase Receptor
  - Insulin acting on cell mem' receptor

  - Activate Tyrosine kinase

  - Shift GLUT4 from cytoplasm to plasma mem'

  - Influx of glucose

**PEGVISOMENT:** GH receptor blocker
- Useful for Thy Acromegaly

**RUXOLITINIB:** JAK enzyme inhibitor
- Useful in Myelofibrosis

**TOPACITINIB:** JAK 1 & 3 inhibitor
- Useful in RA
Intracellular receptors:
- Steroid hormone
- Vit D
- Estrogen
- Progesterone
- Testosterone

Drug acting on nucleus:
- Thyroid hormone

Log dose response curve:

Receptor Antagonism
1. In the presence of competitive antagonist DRC will be shifted parallel to right.
   Efficacy → Same; Potency → ↓

2. In the presence of non-competitive antagonism DRC will just come down.
   Efficacy → ↓; Potency → Same.
**ESD & LD50**

![Graph showing ESD & LD50]

- **Lower the ESD more potent**
- **Lower the LD50 more dangerous drug**

**Drug Safety:**

\[
\text{Therapeutic index} = \frac{LD_{50}}{ED_{50}}
\]

- Theophylline [Narrow]
- Lithium [Narrow]
- Anti-epileptics [Therapeutic index]

- **Warfarin** - assessment by INR

\[
\text{INR} = \frac{\text{Patient Prothrombin (PT)}}{\text{Control Prothrombin}}
\]

- **Heparin** - assessment by aPTT

- **LMWH** - No need for monitoring

- In obese pt. or Renal failure we do assessment by Anti factor Xa.
Teratogenicity:

Preimplantation (0-2 wks)

Implantation (2-8 wks) -> More teratogenicity occurs. -> Organogenesis

Growth & development (9 wks - 9 months)

1) Warfarin: causing Contradi Syndrome (Fetal dry chondrolysisplasia Punctata)

2) Isolrelinoin (Vit A) - Teratogenic

Lithium - Ebstein Anomaly c/f i in pregnancy.

3) Thiocamide:
   - Methimazole -> aplastic culis
   - Carbimazole -> choanal atresia
   - Propylthiouracil

   Bcz of strongly binding & plasma protein less chance of crossing placenta.

4) Alcohol - FAS (Fetal alcohol Syndrome)
5) Valproate - Valproate Syndrome
6) ACE-i - Renal agenesis
7) Indomethacin - Premature closure of ductus arteriosus
8) Cyclophosphamide - Imperforate anus
9) Busulfan & Chlorambucil (Chemotherapy) - Induce cleft palate
10. Tetracycline - Bone & teeth defect (Baby) 
   In mother → Fulminant hepatic failure.
   So, definitely YES in pregnancy.

11. Thalidomide - Phocomelia.
    → Category X drug.

12. Misoprostol - Useful for abortion
    → Teratogenicity → Moebius Syndrome
    → Development of CN VI & VII.

13. DES - Female → Vaginal Ca, hypertrophic baby (can't see of life)
    → Male baby
    If taken in pregnancy.

Drug development:
Preclinical trials - We follow guidelines

CPCSEA = Committee for the purpose of control
& supervision on experiments on Animals.

IAEC = Institutional animal ethics committee.

Clinical trial - Testing on humans
Guidelines - GCP (Good clinical practice)

HEC = Human Ethics Committee.
Phase I: Pharmacokinetics Studies
Not efficacy.

Healthy volunteers (20-100)
Open label (No blinding)
- To know max tolerable dose (MTD)
MTD - Safety & tolerability.

Anti-Cancer drug bypass Phase I.

Phase II: Therapeutic exploratory
both efficacy & safety.

100-150 patients
Single blind
- To establish therapeutic efficacy.
- Dose ranging & ceiling effect.

Phase III: Therapeutic confirmatory.

Upto 5000 pts. from several centres
Double blind
- To confirm therapeutic efficacy.
- To establish the value of drug in relation.

Phase IV: Post market Surveillance.

Ethical clearance is not required.
No time limits
To know rare & long term adverse effect.
Phase 0: Micro dosing studies.

Pharmacovigilence:
- Assessing
- Monitoring
- Reporting
- Adverse effect.

# Longest-acting insulin - Degludec.

Insulin Preparation
- Fast-onset & Short acting (Onset 10-20 min; duration 3-4 hrs)
  - Insulin Lispro
    - Aspart
    - For t/t of PP glucose.
  - Glulisine

- Short acting (Onset - 30 min; duration → 5-8 hrs)
  - Regular Insulin
    - Made of 6 molecules (Hexamer)
    - Dimer → it takes 30 min.
    - Monomer → to reach monomer status.
    - Given 30 min before meal.
    - Given i.v.
    - Use in DKA, Hyperkalemia.

Intermediates (Onset 1-3 hr; duration → 16-20 hr)
- NPH (Isophane Insulin) - Neutral Protamine Hagedorn
- Lente Insulin (30% Semilente, 70% Ultralente)
Longer acting — Glargine (Acidic ⇒ pH = 4)

Longest acting — Degludec

Adverse effect < Hypoglycemia

Wt. gain.

Inhalable insulin:

Exubera — Lack of acceptance by pts & physicians.

Afrezza — Latest

Ultra rapid (↑ in 15 min)

FDA approved.

\( \text{MAD}: \text{Insulin acting on cell mem}^\text{'r} \text{ receptor} \)

Activate tyrosine kinase

Shifting of GLUT4 from cyto plasma to plasma membr

Influx of Glucose.

Insulin Release:

For release of Insulin — at least 30% of β-cell are functioning.

In Type 1 DM — impossible to release insulin

All β cells are destroyed.
Sulphonylurea
• Naglitriande
• Rapaglinide
• Nateglinide

Newer drugs for DM:
GLP-1 analogues:
- Exenatide
  - given s/c
  - S/E - GIT (Nausea, Vomiting, Diarrhea)
- Liraglutide
- Taspoglutide
- Albglutide
- Dulaglutide
  - FDA approved - Liraglutide
  - given for obesity
  - All obtained from GILA MONSTER (Salivary gland venom)

DPP4 inhibitors: Oral
- Sitagliptine -> Excretion: Renal
- Adverse effect
  - Saxagliptine
    - Renal/Hepatic
  - Nasophragitic Liraglutide
  - URTI
  - Vildaglutide
  - Aloglipine

- Vildaglutide: S/E - Hepatic toxicity
  - pt. undergo periodic LFT.

- PRAMINTIDE: Inlet Amyloid Polypeptide analog.
  - given s/c
  - Approved for Type 1 & 2 DM.
**SGLT2 inhibitors:**
- Canagliflozin
- Sotagliflozin
- Dapacliflozin
- Empagliflozin

**Common S/E** - Recurrent UTI (Bezo glycosuria)
Risk of breast/bladder CA.

**GI - in Renal failure:**

**Diabetes - Oral medications:**
- Sulphonylureas
- Biguanides
- Thiazolidinediones
- Alpha-glycosidase inhibitors
- Meglitinitides
- Bromocriptine
- Cholesevelam

**Sulphonylureas**

1st generation:
- Tolbutamide (6-12hr)
- Chlorpropamide (30-60hr) - Longest acting

Cause SIADH (dilutional hyponatremia)

2nd generation:
- Cholesevelam
- Pioglitazone
- Metformin
- Rosiglitazone
- Pioglitazone
- Glimipiride
Glibenclamide — Safe in pregnancy.
Gliclazide — Antiplatelet, antioxidant.

M/c problem of Sulphonylurea — Hypoglycaemia
Wt. gain.

Biguanides: Metformin

- MOA = AMPK activator
  \( \rightarrow \) AMP-activated protein kinase.

- Stimulates — Glucose utilisation
  
  - Skeletal
  - Adipose
  - Muscle
  - Tissue.

- It is insulin sensitizer.

- Suppresses — Glycogenolysis
  Neoglucogenesis

# Useful in T/t of PCOD

# Renal root of excretion so GI in Renal failure.

# Stop metformin 1 day before & 1 day after the
Radiocontrast exposure.

# N-acetylcysteine \( \rightarrow \) t/t of Radiocontrast induced
renal cell injury.

# Metformin Reduces Microvascular
Macrovacular events.
ADR of Metformin: • GI toxicity
  • Inhibit intestinal absorption of glucose, hexose, vitamin.

Metformin causes lactic acidosis in presence of kidney, liver or cardiorespiratory failure, alcoholism.

α - Glucosidase inhibitors: inhibit carbohydrate digestion in small intestine.
  Acarbose
  Voglibose
  Migliitol

  - Useful in PP blood glucose.

γE - Flatulence
  Abdominal distension
  Diarrhoea.

γI - in Renal failure.

Thiazolidinediones:
  PPAR (Peroxisome proliferated-activated receptor)
  Activation-PPAR α
    ↓
  PPAR γ
    ↓
  Insulin Sensitizer
  Stimulate lipoprotein lipase
  TGL (VLDL) ↓
  Older drugs:
  Pioglitazone - Hepatotoxic
  Rosiglitazone - CCF
PPAR α agonist: (GTBG)

Clopabrate - Not in use (Gall stone, GB malignancy)

Myopathy: Fenofibrate (Prodrug, longest t½, ↓ LDL, ↓ Plasminogen, Uricosuric action)
Hepatotoxic: Bezafibrate
Gemfibrozil

# M/C S/E Pioglitazone - Wt gain
Macular edema
Osteoporosis
Anemia
Bladder Ca.

Drug activating both PPAR α & γ:
SAROGLITAZAR
→ Approved in type of Diabetes dyslipidemia.

Statins:
HMG CoA + Acetate
HMG CoA reductase ↓ Statins
Mevalonic acid
↓
Cholesterol ↓

# Statins → ↓ Total Cholesterol
# Statins → ↓ LDL (by upregulation of LDL receptor in liver)
S/E → Myopathy
Hepatotoxic
Teratogenic
# Co-enzyme Q given to control muscle weakness.

# Liver enzyme goes more than 3 times - stop Statins.

**COLESEVELAM**

Only cholesterol lowering agent in pregnancy.

---

# PCSK9 inhibitor:

- **Alirocumab** - monoclonal antibodies
- **Evolocumab** - for hypercholesterolemia.

# Nicotinic acid (Vit B3) - Niacin

- $\downarrow$ LDL
- $\downarrow$ LP(a)
- $\uparrow$ HDL

S/E - Cutaneous flushing $(\text{Niacin promotes the synthesis of vasodilatory PGS})$

So, Aspirin added to Niacin to control flushing.

Hyperuricemia

Diabetes (causing Insulin Resistance)

Hepatotoxicity
EZEZIMIBE: inhibit cholesterol absorption in intestine.

- Bile acid sequestrants:
  - Cholestyramine
  - Colestipol
  - Colesevelam
  - approved for t/c of DM

- MIPOMERSEN: Newer drug
  - Given s/c Once in a week
  - Useful for lowering cholesterol

- PROBUCOL: Inhibits LDL oxidation

- GUGULIPID: ↓ LDL (Not use - Diarrhea)

- CETP inhibitors: (Cholesterol ester transport protein)
  - TORCE TRAPIB
  - Dalcehrapib
  - Evacehrapib
  - Anaacetrapib

- MTP inhibitor (Microsomal triglyceride transporter inhibitor)
  - LOMITAPIDE

- AVASIMIBE: Inhibit conversion cholesterol to cholesterol ester
  - ACAT-1 inhibitor
Antithyroid drugs:

Histology of thyroid gland -

Steps of Synthesis:

1. Sodide uptake
2. Oxidation of iodine & formation of iodine
3. Organisation (iodine + thyroglobulin)
4. Coupling \( \text{MIT} + \text{DIT} = T_3 \)
   
   \( \text{DIT} + \text{DIT} = T_4 \)

\( T_3 \& T_4 \)

# Stored in follicle for 3-4 days.

THIOAMIDES:

- Propylthiouracil (also inhibit peripheral conversion of \( T_3 \to T_3 \))
- Carbimazole (Prodrug)
- Methimazole (active form)

\( \text{M/C S/E of Carbimazole & Methimazole: Maculopapular rash (4-6\%)} \)

- Agranulocytosis (0.1-0.5\%)
- Severe hepatitis - PTU

Causing teratogenicity - Fetal aplastic cutis

Hepatotoxic - PTU

PTU - Used in emergency hyperthyroid crisis.

- May be safe in pregnancy
LUGOL’S IODINE:

- **MOA** - Inhibits release of T2 & T4 from follicle.
  - Fastest-acting antithyroid drug.
  - Used in post-op preparation.
  - Reducing vascularity.

- **S/E** - Iodism - Acne form skin rash.

Peripheral conversion of T4 - T3 inhibitor:

- **β-Blockers**
  - Amodarone
  - Propyl thiouracil
  - Dexamethasone
  - I podate

Iodide uptake inhibitor:

- **POTASSIUM PERCHLORATE**
  - Thiocyanate
  - Used in TSH of iodide induced hyperthyroidism.

Radioiodine therapy:

- \( ^{131}I \rightarrow t_{1/2} = 8 \text{ days} \)
  - \( \text{L} \) emits 2 rays: \( \gamma \)

- Penetrating power = 0.5 - 2 mm.
  - \( \gamma \)-Ray useful for diagnostic purpose
  - \( \beta \)-Ray “” therapeutic “”

- C/I - Pregnancy, young children, Ophthalmopathy.
  - Not useful for TSH of Medullary C4 thyroid.
Newer drug for T/I of Medullary Ca thyroid:

LENVATINIB-BTC
VANDETANIB-MC

Non-hypothyroid drug causing Hypothyroidism:
LITHIUM (stop release of T3 & T4 from follicle)
AMIODARONE (inhibit conversion of T4 to T3)
PROPRANOLOL (inhibit synthesis)
ETHIONAMIDE (inhibit synthesis)
SODIUM NITROPROSCILIDE - inhibit uptake of iodide.

Growth Hormone Release inhibitor
- For t/I of Acromegaly
  OCTREOTIDE S/C
  LANREOTIDE

GH Receptor inhibitors -
PEGVISOMANT S/C

D2 analogue -
BROMOCRIPTINE Oral
CABERGOLINE

Octreotide - 40 times more potent than Somatostatin
  longer acting - 12hr
  Given S/C or i.v.
  Never orally.

Uses - Acromegaly
Carcinoid [Diarrhoea]
AIZ
Portal HPN (Bleeding esophageal varices)
S/E - Gall stone
Vit B12 deficiency (Megaloblastic anaemia)
Rarely DM also.

Dwarfism: T/t
GH releasing factor analogue:
SERMORELIN
HEXARELIN
TESAMORELIN
→ For lipodystrophy in HIV pt.
✓ Abdominal fat.

GH analogues
SOMATREM [also used in - AIDS related wasting
SOMATROPIN
Turner Syndrome.
Pituitary dwarfism.

S/E - Insulin resistance - Type 2 DM
↑ ICT.
→ To rule out Papiledema
→ Fundus exam

# Analogue of IGF + IGF binding protein 3
MECASERMIN (s/c)
↓
to maintain stability.

S/E - Hypoglycemia

Uterine: OXYTOCIN
• ↑ force / frequency of contraction.
• ↑ contractility to fundus & body, lower segment
  not contracted unlike ergometrine &
  methyl ergometrine.
• Useful in induction of labour.
Control post partum hemorrhage
Useful in ejection of milk.

ATOSIBAN – Oxytocin Receptor Antagonist

Tocolytic of choice in heart ds – MgSO4

ZOLEDRONATE – Bisphosphonate given i.v.
   once in a year
   DOC for postmenopausal osteoporosis

NATALIZUMAB – Useful for Multiple sclerosis
   given once in a month

MIPOMERSEN – ↓ cholesterol level
   given s/c once in a week

DALBABVANCIN – Glycopeptide
   Antibiotics
   Give once in 6-10 days
   Single dose act 6-10 days
Drugs for Osteoporosis

Drugs inhibit Osteoclast:
- Bisphosphonates
  - DOC: Zolendronate
- Estrogen & SERM
- Calcitriol
- Calcitriol (Active form of Vit D)
- Calcitonin
- Thiazide diuretics
- Denosumab - RANKL antibody
  - Monoclonal antibodies

Drugs promoting osteoblast:
- Calcitriol (Active form of Vit D)
- Androgene & Anabolic steroids
- Calcium
- Parathormone
  - (hPTH 1-34) → Teriparatide
  - PTH analogue
  - Given only for 1yr (Max 2yr)
  - Long-term therapy cause Osteosarcoma.

STRONTIUM RANALATE
- Dual action < promoting osteoblast
  - inhibiting osteoclast

ZOLENDRONATE:
- Anti osteoclastic activity
- Interference on mevelonate pathway
  - Antilumour activity (calc)
- Faster acting
- DOC in Hypercalcemia (Osteonecrosis of jaw)
- Also used in Paget's ds.
- Less venous irritant
- Renal toxicity

S/E:
- Thrombophlebitis
- During infusion: Fever + Chills
  "Infusion reaction"
- Nephrotoxicity
- Osteoporosis of jaw bone

# M/c drug for steroid induced osteoporosis
  - Bisphosphonate
# Osteonecrosis of Neck of femur - S/E of steroid

**STEROIDS:**

1. **GLUCOCORTICOIDS:**
   - Class A → Short acting (Duration < 12 hrs)
   - Max mineralocorticoid activity: Hydrocortisone
   - Corticosterone

<table>
<thead>
<tr>
<th>Gluco</th>
<th>Mineralo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
</tr>
<tr>
<td>Corticosterone</td>
<td>0.8</td>
</tr>
<tr>
<td>(Least potent)</td>
<td></td>
</tr>
</tbody>
</table>

   Class B → Intermediate acting (duration 12-16 hrs)

   - Prednisone 4 0.8
   - Prednisolone 4 0.8
   - Methylprednisolone 5 0.5
   - Triamcinolone 5 0
CLASS C: Longer acting (> 36 hrs)

<table>
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<tr>
<th>Steroid</th>
<th>10</th>
<th>0</th>
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<tbody>
<tr>
<td>Prednisolone</td>
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<td></td>
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<tr>
<td>Betamethasone</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>(Most potent G)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>(Maxm G)</td>
<td></td>
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</table>

Mineralocorticoids:

* Natural

<table>
<thead>
<tr>
<th>Steroid</th>
<th>0</th>
<th>3000</th>
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</thead>
<tbody>
<tr>
<td>Aldosterone</td>
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<td></td>
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</table>

* Synthetic

<table>
<thead>
<tr>
<th>Steroid</th>
<th>0</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOCAn</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fludrocortisone 10 250

Maxm glucocorticoid action — Dexamethasone
Maxm mineralocorticoid action — Aldosterone

G & max min — Hydrocortisone
Least potent G — Cortisone

Most "" — Betamethasone
Maxm topical action — Triamcinolone

Selective glucocorticoid (No minerals) — TPDB
Selective Mineralocorticoid (No Gluc) — DOCAn

Website: http://mbbshelp.com
WhatsApp: http://mbbshelp.com/whatsapp
Steroid — Anti-inflammatory
  Anti-cancer
  Immunosuppressive

Anti-inflammatory action of steroids
  - By inhibiting Phospholipase A₂

ZILEUTON — Inhibit lipooxygenase
  Not in use
  Severe hepatotoxic

NSAID — Inhibit Cyclooxygenase.

Steroid having anti-cancer activity:
  - Apoptosis of T & B cells
  - Useful for lymphoma.

Steroid having immunosuppressive action:
  - Inhibit IL-1 & IL-6
  - Also catabolism of IgG

Methylprednisolone — Used in pulse therapy.

ACTH
  Cosyntropin — Infantile Spasm.
Adrenal Cortex - Cushing Syndrome

Drug useful for t/t of Cushing Syndrome:
- Metyrapone (11β-hydroxylase)
- Ketoconazole
- Mitotane - chemical adrenalectomy
- Aminoglutethimide
- Trilostane
- Etonidazole (General anaesthetic)

Pasireotide - Somatostatin analogue, useful in t/t of Cushing Syndrome.

Erectile dysfunction:
1. Selective PDE5 blocker:
   - Sildenafil
   - Vardenafil
   - Tadalafil - longest acting
   - Avanafil

- PDE5 enzyme is involved in metabolism of cGMP.
- PDE5 blocker by blocking cGMP metabolism causes vasoconstriction.

Acute adverse effect - Headache
  - Flushing
  - Hypotension
  - Nasal congestion

Long term (chronic) therapy causes blue vision defect.

Blocking PDE6
Drug interaction between Sildenafil & Nitrates:

Nitrates shouldn't be given with Sildenafil

6003 risk of severe hypotension.

Other drug for erectile dysfunction:

Apomorphine (Dopamine)
Trazodone (Atypical antidepressant)
Avanafil (VIP - Vasoactive intestinal polypeptide)
Ketanserin (Serotonin antagonist)
Naltrexone (Opioid Antagonist)

Ginseng
Kava
Gingko

Injectable therapy for Erectile dysfunction:

Alprostadil
Phentolamine
Papaverine.

Drugs useful for PE - Premature ejaculation:

- SSRI
- PDE5 inhibitors

For delayed orgasm:

Amantidine
Buapirone
Cyproheptadine.

For sexual stimulation:

- Yohimbine
Zinc
Ginkgo biloba
Ginseng.
ANTI ANGINAL DRUGS

Stable Angina
Unstable Angina
Vasospastic Angina (Prinzmetal Angina) (Variant Angina)

Cause < Reduction in O2 supply
↑ O2 demand.

Anti-anginal drugs

Vasodilator
Cardiac depressant

Nitrate
CCB
β-blocker

K⁺ channel opener

Pathway of FA oxidation inhibitors (pFoX)

# Fatty acid
÷ oxidation ↔ TRIMETAZIDINE, RANAZOZINE

Free radical
↓
Cytoxicity to myocardial cell.

Angina Anarrhythmia

S/E - GI toxicity (M/C)
Thrombocytopenia
Liver dysfunction
Risk of movement disorder - GI in Parkinsonism
QT prolongation prolongation -

Excretes by Renal pathway - GI in Renal failure
NITRATES

Short acting  Intermediate acting  Long acting  Longest acting
- GTN  - Isosorbide  - Isosorbide  - Pentaerythritol
- Amyl Nitrite  dinitrate  mononitrate  tetranitrate
  (shortest)  (2-3hrs)  (6-10hrs)  (8-12hrs)

# For acute attack - GTN, Isosorbide dinitrate

Least 1st pass metabolism - Isosorbide mononitrate.

S/L drug - Lipid soluble  Non  ionised

Skin rash - Pentaerythritol tetranitrate

MOA of nitrates:
- Nitrates acting on Cysteine receptor, they
  release NO  NO activate Guanyl cyclase
  ↓
  Vaso dilatation  θ→ CGMP (2nd Messenger)
  θ→ PDE5  ↓
  Sildenafil  SMR

NO independent - direct Guanyl cyclase activators:
  RIOCI GUAT
  CINOCI GUAT
- Useful for t/t of Primary pulm. HTN.

# CGMP normally undergo inactivation by PDE5 enzyme.
  So, PDE5 inhibitor = Sildenafil group of drug.
Nitrates may get tolerance due to down regulation of receptors.

Maxim Tolerance - i.v. infusion
& Transdermal patches.

Action of Nitraloi:
Visceral smooth muscle - Relaxed
→ Useful for t/t of Biliary colic pain
→ Useful for t/t of Achalasia cardia

Vascular smooth muscle - Vasodialator
→ Predominantly Venodialator
→ Peripheral pooling of Blood
→ Max. ↓ in Preload.
→ Mild ↓ of afterload.
→ ↓ O2 demand
→ Reduce angina.

Uses: Cardiac uses: Angina
- MI
- CCF

Non-cardiac uses: Biliary colic pain
- Achalasia cardia
- Cynide poisoning:
  ↓ by formation of Methemoglobinemia
ADR - Thrombosing Headache (M/c)

Hypotension

Reflex Tachycardia (due to sympathetic stimulation)

Tolerance

Melanogloobinemia

Rashes

Drug interaction b/w Nitrates & Sildenafil:

- Not combined together bcoz it cause severe hypotension.

- Gap of 8-10 hrs should be maintained.

Sodium Nitroprusside:

- Only i.v. route

- Short acting <10min

Indication - Hypertensive emergency

- Acute aortic dissection

- Drug is sensitive to light

- Covers & black towel

- Containing cyanide (Thiosynapse)

Risk of Hypothyroidism

- CI in pregnancy

β-blockers:

- ↓ Work load of cardiac

- CI in variant angina

- Abrupt withdrawal post angina

- β-blocker + GTN = to prevent Reflex Tachycardia

- Control catecholamine activity
Role of β-blocker on MI:
- Reduces size (zone) of infarction
- Anti arrhythmic action
- Reduces mortality

CCB:
- Chemical Type: Phenylalkylamines
  - Chemical names: Verapamil
- Benzolizepines: Diltilazem
- 1,4-Dihydropyridines (DHP):
  - Nifedipine
  - Niocardipine
  - Niwoodsipine
  - Amlodipine
  - Ni'trendipine (NO releasing property)

# Neviranol: β-blocker having NO releasing property.

DHP:
- Site of action: Peripheral blood vessel
  - Vasodilatation
    - Useful for t of HTN & PVD.
  - Maximally arterial dilatation.
    - max in PVR.

ADR → Hypotension
  - Reflex Tachycardia
  - Ankle edema (Amlodipine max cause ankle edema)
  - Constipation
Nifedipine [Long acting]
Clevidipine [Short acting]

Non-dihydropyridines: Verapamil
Diltiazem

Site of action: AV node (Most imp.)
SA node

Action → Bradycardia
→ Anti arrhythmic agent

Uses → Atrial Tachyarrhythmia (AT)
SVT (Supra Ventricular Tachyarrhythmia)

ADR → Bradycardia
Block AV conduction → Prolongation of PR interval

Ankle edema
Constipation

C/I → WPW syndrome

Diltiazem:
Uses → HTN
Angina
Arrhythmias (SVT/AT)

CCB having anti-arrhythmic property
Verapamil → Class IV
Diltiazem → Antiarrhythmic
Nimodipine: Cerebro-selective CCB
Useful for 1/3 of Sub-arachnoid hemorrhage (SAH)
The purpose of given Nimodipine is to prevent Reflex ischemic damage.

Fasudil - Rho kinase inhibitor
Use - SAH
SSR PHT (Pulm. HTN)
Angina

CCB useful in Prophylaxis of Migraine - Verapamil
Flunarizine
T-type of CCB
Na⁺ Channel blocker
Anti-oxidant

K⁺ channel openers:
Hydralazine - Arteriolar dilator
Minoxidil - Anti-hypertensive
Diazoxide

Nicorandil (Anti-anginal)

Adenosine (PSVT) → DOC

Nicorandil: NO releasing property
Anti-anginal
S/E → Aphthous ulcer
Headache
Hydralazine:
- 75% of HTN-emergency in pregnancy
- NO releasing properly
- Metabolism by Acetylation
- Cause RAFELE

Minoxidil:
- Prodrug
- Active form → Minoxidil Sulphate.
Uses → HTN
Alopecia

Diazoxide:
- causing hyperglycemia by inhibiting insulin release from β-cell of pancreas.
Use → HTN
Insulinoma.
Phenytoin – also inhibit release of insulin 
- Poor man drug for Insulinoma.

IVABRADINE –
- Causing Bradycardia.
- Na⁺ Channel blockers (Ifunny Current)
- Reduce HR.
Two indications: CCF
Angina.

SE - OW chronic therapy - Causes Luminous phenomena.
(Visual disturbance)

Hemoralopia - Trimethadione (Withdrawl - due to
Nephrotoxicity)
Day blindness

Reperfusion - Thrombolysis/PTCA

Drug eluting stent:
SIROLIMUS (Immunosuppressant)
PACLITAXAL (Anti-cancer drug additional
immunosuppressant)

Used to stent to decrease rejection.

ANTI-ARRHYTHMIC DRUGS:
Rapid closure of Na⁺ → PHASE 1
PHASE 2 → Plateau - Ca²⁺ influx
PHASE 3 → Repolarization
K⁺ efflux
Na⁺ influx → PHASE 0
APD
PHASE 4
-60mV

PHASE 3 → T WAVE
PHASE 2 → ST segment
PHASE 0,1 & mid phase of 2 → QRS
APD (Action potential duration) → QT interval.
Any drug having $K^+$ channel blocking property will cause QT prolongation.

- Class Ia & Class III drug having $K^+$ channel blocking property causing QT prolongation.

Classification: Vaughan Williams

Class I - Na$^+$ channel blocker

- Class IA, IB, IC

Class II - $\beta$-blocker

Class III - $K^+$ channel blocker

Class IV - CCB

Unclassified & Miscellaneous agent

Adenosine
Atropine
Digoxin
Magnesium Sulfate
KCl

Class Ia:
- Block Na$^+$ channel + $K^+$ channel block
- Having risk of causing QT prolongation.

Eg: Quinidine
Procainamide
Disopyramide
Quinidine -
Origin - Cinchona bark
\[ \rightarrow \text{Symptom - Cinchonism} \]
\[ \downarrow \text{Sinusus} \]
SLE - Diarrhoea
Hypotension (Bcz of blocking property)
Hypoglycaemia (Bcz Insulin releasing property)
SMR
Thrombocytopenia.

Drug interactions: Quinidine + Digoxine
Quinidine interferes renal excretion of Digoxin.
\[ \therefore \text{aggravating plasma level of Digoxin} \]
\[ \therefore \text{Digoxin toxicity.} \]

Procainamide:
SLE - Undergo metabolism by Acetylation
SLE.

Disopyramide:
Highest anticholinergic action.
Dry mouth, constipation, Retention of urine.
\[ \therefore \text{Not safe in elderly male} \& \text{BPH.} \]

Class IB:
Na⁺ block + K⁺ opening.
- Never causes QT prolongation.
Site of action → Mainly acting on Bundle of His.
\[ \text{Rt. Bundle, Lt. Bundle} \& \text{Purkinje fibre.} \]
only
Used for t/t → Ventricular arrhythmias (Tachycardia)

eg: Lignocaine (Lidocaine)
Mexilitine
Phenytoin
Tocainide.

Mexilitine:
- Lignocaine derivative
- Useful for t/t Ventricular arrhythmias.
- Used for Diabetic neuropathy pain
  (Unlabeled Use)
- Used for Phantom limb pain
  ADR - Severe Nausea & Tremor.

Phenytoin:
- Anti-epileptic
USE - t/t of Digitalis (Digoxin) induced VT

Tocainide:
Bcoz of causing Agranulocytosis it is not used.

Lignocaine:
- Class IB drug
- Never given orally bcoz undergo extensive 1st pass metabolism
- Given i.v.
- Lipid soluble, Cross BBB

S/E - Convulsion
  1st Sign - Nystagmus (1st sign)
  1st Symptom - Currum oral paraesthesia
Use - VT (Ventricular Tachycardia)
VF (Ventricular Fibrillation)
Digitoxin induced VT (DOC: Lignocaine)

Class IB drug has no role in atrial arrhythmias

Class IC:
- Na⁺ blocking + Negligible effect on K⁺ channel
- Max pro-arrhythmic property
- Non commonly used
- Only for anti-arrhythmic drug causing arrhythmia

Flecainide (DOC: for Acute WPW)
Enacainide
Propafenone
Moricizine

PROPafenOne:
- Also β-blocking property

Class III: K⁺ Channel blocker
- Prolong APD → QT prolongation

Amiodarone:
- Sodine containing anti-arrhythmic drug
  Multi MOA: K⁺ Channel blocking
  Na⁺ Channel blocking
  β- Blocker property
  CCB property
- Broad spectrum Anti-arrhythmic
Half life = 53 days.

USES: All type of arrhythmias
Ventricular & Supraventricular arrhythmias.

ADR:
PLZ = Photosensitivity, Pigmentation of skin (Gray-blue)
Check = Corneal deposition (Whorl like pattern cornea)
PFT = Pulmonary fibrosis, Peripheral neuropathy.
LFT = Liver damage, Pseudo alcoholic liver injury & Mallory Hyaline bodies.
TFT = Hypothyroidism

- Due to inhibition of peripheral conversion of T4→T3
Hyperthyroidism

Whorl like pattern cornea - Cornea Verticillata
or Vertex Keratopathy.

Pseudo lymphoma - Phenytain
Pseudo jaundice - Rifabutin

Amiodarone causing Hyperthyroidism due to:

1. Hypothyroidism: Inhibition of peripheral conversion of T4→T3.
2. Contain iodine → Iodine help in synthesis of
   T3 & T4
3. Can cause inflammation of follicle.

For each 200mg tablet there is 75mg of iodine.
Rx: Inhibit iodide trapping
   - Perchlorate
   - Thiocyanate

For inflammation - Rx: Dexamethasone (Steroid)
Class III Drugs:
- Amiodarone
- Dronedarone (Noniodine)
- Brevetilium (Chemical defibrillator)
- Sotalol
- dofetilide
- New drug: Icatibantide (FDA approved for conversion of AF-SR) - i.v.
- Vrenakalant

Class IV: CCB
- Verapamil (Most potent)
- Diltiazem

Miscellaneous Drugs:

Adenosine:
- Given i.v., short acting, Rapid infusion (Roxin)
- Site - Close to heart.
- DOC for SVT
- It is also called Endogenous epileptic.
  - Antagonist - methyl xanthine - theophylline
  - Agonist - Dipyridamole

  Cause → Coronary Steal Phenomenon.

For Acute SVT: i.v. Adenosine

i.v. Verapamil.

→ Prefer in Acute & SVT.

To prevent recurrence of SVT: Oral β-Blocker

Oral Verapamil.
**MgSO₄**

**USE**: 1. CNS

- Long QT syndrome
  - Congenital
  - Acquired
  - β-blockers
  - MgSO₄
  - (Propranolol)

**USE**: 2. Digitalis intoxication

- Hypokalemia
- Hypomagnesemia → Give MgSO₄
- Hypercalcemia

2. Respiratory System

**USE**: Bronchial asthma

3. GIT (laxative property)

**USE**: Constipation

4. Ortho (anti-inflammatory property)

**USE**: Synovitis

5. Obst & Gyn.

**USE**: Eclampsia

**S/E**: Diminished deep tendon reflex (M/c)

Rarely Resp failure

**Safety Limit**: 4 m Eq/L

- If >7 m Eq/L → Patellar reflex ↓
- >14 m Eq/L → Resp failure
Antidote - Calcium Gluconate.

ATROPINE:
- Anti-cholinergic agent.
- Causing Tachycardia.

USE - Bradycardia or Heart Block.

DIGOXIN: Already discuss.

Cardiac glycosides:

<table>
<thead>
<tr>
<th></th>
<th>Digoxin</th>
<th>Digitoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1/2</td>
<td>40 hr</td>
<td>5-7 days</td>
</tr>
<tr>
<td>Route of excr.</td>
<td>Renal</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Plasma conc.</td>
<td>0.8-1.5 ng/ml</td>
<td>15-30 ng/ml</td>
</tr>
</tbody>
</table>

- Both have narrow therapeutic index
  i.e. Unsafe & need monitoring.

Non-

Digoxin S/E: Cardiac S/E

Nausea & Vomiting (M/C)
CNS depression
Yellow vision defect (Xanithopsia)
Gynecomastia (in male)

Cardiac S/E

Atiatal Tachyarrhythmia (AT)
AV block
VT (Ventricular Tachycardia)
Ventricular Bigeminy (M/C)
Non-paroxysmal AT & Variable AV block is Most Characteristic arrhythmia.
For t/t digoxin induced A/T — Propanolol.

# Atropine → AV Block
Lignocaine → VT

# No role of Hemodyalysis & in digoxin toxicity
6000 large Vd.

# Antidote for digoxin toxicity — Digibind.

Check $K^+$, $Mg^{2+}$, $Ca^{2+}$
DIURETICS:

In the PCT → Carbonic anhydrase

Reabsorption of NaHCO₃ (85%)
Reabsorption of NaCl from urine (60%)

Thin descending limb → Absorption of H₂O
→ Concentrating Segment

Thick ascending limb → Na⁺-K⁺-2Cl⁻ Symporter
↓
Absorption of Na⁺, K⁺, Cl⁻, Ca²⁺, Mg²⁺.
(Diluting segment) (25%)

DCT → Na⁺-Cl⁻ Symporter
↓
ReAbsorption of NaCl (10%)
Reabsorption of Ca²⁺ (↑PTH)
& help of

CT → Reabsorption of NaCl (↑ help of aldosterone) (5%)
Secretion of K⁺ & H⁺
Reabsorption of H₂O (↑ help of ADH)

Primary Hyperaldosteronism (Conn’s Syndrome):
↑ Aldosterone

↑F → HTN

Hypokalemia
Metabolic alkalosis.

For ↑ HTN → K⁺ sparing antidiuretic
↓ Spironolactone.
Carbonic anhydrase inhibitors:
- Acetazolamide
- Dorzolamide [Non-competitive & Reversible]
- Brinzolamide

Site of Action - PCT
MOA - Inhibit Carbonic Anhydrase.

ADR - Loss of HCO3
- Metabolic acidosis.

# Acetazolamide causing Alkaluria
- "So used in Alkalization of urine.
- Max" potassium loss.

# CA inhibitor also acting on collecting duct - it inhibit tubular secretion of H+ → so cause Metabolic acidosis & massive Hypokalemia.

# CA inhibitor are Sulpha derivative:
- SE - Hypersensitivity
  - Bone marrow suppression

# C/I - liver disease (hepatic encephalopathy)
- COPD
- Metabolic acidosis.
Loop Diuretics: High Ceiling diuretic (↑ dose → ↑ diuretic action) 
Site of action: Thick ascending loop of Henle 

MOA: Inhibiting Na⁺-K⁺-2Cl⁻ symport 

Less of Na⁺, K⁺, Cl⁻, Ca²⁺, Mg²⁺ 

Eg: Furosemide → Vasodilatory action (USE: RF, LVF) 
bumetanide → Most potent 
Mersalyl → Kidney damage (Not in Use) 
Ethacrynic acid → Highly ototoxic (No CA enzyme inhibition) 
Torsemide → longest t½ 

Role of Furosemide in Renal failure: 
Furosemide promote Vasodilatory action on PG

By ↑ intra renal blood supply

Improving Renal failure 

NSAID + Furosemide → NSAID is not given in Furosemide in Renal failure pt. Bcoz it inhibit 
synthesis of PG. 

# Diuretics of choice in the presence of RF 
Choice - Furosemide 

Ineffective - Thiazides 

Exception - Metolazone 

Guy - K⁺ sparing drugs.
Role of loop diuretics in heart failure:

Furosemide - Only Relief symptoms of CHF.

Main mech: Vasodilation

Bez of vasodilation Furosemide (i.v.)

rapidly relieve breathlessness in CHF.

Side effects of loop diuretics:

Water loss Electrolyte Metabolism Miscellaneous

unbalance

Profound Loss of Na⁺ Hyperuricemia Metabolic alkalosis

ECF depletion K⁺, Cl⁻, Ca²⁺, Mg²⁺ Hyperglycemia Ototoxicity

↓ Hyperlipidemia (Irreversible)

Calcium (Risk of kidney stone) Exception: Aminoglycosides

INDACRINONE Cisplatin

Ethionine acid Vancomycin

derivative Erythromycin

Uricosuric agent

Drug interaction: Loop diuretics + Arrhythmia

- Loop diuretics by causing hypokalemia & hypomagnesemia → causing digoxin toxicity.
Thiazide diuretics:

Site of action: DCT

MOA:
1. Inhibiting Na⁺-Cl⁻ Sympoor
2. Promotes Reabsorption of Ca²⁺
   - Ca²⁺ Excretion → hypercalcemia (Urine Ca²⁺↑)
   - Safe for Renal stones.

3. Also having antidiuretic activity.

E.g.: Indapamide → Vasodilatory action (No CA enzyme inhibitor);
Chlorthalidone → longer acting
Melolazine → Useful even in severe RF.

# A/c to JNC guidelines, the 1st line drugs are:
Thiazides - type diuretics
CCB
ACE inhibitors
ARB’s

Therapeutic effect:

As a diuretic —
1. T/t of Mild edema
2. T/t of HTN

As an anti-diuretic — T/t for Nephrogenic DI.

H + Ca²⁺ Excretion → Idiopathic hypercalcemia
   or William Syndrome
   → T/t of Calcium Nephrolithiasis
Adverse effects:

- Water loss
- Electrolyte abnormality
- ECFV depletion
- Hypokalemia
- Hyperuricemia
- Metabolic alkalosis
- Hyperglycemia
- Hypercalcemia
- LDL
- Impotency
- Erectile dysfunction
- Osteoporosis
- Thiazide causing insulin resistance
- As well as inhibiting β-blockers also
- Insulin release

- HTN and Hyperlipidemia
- (So don’t use thiazide)

- K⁺-Sparing diuretics
  - Aldosterone antagonist
  - Eprosartan (M/C)
  - Canrenone (Active metabolite)
  - Eplerenone (No gynecomastia)
  - Dronrospironedone (Progestrone)

- ENaC Channel inhibitor
  - Amiloride
  - Triamterene
  - Pentamidine
  - Trimethoprim

- ENaC:
  - Na⁺ from urine in Cő is absorbed by ENaC.
Spironolactone:

**MOA:** One & only drug acting on interstitium.

**MOA of Amiloride:** Amiloride acting from lumen & blocking ENaC.

**Therapeutic uses of Spirinolactone:**

- Block Aldosterone

1. **T/t for Primary Hyperaldosteronism (Conn's)**
2. **Dox** **T/t for Edema of liver cirrhosis (Ascites)**
3. **T/t for Heart failure.**

\[ \text{Disease modifying HF} \to \text{Spirinolactone.} \]

**Adverse effects:**

- **Hyperkalemia**

\[ \text{M/c} \left\{ \text{Metabolic acidosis.} \right. \]

- Long term effect in male - Impotence & androgenic action.

\[ \text{Gynecomastia} \]

- in female - Menstrual irregularities.

**Drug causing Gynecomastia:**

- **D** = Digoxin
- **I** = INH
- **S** = Spirinolactone
- **C** = Cimetidine
- **K** = Ketoconazole
- **O** = Oestrogen/anti-androgen \( \to \) Finasteride

\[ \text{T/t of male pattern baldness.} \]
Drug useful in painful Gynaecomastia - Tamoxifen.

Therapeutic effect of Amiloride:

1. T/t of Liddle's Syndrome (↑ ENaC)
2. T/t of lithium induced DI
3. T/t Atezolast - Cystic fibrosis. (Mech not known)

Mannitol - Osmotic diuretics

Site - LOH & PCT

Useful for T/t of
1. Glaucoma (Given i.v.)
2. Cerebral edema
3. Cisplatin toxicity.

Mannitol added to cisplatin to control nephrotoxicity

C/I - Pulmonary edema (LVEF)
Cerebral Hemorrhage

S/E - Hyponatremia
Headache
ANTIDIURETICS

- ADH (Vasopressin)
  - **V_2** Receptor:
    - Location → V_2 seen on medullary portion of collecting duct
    - Action → Water Reabsorption

  - Also seen on Vascular epithelium
    - Action → Releasing VWF & factor VIII

  - Desmopressin:
    - Synthetic analogue of Vasopressin acting on V_2
    -USES: Doc for Cranial diabetes insipidus
      Doc for Nocturnal Enuresis.
    - Useful for Hemophilia
    - """" Bleeding due to deficiency of vWF factor.

- **V_1** Receptor:
  - Seen on Vascular smooth muscle
  - Action → Vasoconstriction

  - **V_1** analogues: Synthetic
    - Terlipressin → Useful to control esophageal varices
    - Pencylpressin
    - Lypressin
      - Doc: Ochotroie
      - Prophylaxis doc: Propranolol

  - # Terlipressin added to lignocaine to prolong the action.

  - Selective V_2 antagonist:
    - Lixivaptan
    - Oral Mozavaptan → Doc for SIADH
    - Tolavaptan
Selective V₁ antagonist:
- Relcovaptan - Useful for HTN
- Nelivaptan - V₁₆ blocker

Undergo clinical trial for lift of Anxiety.

Non-selective V₁ & V₂ antagonist:
- Conivaptan (V₂ > V₁)

⇒ USE: SIADH
  Gwen i.v.

HEMATOLOGY

Thrombolytic Agents:
- MOA - Plasminogen activator ➔ Plasmin (Fibrinolysis)

eg:
- Streptokinase
- urokinase
- alteplase
- Tenecteplase

Antidote of Thrombolytic drugs:
- EACA (Epsilon Aminocaproic Acid)
- Tranexamic acid
- Aprotinin
WARFARIN: Inhibiting vitamin K-dependent factors (II, VII, IX, X)

<table>
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<tr>
<th>Protein</th>
<th>Half life</th>
</tr>
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<tbody>
<tr>
<td>Factor II</td>
<td>72 hrs</td>
</tr>
<tr>
<td>VII</td>
<td>4-6 hrs</td>
</tr>
<tr>
<td>IX</td>
<td>24 hrs</td>
</tr>
<tr>
<td>X</td>
<td>44 hrs</td>
</tr>
<tr>
<td>Protein C</td>
<td>8 hrs</td>
</tr>
<tr>
<td>Protein S</td>
<td>30 hrs</td>
</tr>
</tbody>
</table>

- For full benefit of warfarin occurs, wait for 3 days.
- Not used in acute DVT.
- Useful in prophylaxis of chronic DVT.

- Normal function of protein C → inhibiting factor V & VIII

\[ \Theta \]

- Hypocoagulation

- Side effect of warfarin

- Dermal Necrosis due to protein C inhibition.

- Purple toe syndrome

- Warfarin therapy:
  - Narrow therapeutic index (Only INR done)

- Two isomers
  \[ R \]
  \[ S \text{ (Active)} \]

- CYP2C9 involved in metabolism of Warfarin
- Duration of action → 5 days.
- It undergoes Zero-order kinetics.
Warfarin: $\text{INR} = \frac{\text{Patient PT}}{\text{Control PT}}$

N → 2-3

Prosthetic Value → 2.5-3.5

Long term → 1.5-1.9

GI in Pregnancy → Teratogenic

\[ \downarrow \]

Contradict Syndrome

Fetal Chondrodysplasia Punctata

Antidote of Warfarin:

\[ \text{Natural VitenK1} \]

\[ \text{VitenK2} \]

\[ \text{VitenK3} \]

\[ \text{Phytonadione} \]

\[ \text{Menoquinone} \]

\[ \text{Menadione} \]

Takes about 24hrs
to redución INR

For immediate hemostasis — Fresh frozen plasma (FFP)

# New Oral drugs — direct IIa inhibitor

Ximelaglaror (Cause severe hepatotoxicity)

— Not used

Dabigatrin

# New oral drugs: Direct Xa inhibitors

Apixaban
Rivaroxaban
Edoxaban
Betrixaban
Injecting Anticoagulant acting Via Antithrombin III pathway:

- Heparin (inhibit Xa; IIa)
- LMWH (inhibit Xa)
  - eg: Enoxaparin
  - Dalteparin
  - Fraxiparin
  - Nadroparin

Other injectable drugs acting via Antithrombin III but only inhibiting Xa:

- Fondaparinux
- Edoxaparinex
- Idraparinux

Idrabiota parinex \( \rightarrow \) Antidote \( \rightarrow \) Avidin

Specific antidote for Heparin - Protamine Sulphate

It is chemical antagonist.

1 mg of Protamine Sulphate

Neutralizes 1000 U of Heparin.

Direct Xa inhibitor - Omacoexaban

(Under trial)

Injectable - Direct Thrombin (IIa) inhibitor

- Bivalent:
  - Hirudin
  - Bivalirudin
  - Lepirudin

- Monovalent:
  - Argatroban
  - Eptiexaban (Biliary excretion)
  - Melagatran

*These drugs are used in pt. who develop Heparin induced Thrombocytopenia.*
Adverse drug reactions:

- Heparin
  - $A = \text{Alopecia}$
  - $B = \text{Bleeding}$
  - $O = \text{Osteoporosis (Supplement Ca)}$
  - $U = \text{Urticaria (Hypersensitivity)}$
  - $T = \text{Thrombocytopenia}$
- Warfarin
  - $A = \text{Alopecia}$
  - $B = \text{Bleeding}$
  - $O = \text{Oral (GI intolerance)}$
  - $U = \text{Dermatitis}$
  - $T = \text{Teratogenicity}$
  - Rarely Hyperkalemia

Monitoring:

- Antiplatelet drugs (Aspirin) — Prolongs BT
- Heparin (Intrinsic pathway) — Prolongs aPTT
- Warfarin (Extrinsic ””) — Prolongs PT
- LMWH — No need of monitoring
- If monitor then Antifactor Xa
  - In Renal failure & Obese pt.

ANTI PLATELETS

Drugs inhibiting synthesis of TX-A2:

- Selective COX-1 inhibitor — Low Dose Aspirin
  - (50mg-160mg)

Thromboxane synthase enzyme inhibitor — DEXOBEN

Drugs inhibiting TX-A2 Receptor:

- IFEPTROBAN
- SULTROBAN
- DALTROBAN
- LOSARTAN (ARB having Antiplatelet action)
- VAPIPROST
Drugs inhibiting synthesis of TX-A2 & blocking action of TX-A2 receptor: Dual action
PICOATAMIDE

Newer drug: SERATRODAST (Thromboxane A2 antagonist).

ADP (P2Y12) blockers:
- Ticlopidine - Prodrug
- Clopidogrel
- Prasugrel
- Ticagrelor
- Cangrelor - Given iv.

Ticlopidine - Not commonly used because thrombocytopenia & Hepatotoxicity.
Clopidogrel - Activated by CYP2C19.

# Omeprazol shouldn’t be given with Clopidogrel.
Pantoprazol & Rabeprazol don’t have drug interaction with Clopidogrel.

Glycoprotein IIb/IIIa blocker:
- Abciximab - Monoclonal antibody.
  Given iv
- Eptifibatide
- Tirofiban

PAR1 blocker (Proteinase activated Receptor blocker)
- Vorapaxar
- Atoraxar
Essential Thrombocytoysis:

ANAGRELIDE → Platelet malunion inhibitor.

DOC for Sickle cell Anemia — HYDROXYUREA

Useful in Essential Thrombocytoysis

Drug used for T/t of CCF:

Drugs inhibiting release of Renin:

β-Blocker
Clonidine
Methyl dopa.

Renin inhibitors:

Aliskiren (FDA approved)
Remikiren
Enakiren

ACE inhibitors:

Captopril
Ramipril
Lisinopril
Fosinopril (Renal & Pile exc.,ion)

# All ACE inhibitors are Prodrug except Captopril

# All ACEi are having Renal excretion.

Action → Vasodilation (Equally dilates Artery & Vein)

Useful for → HTN, CCF, M/E, DM, Proteinuria, Scleroderma.

Nephroprotective.
C/I – ① Pregnancy
② B/L Renal Stenosis
③ Severe Hyperkalemia

Bradykinin antagonist: icatibant

Useful for angioedema & dry cough.

Hereditary angioedema:
C1-esterase inhibitor deficiency.

ICATIBANT

RUCONEST → Human Recombinant C1-esterase inhibitor

Ecallantide [kallikrein inhibitor.

APROPRITIN

DANAZOL → Antagonadotropic & anti-androgen action
(impeded androgen)

# Sampatrilat – inhibit Vasopeptidase
Omapatrilat – ACEI

Vasopeptidase: Peptide

ANP  BNP  URODILANTIN

Fusion – Natriuresis –
Diuresis
Vasodilation

Synthetic Analogue Carperitide Nesiritide Ularitide
Nesiritide:

Synthetic analogue of BNP

Action → Diuresis
   
Natriuresis
   
Vasodilatation

Useful for t/l of CCF.

- Given iv, Never oral

- Metabolism → Vasopeptidase
   - Shorter life half life - 20 min

S/E - Severe Hypotension

# Other name of Vasopeptidase - Neprilysin (Neutral endopeptidase).

Selective Vasopeptidase inhibitors:

Exadotril

Sacubitril

Omapatrilat - inhibit Vasopeptidase > Dual enzyme inhibitor.

Salupatrilat - ACEi

ARB's:

Losartan

Valsartan

Telmisartan

Olmesartan

Azilsartan

- Indication & CYI same as ACEi.
Losartan:

- Action: Uricosuric action
- TXA₂ antagonist

Telmisartan
- Agonistic action on PPAR γ
  (Peroxisome proliferator-activated receptor)
- So used in T/I of DM.

Aldosterone Antagonist:
- Spironolactone
- Canrenone
- Eplerenone
- Drospirenone

# ACEi + Spironolactone \( \Rightarrow \) Severe Hyperkalemia.

Any drug blocking RAS pathway will cause hyperkalemia.

Other drug useful for T/I of CCF

Phosphodiesterase 3 inhibitors:
- Amrinone (Inamrinone)
- Milrinone
- Levosimendan

\( \Rightarrow \) M/C S/E - Thrombocytopenia

M/C S/E of Milrinone - Arrhythmia
Heart failure:

**Na⁺-K⁺ pump inhibitor**: Isároxime.

**Direct myosin activator**: Omes camifiv mecabit ( śrotnic)

**Calcium sensitizer**:
- Pimobendan
- Levosimendan (PDE-3 blocker)

**Disease modifying drug**

**Drug reducing mortality in CCF**:
- β-Blocker (Carvedilol, Bisoprolol, Metoprolol)
- ACEi
- Angiotensin Receptor Blockers (ARBi)
- Spironolactone
- ISDN + Hydralazine
- Isosorbole dinitrate

Except these drugs, all other drugs control symptoms only in CCF.
GIT

Drug useful for Acid peptic disease (APD):

H2 Antihistamines:
- Cimetidine - Least potent
- Ranitidine
- Famotidine - Most potent
- Roxatidine
- Nizatidine
- Loxatidine

- Basal acid output & nocturnal (more effective)
  So, give at bedtime.

- Renal excretion

* Cimetidine - Antiandrogonic
  CYP enzyme inhibitor
  Least potent

PPI (*H+K+ ATPase inhibitors*):

- Omeprazole (Metabolism by CYP2C19, CYP3A4)
- Esomeprazole
- Pantoprazole
- Lansoprazole
- Rabeprazole

Short half life for less than 2 hr

But acting for longer duration → Hit & Run drug
(Irreversible inhibition of proton pump)

# Omeprazole not given with clopidogrel.
Rabeprazole > No significant drug interaction
Pantoprazole (preferred with clopidogrel)
Antacids:

Sodium Bicarbonate

Calcium Carbonate - shouldn't be taken with milk

- bcoz Milk alkali Syndrome.

# GELUSIL:

Combination of Aluminium Hydroxide (Constipation) + Magnesium Hydroxide (Diarrhoea)

Ulcer protective drugs:

Sucralfate (Sucrose + Sulphated Aluminium hydroxide)
- Acts only in acid medium (pH below 4)
- It shouldn't be combine with H2 blockers/PPi/antacid.

Bismuth
- Black stool & tongue.
- GI - Renal failure.

Ulcer healing drugs:

Carbenoxolone

\[ \text{\textit{c}} \text{.e.} \text{. it displaces aldosterone from protein binding.} \]

Prokinetic drugs:

- Drugs promoting GI motility.

\[ \text{D2 antagonist:} \]

- Domperidone

- Metaclopramide
**5HT4 agonist:**
- Cisapride
- Mozapride
- Tegaserod
- Neosulpride

**Cholinergic agonist (M3 agonist):**
- Bethanechol
- Neostigmine

**5HT3 blocker:**
- Ondansetron

Antibiotic having prokinetic action: Macrolide

acting on motilin receptor

of small intestine cause diarrhea.

Among Macrolide - max. prokinetic

Erythromycin

Drug used in Anti cancer / Radiation - drug induced vomiting

**5HT3 antagonists:**
- Ondansetron M/C QE - Headache
- Granisetron
- Tropisetron
- Dolasetron → QT prolongation
- Palonosetron → Highly selective 5HT3 antagonist
  
  Long acting (T1/2 = 40h±)

Website: http://mbbshelp.com
WhatsApp: http://mbbshelp.com/whatsapp
Supportive drug: For better efficacy

Ondansetron $\rightarrow$ $D_2$ blocker $\rightarrow$ BZD, Steroid mixed

- Domperidone
- Dexamethasone
- Methylprednisolone

Antiemetic belonging to Cannabinoids

- Nabiximol $\rightarrow$ Antiemetic + Appetite stimulant
- Dronabinol

2-3 days after chemotherapy $\rightarrow$ Late phase Vomiting

T/t
- Aprepitant (oral)
- Fosaprepitant (i.v.)

Neurokinin 1 antagonist

Palonosetron

IBS
T/t of Constipation dominant IBS:

- Magnesium hydroxide
- Methyl cellulose
- Lactulose syrup $\rightarrow$ Also useful for Hepatic encephalopathy

- Tegaserod $\rightarrow$ 5HT4 antagonist
- Prucalopride

- Lupiprostone $\rightarrow$ CLC-2 (Type-2 chloride channel activator)
Linacotide (Guanulate-cycase-C activator)

Cystic fibrosis transmembrane conductance regulator Activator (CFTR activator)

Cofelemer - Inhibitor of CFTR

USE - HIV drug induced diarrhea.

Antibiotic used for t/t of constipation in IBS:
Neomycin (Orally) -> For t/t of Hepatic encephalopathy
Rifaximin -> Pre-op Bowel Sterilization
Probiotics.

Rifaximin:
Useful for:
1. IBS
2. Hepatic encephalopathy
3. Traveller's diarrhea
4. Pseudomembranous colitis.

# For t/t of opioid induced constipation:
Methyl naltrexone (S/C)
Alvimopan (Oral)

Diarrhea in IBS:
5-HT3 antagonist for t/t of diarrhoea in IBS:
Alosetron
Ramosetron
Cilansetron

Alosetron - Rarely cause dangerous problem
It cause Ischemic colitis
So withdrawn
- But if use—give e great caution & Informed consent.
  - Only in female

Other drugs for diarrhea:
  Cholestyramine resin

Opioid for diarrhea:
  Loperamide
  Diphenoxylate + Atropine \(\Rightarrow\) Control addiction.
  Codeine.

For I\(\text{I}^\text{t}\) Abdominal pain:
  Anticholinergic drugs / Muscle relaxant
  Domperidone / property.

Cholecystokinin antagonist:
  Lerglumide / Inhibits GI motility
  Loxiglumide
  Useful for IBS (diarrhea)
BRONCHIAL ASTHMA

- Methylxanthines - Aminophylline, Theophylline → Bronchodilator
  
- MAO - Adenine antagonism → Lead to seizures
  
- Non-selective PDE inhibition

Side effect: 
- Nausea & vomiting
- Headaches
- Gastric discomfort

Proposed mechanism:

Diuretic → A1 receptor antagonism

Epileptic seizures → A1 receptor antagonism

Cardiac arrhythmias → PDE3 inhibition

# M3 Blocker → Bronchodilator

β2 agonist → M1c for acute Asthma

Leukotriene antagonists:

- Arachidonic Acid
  
  ↓ 5-lipoxygenase

  LTA4

  ↓

  LTB4

  ↓

  BLT

  LTA4

  ↓

  LTC4

  \[\text{Cysteine-\text{LT}_{2}}\]

  Receptor

  ↓

  LTD4

  \[\text{Cysteine-\text{LT}_{4}}\]

  Receptor

  ↓

  LTE4

  \[\text{Cysteine-\text{LT}_{6}}\]

  Receptor
Lipoxygenase Inhibitor
Zileuton

→ Not used 600g Hepatitis

Leukotriene antagonist:
- Zafirlukast
- Montelukast
- Pranlukast

Chronic therapy cause - Churg Strauss Syndrome

Headache
Eosinophilia
Vasculitis

For t/t: Mepolizumab
(IL-5 antagonist)

Mast cell stabilizers:
- Sodium cromoglycate
- Nedocromil
- Ketotifen (Additional Antihistaminic property)

Monoclonal antibodies:
- Omalizumab → IgE antibody agonist.
  → s/c, Hypersensitivity

Newer drug - Reslizumab
Mepolizumab (IL-5 antagonist)
PDE inhibitors:

- **Methyl xanthines**
  - PDE I, II, III, IV
  - Asihua

- **Cilomilast, Rofumilast**
  - PDE IV
  - Asihua

- **Apresmilast**
  - PDE IV
  - Active Psoriasis arthritis

- **Aminimone, Milrinone**
  - PDE III
  - CCF

- **Sildenafil, Vardenafil**
  - PDE V
  - Erectile dysfunction

- **Tadalafil**
- **Pentoxiphylline**
  - Non-selective
  - PVD

- **Cilastazol**
  - PDE III
  - PVD

- **Vinpocetine**
  - PDE I, Vasodilator
  - Parkinson
  - Alzheimer's ds.

Expectorants:

- **Mucolytics**
  - Carbocysteine
  - Methyl cysteine
  - Erabisteme
  - Bromhexane
  - Dorsane alpha
  - N-acetyl cysteine

Cough suppressant:

- Codiene
- Phol codiene
- De xitromethorphan
Antihistamines

1st Generation  2nd Generation

→ Antihistaminic + Anti-Cholinergic action

Use:
- Allergic conditions
- Insect bite
- EDS
- Motion sickness

1st Generation Drugs:
- CPM (Chlorphenarnamine Maleate)
- Promethazine (Most sedative, Highest anticholinergic)
- Diphenhydramine
- Cyclizine
- Meclizine (Useful for Sea sickness)
- Cyproheptadine (Antihistaminic + Anticholinergic + Antiserotonergic action)

Appetizer, Useful in Migraine
- Cause Serotonin Syndrome
- Hydroxyzine (Antihistaminic + Anti-anxiety)
  - produces metabolites - Cetrizine
- Doxepin → Given topically (for itching)
  - TCA - Atopic dermatitis, Lichen simplex
- Cinnarizine (H1, H4, M + 5HT2)
  - Use in Vertigo
  - Betahistine (Histaminergic drug)
2nd Generation drugs:

- Terfenadine → Causes QT prolongation
- Astemizole → Withdrawn
- Ebastine → Still available

- Fexofenadine
- Cetirizine (Metabolite of Hydroxyzine)
- Levocetirizine
- Azelastine (Maximum topical, nasal spray)
- Marezastine
- Terivastin

- Loratidine (longest)
  - Active form: Desloratidine
  - Rupatidine (Platelet-activating factor antagonist)

- Topical antihistamines:
  - Azelastine — Nasal spray
  - Olopatadine — Nasal spray,
    → Ophthalmic drop
  - Mast cell stabilizing — Oral

- Alcaftadine, Epinastine — Eye drop.

- H3 antagonist / inverse agonist:
  - Pitolisant (Tepo reefsant) → Orphan drug
  → T1/2 of Narcolepsy
Prostaglandins

PGE₁:
- Misoprostol:
  - Useful for T/t gastric ulcer (NSAID induced)
  - Used for abortion
  - Teratogenicity → Meesius Syndrome
- Alprostadil
  - Vasodilator
  - Useful for Erectile dysfunction (Given injectable)
  - Useful for maintain patency of ductus arteriosus.

PGE₂:
- Dinoprostone
  - Uterine contracting agent
  - Useful for abortion.
- Eprostil
  - Useful for t/t of Gastric ulcer.
- Risprostil

PGF₂α:
- Carprofest
  - USE: Post partum Hemorrhage (PPH)
- Dinoprost
  - USE: Uterine contracting agent for abortion.

![Latanoprost](Image)
- USE: Glaucoma
- Iris pigmentation
- Tranosprost
  - Causes Unoprostone
  - Use: via Uveoscleral route
  - Hypertrichoses
  - by promoting drainage of eyelash
PGI₂: Prostacyclin
   Epoprostenol - Useful for 1° pulm HTN
   Treprostinil
   Beroprost
   Iliprost

Drug used for 1° pulm HTN:
   1. Inhaled NO - Vaso dilator
   2. CCB (Nifedipine, Diltiazem)
   3. PDE5 blockers → Sildenafil, Tadalafil
   4. Endothelin receptor blocker → Bosentan
   5. Direct guanylate cyclase inhibitor → Riociguat
   6. PGI₂ → Epoprostenol
      Treprostinil
      Beroprost
      Iliprost
   7. New drug → Selexipag (Prostacyclin receptor agonist)
      → Useful for 47% of 1° pulm HTN
   8. Rho kinase inhibitor → Fasudil
NSAID

Blocks both

COX-1  COX-2

Aspirin:
- Analgesic
- Anti-inflammatory
- Prevent Colonic & rectal cancer
- All are property of all NSAID.

Aspirin + Nicotinic acid \(\Rightarrow\) Prevent flushing.

C/I - in t/t viral fever in children \(<12\) yrs.
- Cause Reye's syndrome.
  - Liver damage
  - Encephalopathy
  - Febrile illness

M/C s/e of aspirin & other NSAID:
- Gastric ulcer

Non-selective COX Inhibitor
- Indomethacin
  - Anti-inflammatory
  - Use: Frontal headache
  - Closure of ductus arteriosus
  - Bartter's syndrome
Phenylbutazone
- may cause bone marrow suppression

Ibuprofen - safe in children

Mefenamic acid - useful in dysmenorrhea

Piroxicam - longest acting NSAID

Preferable COX2 inhibitor:
- Nimelide
  ➔ Cause severe hepatotoxicity in children (Unsafe)
- Nabumetone
- Etodolac
- Meluxicam

Highly selective COX-2 inhibitor:
- Rofecoxib
- Celecoxib ➔ Risk of developing HTN & CCF
- Valedoxib
- Etoricoxib
- Parecoxib
- Lumbroxib

Cox-3 blocker
- Paracetamol
  ➔ Causes liver toxicity

Other analgesic: Other than NSAID & opioids:
- Ziconotide (Conotoxin)
  - N type CCB
  - Intrathecal given
For anti-inflammatory action of Aspirin → 300-600 mg
aspirin required & cause \( \text{HCl} \) acid.
\& > 3 mg → Gastric perforation.

Nefopam – Annie uptake inhibitor
\( \text{Na}^+ \text{ channel blocker} \)

Cannabimex – Cannabinoid
\( \rightarrow \) USE – Cancer pain

Entonox – \( \text{N}_2\text{O} + \text{O}_2 \)
\( \rightarrow \) for painless labour.

Drug useful for t/t of Gout:

**Acute Gout:**
Give NSAID or Steroids or, colchicine

Colchicine \( \rightarrow \) Acting by disruption of microtubule
\( \rightarrow \) Neutrophil drunken walk.
\( \rightarrow \) Diarrhoea (Bloody)
Unsafe in RF

NSAIDs → Naproxen
Endomethacin
Sulindac
\# Aspirin is C/I for gouty arthritis.

Drug used for chronic gout:
Xanthine oxidase inhibitor:
Allopurinol
Febuxostat
6-Mercaptopurine.
Uricosurics:

Probenecid (Unsafe in RF)
Sulfapyrazone
Benzbromaronone
Lesinurad.

Other drug having uricosuric actions are:
Losartan
Fenofibrate
Amlodipine

Newer drug:
For aggressive control of Gouty arthritis
> Give intravenously
  • Rasburicase causes rapid metabolism
  • Pegloticase of uric acid.

Newer drug for T/t of RA:
Normal – Cytokine balance

Pro-inflammatory = Anti-inflammatory cytokines

TNFα, IL-1, IL-6

TNFα blocker:

Infliximab (i.v)  Test
Before giving TNFα blocker
TB should be ruled out
PPD test

Immune suppressant
Enanercept (s/c)
Adalinumab (s/c)
Golimumab (s/c)
Certolizumab (s/c)
- All are unsafe in Hepatitis B virus infected pt.

Analogue of Interleukin 1 (IL-1) Receptor Antagonist: ANAKINRA

IL-6 blocker:
- Tocilizumab
- Sarilumab

Newer drug - Rituximab (CD20 receptor antagonist)

Targeting against CD30/86 Receptor
- Abatacept
- Ocrelizumab
- Tofacitinib – JAK 1 & 3 blocker

Use – RA

- Leflunomide

Inhibit dihydro orotate dehydrogenase
SLE – Hepatotoxic
C/I – Pregnancy
ANTI CANCER DRUGS

Cell cycle:

\[ M \rightarrow G_0 \rightarrow G_1 \rightarrow S \rightarrow G_2 \rightarrow M \]

DNA synthesis:

- G1 (40%) → Minor development take place.
- S-phase → DNA synthesis
- (39%) By Topoisomerase II enzyme
  Folic acid, Purine, Pyrimidine
- G2 (19%) → Extra development take place
  By Topoisomerase
- M (2%) → Multiplication

Drugs acting on G1 phase:
- L-Asparaginase (enzyme)
- Steroids

- L-Asparaginase
  - Origin from E.Coli (Naturally occurring)
  - Useful for all
  - SE - Hemorrhagic pancreatitis
  - Hypercoagulation
  - No significant Myelosuppression.
  - Thrombomelbic Complications.
Drugs acting on S-phase:
- Anti-metabolites
  - Etoposide
  - Teniposide

Drugs acting on G2 phase: Topoisomerase-1 inhibitors
- Camptothecins < Irinotecan - Chelino unwrapping property.
  - Topotecan
  - Ye - Diarrhoea.
    - (Dose related toxicity)

- Bleomycin (Anticancer + Antibiotic)
  - All anticancer + antibiotics are C-cycle non-specific except Bleomycin.

Drug inhibiting mitosis:
- Vinca alkaloids - Vinblastine, Vinorelbine
- Taxanes - Paclitaxel, Docetaxel, Cabazitaxel

- Newer drug - Ixabepilone > Useful for Breast Ca.
  - Eribulin

For HER2 +ve Breast Ca - Trastuzumab
For Her1 or HER2 - TK Blocker - Lapatinib.
Newer drugs in Cancer therapy:

**Tyrosine Kinase inhibitor (TKi's):**

- Tyrosine Kinase Receptor - EGFR (HER-1)
- VGFR
- PDGFR

**TKi's acting EGFR blocker:**

- Gefitinib - Useful for T1E of Metastatic Small Cell lung Ca.
- Erlotinib - Also useful for Pancreatic Ca.
- Afatinib

DOC: Gemcitabine

SI/E - Dysmorphic eyelashes (Erlotinib)

**VGFR blocker:**

- Sorafenib - Useful for RCC, HCC
- Sunitinib - Useful for RCC, GIST
- Lenvatinib - Useful for DTC

**PDGFR blocker**

- Imatinib - DOC for CML
  - Useful for GIST (C-kit)
  - 1st gen. TKi

  - due to alteration of C-kit - Resistance
  - T1E of Resistance CML
  - **Dasatinib** - 2nd gen. TKi
  - **Nilotinib**

**Multi-targeted TKi:**

- Vandetanib - Useful for Medullary Ca Thyroid
  - Target against EGFR & VGFR
- Axitinib - Targeting against VGFR & PDGFR
- Pazopanib - Useful for RCC
# TRASTUZUMAB → For HER-2 +ve Breast Ca.

# LAPATINIB → Against HER-1 & 2 +ve Breast Ca.

# All the TKi are taken orally.
Common S/E - GI toxicity
(Nausea, Vomiting, Diarrhoea)
Any drug block EGFR causes HTN.

Monoclonal antibodies (MABs)

\[
\text{TRASTUZUMAB}\uparrow
\]

Target → Source

\(Tu\) = Tumor
\(Zu\) = Humanised
\(Li\) = Lowering
\(Xi\) = Chimerical (Non human ex. Mice)
\(Ci\) = Target circulation
\(Vi\) = Virus

\[
\text{Basiliximab} - \text{Target against IL-2}
\]
\[
\text{ABCiximab} - \text{Target against GP2B3A}
\]
\[
\text{Pallizumab} - \text{Target against RSV}
\]

\[
\text{Trastuzumab} -
\text{Target against HER-2 receptor}
\text{Useful for HER-2 +ve Breast Ca.}
\]

# Most of MAB given by i.v. infusion

Specific S/E → Cardiomyopathy
Infusion reaction
Rituximab:
Target against CD20 on B-cell.
Useful for B-cell lymphoma
Other uses: C = CLL

H = Hemolytic anemia
I = Idiopathic Thrombocytopenic Purpura (ITP)
N = NHL (Non-hodgkin Lymphoma)
A = Arthritis (RA)
M = Myasthenia Gravis.

M/e S/E = PML

Bevacizumab: Target circulation.
Target against VEGFR
Useful for Metastatic colorectal CA (i.v.)

M/e → 5FU
Useful for RCC & Diabetic Retinopathy.

S/E = HTN

Newer drug: RAMUCIRUMAB
- Target against VEGFR
- Useful for Gastric Cancer.

Brentuximab
- Target against CD30 on B cell.
- Useful for Hodgkin lymphoma.
Omalizumab - Target against IgE → USE: Bronchial Asthma (BA)
Resilizumab ] - Target against IL-5 → USE: BA
Mepolizumab ]
Denosumab - Target against RANK-L → Osteoporosis.
Eculizumab - Target against C5 → Paroxysmal nocturnal hemoglobinuria.
Evolocumab ] - Target against PCSK9 → Lipid lowering.
Alirocumab ]
Ibalizumab - Target against HIV (entry inhibitor)

Macular degeneration (MD)

Dry type
less blood supply

Wet type
Age related MD (ARMD)

Drugs useful for Wet type MD:
Photodynamic therapy
VERTEPORFIN - i.v.

VEGF inhibitor:
Bevacizumab ] - Subretinal inj.
Ranibizumab ]
Pegaptanib
Afibercept
Drug for Vitreomacular degeneration:
- Ocriplasmin (Newer drug).

- Bull's eye Retinopathy - Caused by Chloroquine.
- Crystalline Maculopathy - Caused by Tamoxifen.

- Field of Vision defect - Vigabatrin.
- Whirl-like pattern - Already done.

- Kayser-Fleischer ring - Wilson's ds (Ceruloplasmin deficiency).

Chelating Agents:
- Metal $T/↑$
- Copper
- Penicillamine (SLE, optic Neuritis)
- Trienline
- Zinc sulphate (Safest)
- Potassium Sulfide

- Hepatitis or Cirrhosis
  - Zinc
  - $→$ decompensation

- Mild - Moderate hepatic decompensation
  - Trienline $+ Zn$

- Neurological or Psychiatric symptom
  - Triethylenemelamine $+ Zn$

- For maintenance in pregnancy & children
  - Zinc
**Metal**

**Lead**
BAL

**Arsenic**
BAL
C/I in Iron & Cadmium poisoning.

**Mercury**
BAL

**Iron**
Desferrioxamine
Desferiprone
Desferroxamine.

# DOXORUBICIN

S/E - Cardiomyopathy

Antidote for Doxorubicin poisoning - Desferroxamine.

Anti-metabolites:
Anti cancer + Immunosuppressive.

Drug acting against folic acid:

Meloflaxate

Pemidexate - Useful for Mesothelioma

Trimelizate - NSCLC

Pralatexate - For T-cell lymphoma.

Meloflaxate:

\[ \text{N} \quad \text{DHPA} \xrightarrow{\text{DHFR}} \text{THPA} \]

MAO: Meloflaxate actively penetrate into cancer cell
it inhibit DHFR, ultimately inhibiting DNA synthesis, So stop S-phase of cell cycle.

# Resistance due to allelism/mutation of DHFR.
Specific antidote - Folic acid or Leucovorin antagonist.

# Folic acid can't be given in Renal failure.

GLUCARPIDASE - Newer drug useful for the treatment of Methotrexate toxicity in a patient with impaired kidney function.

USES OF MTX: Anticancer:
- DCC for Choriocarcinoma
- Useful for Osteosarcoma

Immunosuppressant:
- RA (DMARD, low dose 7.5 mg/wk)
- Psoriasis
- Long term therapy.

C = Chorio CA
A = Abortion
N = NHL
C = Chronic C
E = Ectopic pregnancy
R = RA.

S/E - Myelosuppression (M/C)
- Alopecia
- Mucosal damage (GI toxicity)
- Liver damage (on chronic therapy - in RA)
  → Undergo LFT
  Crystalluria
  → Lithotripsy & Alkalization.

Website: http://mbbshelp.com
WhatsApp: http://mbbshelp.com/whatsapp
Antibiotic causing Crystal
Ciprofloxacine (Alkaline)
Sulfonamide (Acetic)

Antiviral
Indinavir → HIV
Causin Crystal Acyclovir

C/I of MTX - Pregnancy.

Purine Anti metabolites:
6 - Thioguanine
6 - Mercaptopurine
Fludarabine → Doc - cell
also useful for Cladribine → Doc - hairy cell leukemia
Multiple Sclerosis Pentostatin

6 - Mercaptopurine:
6 - Mercaptopurine
\[ \rightarrow \text{HGPRT enzyme} \]
6 - Thioctic Acid

Cause of Resistance - Deficiency of HGPRT enzyme
(Lesch-Nyhan Syndrome)

6 - MP normally undergoes excretion (metabolism)
by HGPRT.
If we give Xanthine oxidase inhibitor - ↑ plasma level
of 6MP.

When we give Allopurinol the 6MP
reduce the close 50-75% of 6MP.
Drugs useful for Multiple Sclerosis (MS):

Disease modifying drugs:
- Interferon Beta 1A & 1B
- Glatiramer Acetate
- Natalizumab (α4β1 integrin) (iv once in 2 months)
- Teriflunomide (oral)
- Dimethyl fumarate
- Cladribine (oral)
- Alemtuzumab (Antibody)
- Milotuzumab (Anti-cancer + Antibiotic)
- Tefgalimod (oral)
- Dalfampridine (oral)
- Prolacitin
- Pyrvinium Pamoate
- Pregabalin

Teriflunomide:
- Useful for Lambert Eaton Syndrome
- Useful in MS in improving walking
- Derivative of Leflunomide
- Use in pregnancy & MS

Pyrazinamide Antibiotics:
- Cytarabine (Cytosine arabinoside)
- Capricitabine ( cause cerebellar ataxia)
- 5Fu
- Gemcitabine (Doc for Pancreatic Ca)
- Hydromorphone
- Levamisole

Capacitabine (cause hand foot syndrome)
Gemcitabine - Myelosuppression
Fell-like symptom
Very potent radio sensitizer.
Doe for Pancreatic Ca

Drug causing Hand foot Syndrome:
Capecitabine
5-FU
Doxorubicin
IL-2
Pemerezhed.

Anti-cancer Antibiotics:
Actinomycin D (Dactinomycin)
⇒ Causes Radiation recall phenomenon.

Doxorubicin - Anthracyclines
[Protect spectrum ⇒ Doxorubicin]
⇒ Inhibit Topoisomerase II

Mitoxantrone
⇒ may cause blue colour fingernails, sclera & urine

Mitomycin
 Bleomycin
Mithramycin (Plicamycin)
⇒ Useful for hypercalcemia

Doxorubicin:
- Causes dilated Cardiomyopathy (DCMP)
- Doxorubicin is in presence of iron form free radical injured myocardium

⇒ Trentaloxane + Alpha tocoherol (vit-E)
⇒ Chelator ⇒ antioxidant
Mitomycin:
- Useful for urinary bladder Ca.
  Usually Intravesical therapy: BCG
  For BCG resistance - Mitomycin Valrubicin
- Useful for laryngo-tracheal stenosis.
  due to Anti-fibroblastic action.

Bleomycin:
  Cell cycle specific acting on G2 phase of cell cycle.
  M/C S/C - Pulm. fibrosis.

Bleomycin hydrolase is not seen in lung.
  so large accumulation of Bleomycin in lung.

Type I pneumocytes - Necrosis/destruction
Type II " - Hyperplasia/ Metaplasia.

# Anticancer drug & No myelosuppression:
  Vincristine -> Cause Peripheral neuropathy.
  Bleomycin
  Asparaginase cause Pancreatitis
  Hypercoagulation
Acylating agents:

Busulfan

[Nitrosourea → Lomustine]  
Semustine  
Carmustine  
Delayed myelosuppresast.

Highly lipid soluble

Useful for:

Temozolamide → also for Melanoma.

Streptozocin (Chemical Pancreatectomy).

Chlorambucil (USE: CLL)

Cyclophosphamide, Ifosfamide

Melphalan (Use for Multiple myeloma)

Procarbazine, Vincristine.

Thiotepa

Mechlorethamine.

→ Cause skin vesicant

 Procambazine -

• Disulfiram like reaction

• Among the acylating agent Procambazine & Melphalan cause secondary cancer.

Cyclophosphamide - less secondary cancer.

• MAO inhibitory action

 Drugs for Multiple myeloma:

Melphalan

Thalidomide

Lenalidomide

Bortezomib (Proteasome inhibitor)

g→ DOC

→ Punch out lesion.
Cyclophosphamide (Anti-cancer + Immunosuppressive):
- Prodrug.
  In liver it forms Aldophosphamide
  Phosphoramido Acrolein (Toxic)
  mustard

DOC for Wegner's granulomatosis:
M/c SE - Hemorrhagic cysts
  → Due to Acrolein

Antidote - MESNA
Supportive drug - Formalin
  N acetyl cysteine
  Carboxprost (PGF2α agonist)
  USE:
    Paracetamol poisoning
    Radiocontrast
    Nephrotoxicity
    Mucolytic

Cyclophosphamide cause < SLDH
  Cardio-toxicity.

Ifosfamide:
  Active form - Acrolein
  ↓ Antidote
    MESNA

# Drug Q1 in Melanoma - LEVODOPA
Drugs for Multiple myeloma:
- Temozolomide
- BRAF V600E inhibitor - Vemurafenib
- Dabrafenib
- Tuvacafenib

Newer drug - Nivolumab
- Opelimunab

Aleleucin - IL2
- ULE: RCC, Multiple Myeloma

Busulfan:
- Used for CML
- S/E - Pulm. fibrosis
- Adrenal insufficiency (Addison's)
  - Hyperpigmentation

# All alkylating agent action - N7 Guanine Residue
# All "are cell cycle non specific"

S/E of alkylating agent - Venocclusive ds of livers

(Budd Chiari Syndrome

Minimized by DEFIBROTIDE

- Permanent sterility
Least emetogenic - Vinblastine
Chlorambucil

Cisplatin:
  Highest emetogenic
  S/E - Ototoxicity
    Nephrotoxicity (dose limiting toxicity)
    Neurotoxicity

Antidote - Amifostine

Carboplatin:
  S/E - Myelosuppression

Oxaliplatin:
  S/E - Neurotoxicity
    Pharyngeal paraesthesia

Vincristine:
  S/E - Peripheral neuropathy (Sensory & motor)
    SLADH
    Vesicant

  Advantage - less myelosuppressant
     less nausea

Vinblastine:
  - Myelosuppression

Taxane (Paclitaxel, Docetaxel):
  - Myelosuppression
  - Peripheral neuropathy (Glove & Stock Neuropathy
  - Allergy
Role of hormones in Cancer:
For all premenopausal women with Breast Cancer, the 1st line choice is SERM. If Resistance give SERD.

# For postmenopausal women with ER+ Breast Cancer, give Aromatase inhibitor.

SERM useful for t/t of Breast Ca:
Tamoxifen
Toremifene
Novoxifen
Raloxifene.

Tamoxifen—
Antagonistic action only on ER of Breast → Useful for t/t ER+ve Breast Ca.

Agonistic action on blood vessel

ADR—Hot flushes
Endometrial cancer
DVT
Raloxifene:
Antagonistic action on Breast → So use in BreastCa.

""" Uterus

S/E - Flushing
DVT
Not cause Endometrial Ca.

Aromatase Inhibitors:
Aminogluthethimide (Chemical adrenalectomy)
Formostane
Exemestane
Vorozole
Fadrozole
Letrozole
Anastrozole

Extra information:
SERMs for DUB: Ormeloxifene
(Centchroman)
- Use as Contraceptive pill.
Twice in wk 5 gap of four day - first
3 month later once in a week.

SERMs for Dyspareunia - Ospreoxifene

SERMs for induction of Ovulation - Clomiphene.
SPRM:
- Ulipristal - Emergency Contraceptive (Can take 5 days after
  Coitus)
- Aprotinin
- Terapristone - Useful in Uterine fibroid
  Endometriosis

Prostatic Cancer:
  Becoz of excess androgenic action.

Hypothalamus
  (GnRH) - Pulsatile release
  \( \theta \)
  (60-120 min)

Pituitary
  (Gonadotropins - LH/FSH)
  \( \theta \)

Testes
  PSH \rightarrow\text{ spermatogenesis} \leftrightarrow\text{ Seminiferous cell}
  LH \rightarrow\text{ Leydig cell - Testosterone production}
  \overproduction\text{ Cause Prostatic Ca.}

Drugs \& Testosterone production:
1. GnRH agonist (in continuous manner):
   - Leuprolide
   - Goserelin
   - Buserelin
   - Nafarelin
   - Desoerlin
   - Histrelin
   - Triptorelin
GnRH antagonist:
- Genirelix
- Cetorelix
- Abarelix
- Degarelix

Comparison:

<table>
<thead>
<tr>
<th>Agonist</th>
<th>Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial flare up</td>
<td>No initial flare up</td>
</tr>
<tr>
<td>Histamine release</td>
<td>No histamine release</td>
</tr>
</tbody>
</table>

Testosterone cause:
- Hot flush
- Loss of libido
- Impotence
- Sarcopenia (Reduce muscle mass)
- Osteoporosis
  - Supplement Vit D
  - Bisphosphonates
  - Denosumab

Drugs having histamine releasing property:
- a-Tubacurarine
- Morphine
- Dexseroxamine
- Amphotericin B
- Polymyxin B
- Vancomycin (Red Man Syndrome)
Anti androgen:
- Flutamide
- Nilutamide
- Bicalutamide
- Enzalutamide
- Cyproterone
- Abiraterone.

Thalidomide:
- Sedative + Anti-emetic
- S/E - Phocomelia
- GI - Pregnancy,
  Category X.

- It has Anti-cancer + Immune modulation property.
  Indication: Multiple myeloma
  ENL
  Aplastic anemia
  SLE.

Isomer < R (Therapeutic use & Teratogenicity)
S (Sedation)

M/c S/E - Constipation
  Severe peripheral sensory neuropathy.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Antidote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mexiatrastate</td>
<td>Folinic acid</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Deoxazoxane</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Mesna</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Amifostine</td>
</tr>
<tr>
<td>Palifermin</td>
<td>Myelositis</td>
</tr>
</tbody>
</table>

**Drugs useful for HT neuropenia:**

- Colony stimulating factor (CSF)
  - rG-CSF
  - GM-CSF
  - Filgrastim
  - Sargramostim
  - Pegfilgrastim
  - Mlgr支持

**Drug useful for Anemia:**

- Epoetin (Recombinant - Erythropoietin)
- Darbepoetin
- Peginesatide (Erythropoietin Receptor Stimulant)

Drug useful for Thrombocytopenia:

- Oprelvekin (IL-11)
- Thrombopoetin

Neuer [Romiplostim(®) for ITP → by plasma exchange

- Drug [Eptremboag 
  → Oral]
Anti-emetic useful for Anticancer Eft:
Already done.

Immuno suppressant:
- Cyclosporin
- Tacrolimus (FK506)
- Sirolimus
- Everolimus

Drugs inhibiting synthesis of IL-2:
- Cyclosporin → Calcineurin inhibitor.
- Tacrolimus (FK506)

Both cause Nephrotoxicity
- Tacrolimus > Cyclosporin

Tacrolimus - Macrolide comp.

Common problem - Nephrotoxicity (Dose limiting).
- Neurotoxicity
- Hepatotoxicity
- DM
- Diarrhea
- Alopecia

Specific use of Cyclosporin - Hypertrophy of Gum

Hirsutism

HTN → T/t: Nephrotoxic,
Hyperkalemia
Hypokalemia → Cisplatin, Amphotericin B.

m-Tor blockers:
- Sirolimus
- Everolimus

Azathioprine:
- Purine anti-metabolite
- Immunosuppressant action (CMI)
- No anti-cancer action.

USE — RA
- IBD (U. colitis)
- Organ transplantation

S/E — Myelosuppression

Azathioprine converted in body → 6-Mercaptopurine

Metabolism by Xanthine Oxidase.

Immunostimulants:
- Cytokines
- Aleutokinin (Recombinant IL-2) (for REC & MM)
- Interferon γ (Chronic granulomalous disease)
- BCG Vaccine (Intra vesicle - Urinary bladder Ca)

Valrubicin, Mitomycin
Laryngotracheal Stenosis
Levamisole (Anti helminthic property)  
- Immuno stimulant.

IL- modulators:

Analogue of IL-1 receptor antagonist: Anakinra
  (USE - RA)

IL-3 & 4 antagonist: Pitrakirna
  (USE - BA)

Analogue of IL-2: Aldebulimab
  (USE - RCC, Malignant Melanoma)

IL-2 receptor blocker: Basiliximab
  Daclizumab.

IL2 + Diphtheria toxin: Denilukin diphthera
  USE: Cutaneous T cell lymphoma

Histone deacytalase inhibitor
  Vorinostat
  Romidepsin

IL-5 blocker: Resilizumab (Severe eosinophilia, BA)
  Mepolizumab
  USE: Hypereosinophilic syndrome
  Churg Strauss syndrome.

IL-6 blocker - Toceлизumab
  USE - RA

IL-1, 6 antagonist - Steroids

Analogue for IL-11 - Oprolukin
  USE - Thrombocytopenia.

IL-17 Blocker - Ilekizumab
  USE: plaque psoriasis.
  Brodalumab
IL 12 & 23 - Ustekinumab

\[ \text{USE} \rightarrow \text{Psoriasis} \]

- Apatant, Lexipafant, (PACBlocker) - For Acute Pancreatitis
- Iviqimod - For Cystic Fibrosis
- Iviqimod - For Chondromatosis (HPV)
- Alefacept - For Psoriasis
- Resiquimod - For HSV
- Lu-Dotatate - For Midgut endocrine tumor
- Anagrelide - For Essential thrombocytosis
- Belimumab - For SLE
- Defibrotide - For Budd Chiari Syndrome
- Hydroxyurea - For Sickle cell anemia
- Olapalib - For ovarian Cancer
  - Acting by Poly ADP ribose polymerase (PARP) inhibitor.
- Palbociclib, Amebiciclib, Ribociclib - For Breast Cancer
  - CDK 4/6 (cyclin dependent kinase) inhibitor
- Edoxavone - (Antioxidant) for ALS

- Mycophenolate mofetil - Inhibit inosine monophosphatase (Immunosuppressant) dehydrogenase
- Penlo statin - Inhibit Adenosine deaminase
- Vorinostat - Inhibit histone deacetylase
- Leflunomide - Inhibit dihydroorotate dehydrogenase
  - Toxicity caused
- Cyclosporine - Nephrotoxicity
- Leflunomide - Hepatotoxicity
- Sirolimus - Bone marrow suppression
- Azathioprine - Hypertriglyceridemias
- Muromonab - Cytokine release syndrome
ANTIMICROBIAL DRUGS

Antibiotic acting by inhibiting cell wall synthesis:

\[ \text{N-acetyl muramic acid} \]
\[ \text{N-acetyl glucosamine} \]
\[ \text{Acid peptides} \]

Step 1:

The first enzyme initiating cell wall synthesis
- Alanine ligase/Racemase

\[ \text{Cycloserine} \]
\[ \text{2nd line drug of TB} \]
- Bacteriostatic
- SPE - Psychosis

Step 2:

Enolpyruvate-Transf. \( \rightarrow \) Fosfomycin
\[ \text{For UTI} \]
- Cause severe diarrhea
- So not in use.

Step 3:

Dephosphorylation of Baclofenol \( \rightarrow \) Bacitracin
- Polypeptide group of Antibiotic
- USE: Wound/skin healing
  (Given topically)

Step 4:

Elongation of peptide chain
\[ \text{\( \rightarrow \) help of Transglycosylase} \]
\[ \text{\( \rightarrow \) Vancomycin} \]
- If Alter \( \rightarrow \) VRSA
Step 5:
Cross linking of elongated peptide chain
by Transpeptidase \( \rightarrow \) Beta Laclain
(Penicillin binding protein) (Penicillin)

If alleviated \( \rightarrow \) MRSA
(Resistence)

Inhibiting Antibiotics acting by protein synthesis:

Aminoglycosides \& Tetracycline binding \& 30s Ribosome \& inhibit protein synthesis.

Drug acting on 50s Ribosome \& inhibit protein synthesis:

Chloramphenicol \( \xrightarrow{\text{Resistance due to enzyme degradation}} \) Acetyl transferase

Linomycin

\( M = \) Macrolides

\( L = \) Lincosamides (Clindamycin)

\( S = \) Streptogramines

MLS resistance \( \rightarrow \) Methylation of 50s ribosomes.

Tetracycline resistance \( \rightarrow \) Development of efflux pump.

Tetracycline - Resistance to efflux.

Due to enzymatic degradation \( \rightarrow \) Aminoglycosides

Resistance

Do not develop [Amikacin resistance - Nefilmicin]
# All antibiotics acting by inhibiting protein synthesis are bacteriostatic except for Aminoglycoside and Streptogramins.

**Antibiotics**

**Penicillin:**

- Commercial source - *Penicillium chrysogenum*.

- Acid Resistant: Orally.
  - V = Penicillin V
  - O = Oxacillin
  - D = Dicloxacillin
  - R = Cloxacillin
  - A = Ampicillin/Amoxicillin

- Penicillinase resistant:
  - C = Cloxacillin
  - O = Oxacillin (hepatitis)
  - N = Nafcillin (Neutropenia)
  - D = Dicloxacillin
  - U
  - M = Meloxicillin (Interstitial nephritis)

- β-Lactamase inhibitor:
  - Clavulanic Acid + Amoxycillin
  - Sulbactam + Ampicillin
  - Aztreonam + Piperacillin

- # FDC (Fixed drug combination):
  - Same volume of distribution
  - Or same half-life
Extended spectrum Penicillins:

Aminopenicillins → Enterococci

Beta-lactamase

Amoxicillin → Causing diarrhea due to incomplete absorption.

Carboxy penicillins (Enteroaggregates + pseudomonas)

Carbenicillin → Cause bleeding due to disturbing platelet.

Ureidopenicillins

(Enteroaggregates + pseudomonas + Klebsiella)

Azlocillin

Piperacillin

Mezlocillin

# Aminopenicillins are 1/3 in Infectious mononucleosis;

# 2nd line Anti TB 1/1 in HIV pt & TB: Thiacetazone

#

# OCP + Amoxicillin → Risk of OCP failure

# Skin Rash:

- Jarisch Herxheimer Reaction
- Secondary Syphilis
- No treatment
- Only symptomatic - Aspirin & Sedation

Atypical beta-lactam antibiotics:

Carbapenems:
- Imipenem
  - Broadest spectrum
  - Shortest acting
  - Rapidly undergo inactivation by
    Dehydropeptidase 1 enzyme.
- Add Cilastatin

S/E - Seizures

- Meropenem
- Ertapenem

Monobactams:
- Aztreonam
  - No cross reactivity
  - Useful for Aerobic gram-negative infection
    Similar to aminoglycosides

# for Anaerobic infection - Metronidazole

- Clindamycin
  - S/E - Pseudomembranous
    Colitis
Cephalosporins

Fourth generation drugs:
- Cefepime
- Cefpirome
- Cefclidin

Fifth generation drugs:
- Ceftrabiprole
- Ceftraroline

USE - MRSA
Community Acquired Pneumonia

Glycopeptide Antibiotics: Vancomycin

- IV of GM +ve infection
- Oral Vancomycin - Useful for Pseudomembranous colitis
- IV Vancomycin - DOC for MRSA
  - Caused by Clostridium difficile
  - Caused by 3rd gen. Cephalosporins

Newer drug for PMC - Rifaximin
- Fidaxomicin

ADR of Vancomycin: Red Man Syndrome (M/c)
- Ototoxicity
- Nephrotoxicity
Other Glycopeptide antibiotics:

- Telavancin
- Dalbavancin - longest acting (6-10 days)

Drugs used for T/c MRSA/VRSA:

VRSA → Linezolid

- SLE - Thrombocytopenia (M/C)
- Ophthalmic & peripheral neuropathy
- Also used for MDR TB
- MAO inhibitory property

VRSA → Streptogramine

- Quinupristine : Dalbopristine = 70:30
- SLE - Infusion reaction
- Arthralgia

VRSA → Daptomycin

→ causing myopathy

VRSA → Tigecycline

- Given in tetracycline
- Resistant to efflux
- Excretion - Bile
- Safe in Renal failure
Sulfonamides:

- Sulfasalazine
  - On GIT split in 2 components
- Sulfapyridine
  - 5 amino salicylic acid.
  - Useful for RA.
  - Useful for ulcerative colitis

ADR – Allergy

- Oligospermia (in male) → Infertility.

Topical – Sulfacetamide – For eye drop.

- Silver sulfadiazine – Has anti-pseudomonal action
- Metronidazole → CA inhibitory action
  - Metabolic acidosis.
  - Useful for fungal keratomycosis.

- Sulfadoxine + Pyrimethamine → For 7/1 of Malaria.

- Toxoplasmosis:
  - For 1/t: Sulfadiazine + Pyrimethamine + Folic acid.

Safest drug for 1/t of Toxoplasmosis in pregnancy
- Spiramycin (Macrolide)

- Cotrimoxazole: Sulfamethoxazole (400mg) + Trimethoprim (80mg).
- Cotrimoxazole DS: Sulfamethoxazole (800mg) + Trimethoprim (160mg).

DOC: Pneumocystis carinii pneumonia.
Aminoglycosides.

For 1st of TB → Streptomycin (1st line drug)
   Kanamycin  
   Apramycin  [2nd line drug]
   Amikacin

- All are ionised molecule so not absorbed via orally.

Streptomycin – DOC for Plague (mass prophylaxis)
   Doxycyclin

Also useful in – TB, Tularemia.

Aminoglycoside useful for Pseudomonas:
   T = Tobramycin
   A = Amikacin
   G = Gentamycin

Among Cephalosporin
   - Ceftazidime
   - Cefoperazone

For severe Pseudomonas infection – TOC is combination of Cephalosporin & Aminoglycoside.
   eg: Ceftazidime + T or A or G.

Last option for severe resistance case of Pseudomonas
   → Polymyxin B.
Paraamomycin -
Oral - Amoebiasis
i.v. - Kala-azar.

Neomycin:
- generally parenterally
- Oral - Gut sterilization
- Hepatic encephalopathy

# Aminoglycoside follow conc dependent killing pattern
so given OD dose.

# Beta lactamin follow Lin's dependent killing
so given TDS / QID.

Post antibiotic effect of Aminoglycoside:
Even though the drug level is lower than the MIC value still produce action.

# Common s/e of Aminoglycoside:
- Nephrotoxicity
- Ototoxicity
- Neuromuscular block (Neomycin)

Among the Aminoglycoside - Gentamycin highly
Tobramycin / Nephrotoxic
Neomycin
least Nephrotoxic - Streptomycin
Maximal deafness caused by - Kanamycin
(Amikacin) Max
Neomycin

Deafness 1st high frequency sound \(\rightarrow\) lastly low frequency sound.
First damage base of hair cell \(\rightarrow\) lastly apex of hair cell.

Vestibular damage - Streptomycin
Gentamycin
Equal - Tobramycin
Least - Netilmicin

Quinolones:

MOA: inhibits DNA Gyrase in Gram -ve
inhibit Topoisomerase IV in Gram +ve.

Route of Excretion - Kidney.
\(\rightarrow\) So not given in Renal failure.

Excretion via liver - Prefloxacin
Trovafloxacin \(\checkmark\) (Safe)
Moxifloxacin

Ciprofloxacin:
DOC for Typhoid
\(\rightarrow\) Currently 1st line choice
- Ceftriaxone (iv)
\(\text{(in children/ Pregnancy)}\)
or in Ciprofloxacin Resistance.
Drug interaction of theophylline:
Ciprofloxacin is microsomal enzyme inhibitor, When given with theophylline, theophylline level ↑ in plasma which causes convulsion/seizures.

Withdrawn Quinolones:

- Trovafloxacin – liver toxicity
- Grepafloxacin – QT prolongation
- Gatifloxacin – unpredictable glucose profile
- Only systemic use was withdrawn
  Eye drop available

Clinafloxacin – Phototoxic
available
- Sparfloxacin (longest action)
Quinolones – Lomefloxacin

Macrolides:

Clarithromycin:
Useful for – MAC
  H. pylori
  Leprosy

Azithromycin:
Useful for – MAC
  Gonococci / Syphilis / Chancroid
  Chlamydia
  Legionella
  Campylobactor jejuni
Common SE of Microlites:
- GI toxicity → due to motilin
- Hearing Impairment
- Hepatitis
- Cholestalic jaundice caused by erythromycin estolate
- Erythromycin estolate

Drug interaction:
- All microlites are microsomal enzyme inhibitor
  Erythromycin → Maximal microsomal enzyme inhibition
  Azithromycin → Least microsomal enzyme inhibition
  # Azithromycin may cause QT prolongation

# Erythromycin aggravates pyloric stenosis.

Tetracycline

Tigecycline -
Given i.v.
Useful for MRSA/VRSA
Excreted by bile, so safe in kidney failure.

Doxycycline -
Excreted via bile, safe in RF

Demeclocycline -
Phototoxic
Causes DI
Useful for SIADH.
Minocycline:
Used for leprosy.
\[ \rightarrow \text{Rifampicin} \]
\[ \text{Oxytetracycline} \]
\[ \text{Minocycline} \]

\# Vestibular toxicity.

\# All tetracycline having risk of causing elevation of IOT called pseudo tumour cerebri.

\# Outdated tetracycline may cause Fanconi syndrome.

\# Tetracyclines are DOC for:
1. Rickettsia infection
2. Chlamydia infection
3. Lymphogranuloma venereum (LGV)

Tetracycline used as prophylaxis of:
- Cholera
- Brucellosis
- Plague

GI in pregnancy — Fulminant hepatic failure
Baby < Bone & teeth problems.

Most safest antibiotics in pregnancy -> β-lactam
Cephalosporin & Penicillin > Azithromycin
Antibiotic & Colour association:
- Grey baby - Chloramphenicol
- Yellow baby - Sulfonamide
- Red man Syndrome - Vancomycin
- Discoloured teeth - Tetracycline
- Coffee coloured teeth - Nitrofurantoin
- Loss of red/green perception - Ethambutol
- Reddish black - Clofazimine

Tuberculosis

Anti-tubercular drugs:
- Isoniazid (INH):
  - Activated via the help of INH A-gene & catalase peroxidase.
  - MOA: Inhibiting mycolic acid synthesis.
  - Undergoes metabolism by acetylation.

SLE - Hepatotoxicity (MC)
  - Due to formation of Acetyl hydrazine
  - Neuropathy
    - Slow administration of Vit B6
      - Prophylactically - 10mg/day
      - Neurotoxicity - 100mg/day
  - Memory impairment
  - Psychosis
  - Shoulder hand syndrome
  - SLE
  - Cheese Reac
It is micro enzyme inhibitor.

Doesn't require dosage adjustment in pts with renal disease.

Useful for prophylaxis of TB.

Max CSF penetration.

Isoniazid → derivative of isoniazid.

Used for elevating mood.

Rifampicin:
- Activated to help of rep B gene.

MOA: Inhibit DNA dependent RNA polymerase.

- Excretion via bile & feces
  
  So safe in RF.

Side - Non serious:

Reddish orange colour (Urine, Sweat & tears)

Staining of contact lenses.

Serious:

Hepatitis

Respiratory syndrome

Hemolytic

Purpura.

It is microsomal enzyme inducer.

pt of HIV Receiving antiviral drug, if we use Rifampicin for TB, liver failure occurs.

Alternate drug → Rifabutin → Causes Pseudo jaundice.
Pyrazinamide:
- Act by inhibiting mycolic acid synthesis.

S/E - Hepatotoxicity
Hyperuricemia

- No drug interaction bcz neither microsomal enzyme inducer or inhibitor.

- Undergoes renal route of excretion so need dosage adjustment in RF pt.

Ethambutol:
- Bactericidal

MOA: Inhibiting Arabinogalactan synthesis.

S/E → optic neuritis
- Loss of ability to differentiate red from green
- Supplement of HydroxycoBALAMINE (Vit B12)
- Hyperuricemia

- Undergoes renal route of excretion
  - Need dose adjustment in RF pt.

Streptomycin:
- CL in pregnancy bcz cause permanent deafness in children.
TB in liver as pt:
Avoid - Isoniazid, Rifampicin, Pyrazinamide
Safe - Streptomycin, Ethambutol

TB in a Real pt:
Avoid - E, P, S
Safe - R, H

Newer drug for MDR-TB:
Bedaquiline:
Inhibit mycobacterial ATP synthase
Good absorption
Cross resistance to clofazimine
May cause QT prolongation
→ Cardiotoxicity

Delamanid
Pretomanid
Inhibit Mycolic acid synthesis

Safegolid - Derivative of linezolid

Anti TB drug causing:
1. Hypothyroidism – Ethionamide (also used for leptospirosis)
2. Psychosis – INH, Cycloserine

Antibiotic useful in MAC = Azithromycin,
Clarithromycin
REC Regimen (R = Rifabutin, E = Ethambutol, c = Clarithromycin)

4. Uveitis - Rifabutin

Anti-leprosy drug.

- ATT drugs → Rifampicin
  Ethionamide

Other drug → Clofazimine
Dapsone

- Antibiotic useful for leprosy - Ofloxacin
  Minocyclin
  Clarithromycin

Dapsone - Sulphonamide

Uses of Dapsone –
  DOC for dermatitis herpetiformis.
  # Inj. Ac dapson (im) one dose acting for 3 months.
  GE - Allergy (M/C)
  Hemolytic Anemia.

Clofazimine -
  Bacteriostatic
  Anti-inflammatory property.
  Also useful for lepra reaction.

GE - Reddish black skin discolouration
  Dermatological.
Leprosy Reaction:

Type I - Cell mediated immunity to M. leprae.

Type IV hypersensitivity.

T&O - Prednisolone (Steroid).

Type II - Immune complex deposition.
  Type III Hypersensitivity.

T/t - Steroids
  Clofazimine
  Chloroquine

Virology.

Drugs useful for HIV:

Fusion inhibitors:
  Enfuvirtide
    - Given SC
  S/F injection site reaction
    Pneumonia (Rare)

CCR-5 inhibitor:
  Maraviroc - FDA approved
  Aplaviroc [under trial]
  Vicriviroc
NRTI's (Nucleoside Reverse Transcriptase inhibitor):

Zidovudine (M/C)

- Myelosuppressant (Macrocytic Anaemia)
- Lipodystrophy → due to mitochondrial DNA polymerase

Didanosine

- Pancreatitis

Stavudine - Worst drug:

- S/E - Severe Neuropathy
- Lactic acidosis
- Lipodystrophy

Abacavir (Rule out HLA B5701 allele, MI, Safe in RF)

Zalcitabine

- Also useful for HBV

Lamivudine - Best drug (No serious adverse effect)

- Emtricitabine

Tenofivir - Causes GIT toxicity, Fanconi’s syndrome.

- Really a nucleotide inhibitor.

NNRTI:

1st generation:

- Efavirenz
- Nevirapine, NVP
- Delavirdine

2nd gen:

- Etravirine
- Rilpivirine

Common S/E - Skin Rash
- Stevens Johnson Syndrome
- Toxic epidermal necrolysis
Nevirapine
  \( \rightarrow S/E - Hepatitis (LFT) \)
Efavirenz
  \( \rightarrow S/E - Neuropsychosis \)

Integrase inhibitor:
  Raltegravir
  Elvitegravir \( \rightarrow \) Best drug.
  Dolitegravir

Protease inhibitor:
  Saquinavir \( \rightarrow \) Best tolerated
  Indinavir \( \rightarrow \) Nephrolithiasis
  Nelfinavir
  Rifabavir \( \rightarrow \) Powerful microsomal enzyme inhibitor \( \text{(CYP3A4)} \)
  \( \rightarrow \) Called Booster.
  Amprenavir
  Fosamprenavir
  Atazanavir \( \rightarrow \) Not cause lipodystrophy.
  Lopinavir.
  \( \rightarrow \) may cause intracranial hemorrhage.
  Tipranavir \( \rightarrow \) Sulfonamide
  Darunavir

Common S/E - Hyperglycemia
  Fat redistribution
  Hyperlipidemia.
# Tezamorelin - GHRF

- Reduce abdominal fat in HIV & lipodystrophy.

CROFLEMER - CFTR inhibitor

- Use - HIV induced diarrhoea.

Malanin inhibitor.

- Bevirimat (Under Trial)

# HAART / CART (Highly active antiretroviral therapy):

- 2 NRTI + 1 NNRTI
- NRTI + NNRTI + PI

Triple drug therapy

- To prevent drug resistance.

NACO 2011 → Zidovudine + Lamivudine + Nevirapine.

CMV (Cytomegalovirus) → Cause Retinitis.

- Ganciclovir (DOC)

- Use for 5/3E - Myelosuppression.

- Valganciclovir
- Fomivirsen
- Foscarnet
- Cidofovir
- Maribavir

Foscarnet:

- Useful for HSV (resistant to Acyclovir)
- CMV (Ganciclovir resistance)

ADR - ARF

- Penile ulcer.
Cidofovir – Useful for Reap* papillomatosis.

Drug for Herpes simplex Virus

Acyclovir – For HSV
ADR – Renal Failure

Docosanol – Viral entry inhibitor
given topically

Famciclovir – Prodrug
Active form – 6-deoxy penciclovir.

Drug Useful for Hep B:
Injection are < IFN-α
PEG-INFα

Oral agents:
1st line – Entecavir
Tenofovir (ant-HIV drug)

2nd line – Lamivudine
Adefovir
Telbivudine
Drugs for HCV:

Commonly use PEG INFα plus ribavirin.

Sofosbuvir - Given orally
Renal excretion
Causes bradycardia

Other drugs -

Telaprevir
Boceprevir
Simeprevir
Grazoprevir
Elbasvir

Daclatasvir
Velpatasvir
Ombitasvir

Ledipasvir
Virmididine - (Under trial)
**Antifungal Drugs**

- **Membrane Active Antifungal Agents**

  - Squalene → Lanosterol → Ergosterol → Fungal cell mem
  - Squalene
  - 14 α-demethylase
  - Epoxidase
  - Cyp 2450
  - Terbinafine
  - Azoles
  - Polyene antibiotics
  - Amphotericin B + Ergosterol → Forms a pore in fungal cell
  - Act on fungal cell wall
  - Destroy fungus

  **Amphotericin B**
  - Usually given as a slow iv infusion
  - Very well distributed all over body
  - Poorly distributed in CNS

  **ADR** - Infusion related reaction (Fever, chills)
  - Nephrotoxicity (Dose limiting toxicity)
  - Hypokalemia
  - Hypomagnesemia
  - Anemia
  - Seizure

  To avoid Nephrotoxicity - Give Hydration

**Newer formulation**:
- ABCD (Colloid dispersion)
- ABLC (Lipid complex)
- Less systemic toxicity
Drug interaction - Be careful while using Amphotericin B with other nephrototoxic agents like -

- Aminoglycosides
- Vancomycin
- Cyclosporin.

Azoles + Amphotericin B: Mutually antagonistic

\[ \text{Inhibit Ergosterol} \quad \text{No action on Ergosterol.} \]

Terbinafine - Squalene epoxidase inhibitor.

5-Flucytosine - Antimetabolite acting on fungal nucleus.

5 Flucytosine + Amphotericin B => Synergism.

Grasofulvin -
- Acting by inhibiting microtubule.
- Useful for dermatophytosis
- Orychomycosis.
- Given orally.
- Microosomal enzyme inducer
- Disulfiram like reaction.

Newer Antifungal - Echinocandins
eg: Caspofungin
- Micafungin
- Anidulafungin.

MOA - Acting on \( \beta-1,3 \)-glucan synthase inhibitor.

Uses - Candida & Aspergillosis.
**Nikkomycin** - Inhibit Chitin Synthesis
Useful for Candida & Aspergillosis.

**amoebiasis**

Lumen Amoebiasis  
- Diloxanide furoate  
  (Flutivate)  
  Extraintestinal & Extra intestinal
- Nitazoxanide  
  Use in Cryptosporidiosis
- Quinodochlor → Cause Subacute myelo optic neuropathy (SMO)

- Tofotinol

- Paromomycin (oral) → i.v. for kala-azar.
- Tetracyclines

Extraintestinal:
Chloroquine.

Both:
- Metro nimdazole
- Tinidazole
- Secnidazole (Single dose) - M/e GE - Nause, Vomitting
- Ornidazole
- Itraconidazole (less neurological ADR)
- Emetine
- Dehydroemetine.
Guinea Worm: For complete removal of worm
Doc - Niridazole.

Helminthiasis

Nematodes  Ceptodes  Nematodes
Doc - Praziquantel  Doc - Praziquantel  Doc - Albendazole

Except - Fasciola hepatica  Except - Echinococcus  Except - Ochoecera


Ova

Ivermectina

Albendazole (hepatotoxic)  Strongyloides  Scabies

W. bancrofti

Leishmaniasis

Kala-azar  Cutaneous  Mucocutaneous

For all forms  Sodium  Glucoconate

(Doc) Amphotericin B (in India)

Pentamidine (ENAC Helier)

Paromomycin  Fluconazole  Amphotericin B

Oral: Miltefosine  Metronidazole

Sulfaquine
Trypanosomiasis.

African
- Sleeping sickness.
  T. gambiense
  & T. rhodesiense

South American
- Chagas de
  T. cruzi

DOC
- Benzimidazole
  Nifurtimox.

Early hemolymphatic stage
Suramin (doc)
Pentamidine

Late - CNS stage
Malarsoprol (doc)
Eflornithine

Anti-Malarial drug
Chloroquine (M/c)
  → Very large apparent Vol of 100-1000 L/kg.
Uses:
R - Rheumatoid Arthritis
E - Extra-intestinal Amebiasis
D - DLE (Discoid lupus erythematous)
L - Lepra reac
I - Infectious mononucleosis
P - Photogenic reac
M - Malarias
G - Giardiasis

- Safe in Pregnancy.
S/E → GI toxicity (Nausea & Vomiting)
CVS (Bradycardia, HTN)
Chronic therapy cause Bull’s eye maculopathy. Lives damage.

Mefloquine:
For infusion & prophylaxis of Malaria.
Long half-life.
Single oral dose.
S/E - Neuropsychosis.

If combine with Halofan, Quinine - Risk of QT prolongation.

HALOFANTRINE, LUMEFANTRINE:
Absorption ↑ in food.
Halofantrine - more Cardiotoxic.

Lumefantrine + Artemether ⇒ ACT

# Primaquine
- Vivax curative
For G6PD deficiency → Cause hemolytic anemia.
Can in pregnancy.

Artemisinin:
Artemunate
Fast acting drug
Artemether
Short acting - Recurrence more
Arteether

For extending duration of action combine with Mefloquine.
Indications:

- Multidrug resistance Malaria
- Cerebral Malaria
- Not indicated for chemoprophylaxis of Malaria

S/E - GI toxicity (M/C)

CVS → QT prolongation, 1st degree AV block.

Hematology → Reversible leucopenia.

WHO approved Combiné therapies:

FDC = Artemether / lumefantrine

  Artesunate + amodiaquine

  Artesunate + SP

  Artesunate + Mefloquine

ACTs

Unsafe Antimalarial drug in Pregnancy:

Halofantrine

Tetracycline/ Doxycycline

Primiquine