1. GENERAL PHARMACOLOGY

- **Pharmacokinetics**
  - Study of how the drug moves inside the body
  - Body's action on the drug
- **Pharmacodynamics**
  - The effect produced by the drug after binding to its receptor
  - Drug's action on the body

PHARMACOKINETICS/ADME STUDY

- **Absorption:** Drug crossing cell membranes (e.g., GI tract) to enter the blood
- **Distribution**: Movement of the drug from the blood to various body organs
- **Metabolism:** Chemical change converting a drug into a water-soluble form
- **Excretion:** Removal of water-soluble drugs via urine, sweat, or saliva
  - **Elimination:** Combined process of Metabolism + Excretion

Primary Pharmacokinetic Parameters

- Bioavailability (BA): Calculated during Absorption
- Volume of Distribution (Vd): Calculated during Distribution
- Clearance (CL): Calculated during Metabolism and Excretion

Secondary Parameters

- Calculated from primary parameters
- Includes
  - Loading dose
  - Maintenance dose
  - Half-life

Mechanism of Drug Absorption

Simple /Passive Diffusion

- Most common method for drug transport
- Requires lipid solubility (cell membranes are phospholipid-based)
- Lipid-soluble drugs:
  - Non-ionizing and non-polar
  - Cross cell membranes easily
  - Absorbed orally and crosses the Blood-Brain Barrier (BBB)
- Water-soluble drugs:
  - Highly polar and strongly ionized
  - Do not cross cell membranes. Not absorbed orally; does not cross the BBB
  - Examples: Vancomycin, Heparin (the strongest acidic substance), and Aminoglycosides (Streptomycin, Gentamicin)

Weak Ionic Drugs

- Most drugs are weak acids or weak bases
- pKa: The pH at which a drug is 50% ionized (water-soluble) and 50% non-ionized (lipid-soluble)
- Henderson-Hasselbalch Equation:
  - pKa= pH + log10 (Ionized/Non-ionized)
  - Change in pH by 1 → Ionization changes by 10%
- Example:
  - Aspirin (pKa= 3.5)- Weak acidic drug
  - Morphine (pKa= 8.5)- Weak basic drug
  - If aspirin is placed in media of 3.5, it becomes 50% ionic and 50% non-ioninc
  - Absorption Rules
    - → Same Medium → Drug becomes non-ionized/lipid-soluble → ↑ Absorption.
      - Acid + Acidic Medium (e.g., Aspirin in Stomach)= More acidic
      - Base + Basic Medium (e.g., Morphine)= More basic
    - → Opposite Medium → Drug becomes ionized/water-soluble → ↓ Absorption

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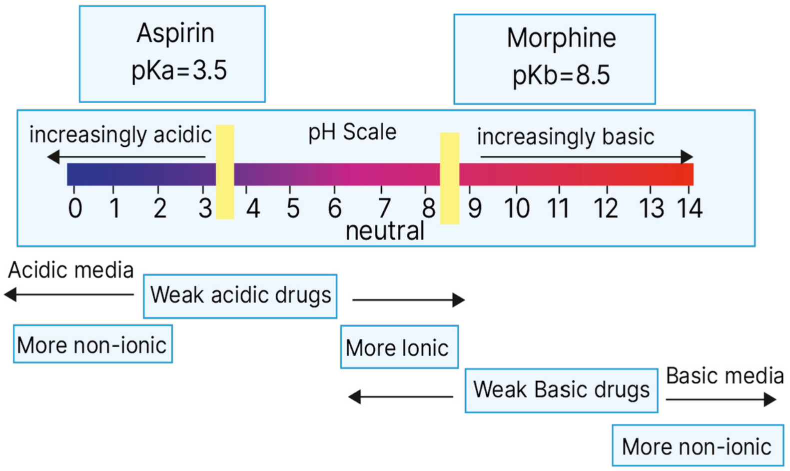
      - Acid + Basic Medium
      - Base + Acidic Medium



ION Trapping

- Aspirin (pKa 3.5) enters stomach cells (acidic medium → non-ionized)
- Inside the cell (pH 7.4/basic compared to stomach) → Aspirin becomes ionized/water-soluble
- Drug cannot cross back out → Ion Trapping occurs
- Result → Gastric/Peptic ulcers
- Treatment: Proton Pump Inhibitors (PPIs) like Omeprazole or Pantoprazole

Other Pathways

- Endocytosis/Pinocytosis→ Botulinum toxin, Vitamin B6
- Filtration→ Subcutaneous Insulin (passes through paracellular spaces)
- Facilitated Diffusion→ Requires a transporter; no ATP used (e.g., 5-Fluorouracil)
- Active Transport→ Requires a transporter + ATP (ATPase) (e.g., Methyldopa, Levodopa)

P Glycoprotein

- Function: Efflux transporter that pumps drugs out of cells
- ABC Protein (ATP Binding Cassette), MDR-1, or MDR-2 (Multi-Drug Resistance protein)
- Impact on Drug Levels

- GI Tract → ↓ Absorption/Bioavailability
- Kidney/Liver → ↑ Excretion
- Barriers (BBB, Placenta, Cancer cells) → ↓ Drug entry → Drug resistance

- Substrate of P-gp: Digoxin
- Modulators:
  - P-gp inducer: Rifampicin (↑ P-gp activity → ↓ Digoxin effect).
  - P-gp inhibitors (QUACK) (increase the digoxin toxicity if combined)
    → Quinidine
    → Verapamil (Verapamil inhibits ABC/P-gp transporters)
    → Amiodarone
    → Clarithromycin/Erythromycin
    → Ketoconazole
- Verapamil inhibits ABC/P-gp transporters
- Cyclosporine inhibits P-gp in the liver → ↓ Bile excretion → Cholestatic jaundice

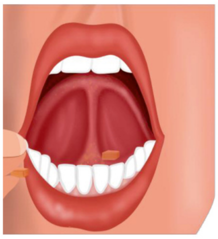
Routes of Administration

Oral Route

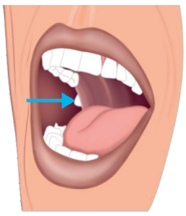
- Absorbed mainly from the small intestine (large surface area) → Portal Vein → Liver → Heart
- First Pass Metabolism (FPM): Liver degrades the drug before it reaches systemic circulation
- FPM → ↓ Bioavailability
- Drugs with High FPM (Not given orally or require high dose):
  - Fentanyl
  - Lignocaine
  - Natural Estrogen (Estrogen patches used instead)
  - Propranolol (high oral dose needed)
  - Morphine
  - Nitrates

Bypassing First-Pass Metabolism

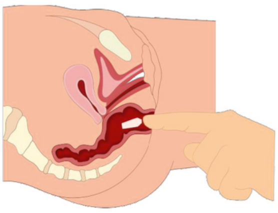
- Sublingual→ Drains to the Superior Vena Cava (SVC) → Heart
  - Fast acting→ Used for acute angina (Sublingual Nitrates)
- Rectal: External hemorrhoidal veins drain to Inferior Vena Cava (IVC) → Heart
  - Example: Rectal Diazepam for febrile seizures in children
- Intramuscular (IM) - Z-Technique:
  - Pull skin down → Inject at 90° → Push skin back.
  - Prevents the drug from leaking into subcutaneous fat and causing staining
  - Used for
    → Iron injections
    → Antipsychotic drugs

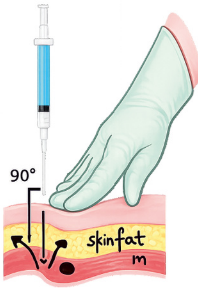


Sublingual

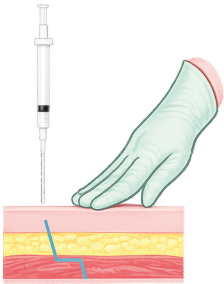


Buccal Route





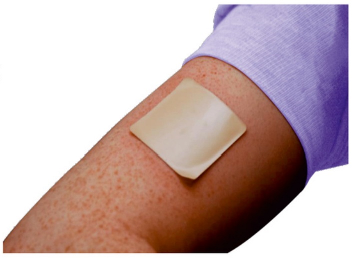
Skin (Subcutaneous, SQ) Injection



Intramuscular (IM) Injection

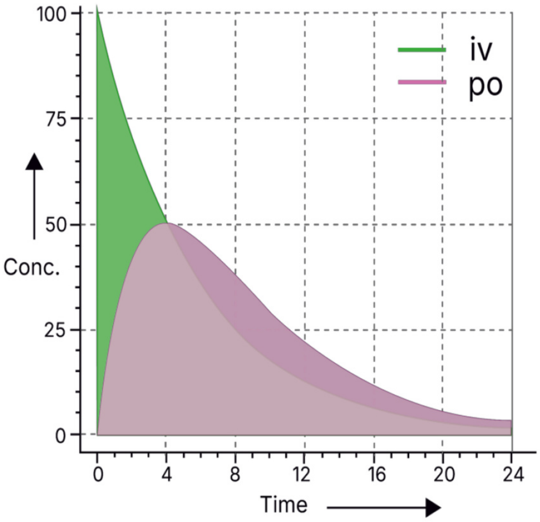
Transdermal Patches

- Long-acting route providing sustained/non-fluctuating plasma levels



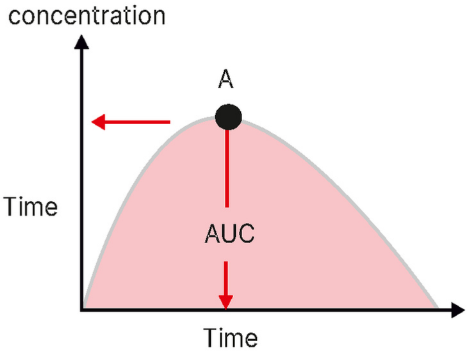
- Sites of Absorption:
  - Maximum: Posterior auricular area (behind pinna/mastoid), Scrotum, Face/Neck
  - Minimum: Palms and Soles (thick skin)
- Clinical Examples:
  - Nicotine: Smoking de-addiction
  - Scopolamine/Diphenhydramine: Motion sickness
  - Nitrate: Chronic angina
  - Clonidine: Hypertension
  - Selegiline: Depression
  - Rivastigmine: Alzheimer's disease
  - Rotigotine: Parkinson's disease
  - Estrogen: Hormone Replacement Therapy (HRT)

Bioavailability

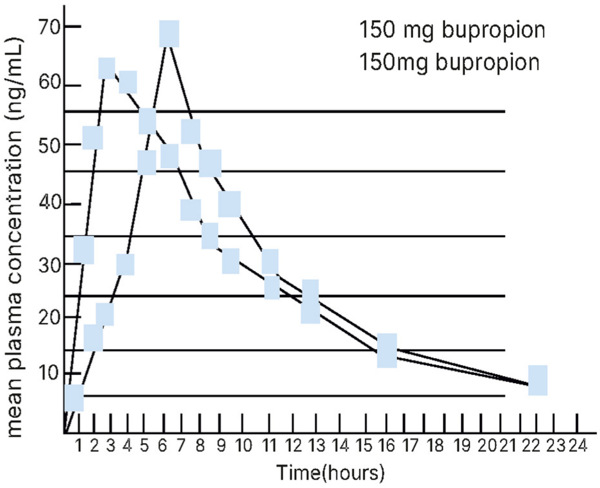


- Fraction of the drug reaching systemic circulation in unchanged form
- Intravenous (IV) BA: Always 100% (Standard)
- Calculation:
  - **F= AUC (Oral)/AUC (IV)**
    - → AUC (Area Under the Curve): Total extent of drug entering the blood
    - → Calculated via the Trapezoidal Rule
    - → No units

- Cmax: Maximum plasma concentration
- Tmax: Rate/speed of absorption



Bioequivalence



- Comparison of BA between different brands of the same generic drug
- Acceptable Variation: 80% to 125%
- Exception: Phenytoin
  - Different brands are bio-inequivalent
  - Brand switching can lead to toxicity; brands should not be changed

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Volume of Distribution

- The movement of a drug from plasma into extravascular organs
- Apparent Volume of Distribution: False/assumed volume based on plasma concentration
- Vd- Volume of plasma (in liters) required to contain a drug in equal concentration as that of plasma

Factors affecting Vd

- ↑ Lipid solubility → ↑ Vd (drug enters fat/organs)
- ↑ Plasma protein binding → ↓ Vd (drug stays in blood)
- Main Determinant: Plasma protein binding (e.g., Warfarin is 99% albumin-bound & highly lipid soluble)
- Pt's Factors
  - Age
  - Gender
  - Pregnancy
  - Liver disease (↓ proteins)
  - Nephrotic syndrome/CKD (protein loss)
  - Hemorrhage, shock

Drug Displacement from Plasma Proteins

- Drugs can displace each other from binding sites, leading to toxicity
- All antiepileptics increase each other's toxicity. E.g., Phenytoin and Valproate
  - Valproate competes for the same Albumin binding sites as Phenytoin
  - Valproate displaces Phenytoin → ↑ Free Phenytoin in plasma → Entry into unwanted organs → Toxicity
- Sulfonamides (cotrimoxazole) cause kernicterus in neonates/3rd trimester?
  - Sulfonamides/Cotrimoxazole displace Bilirubin from Albumin
  - Contraindicated in neonates and third-trimester pregnancy
  - Free Bilirubin crosses the immature Blood-Brain Barrier (BBB) → Brain damage/death (Kernicterus)

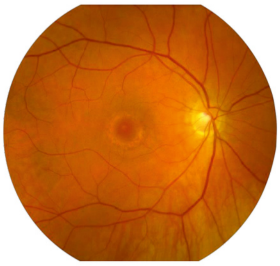
Vd and Hemodialysis

- High Vd / High Protein Bound drugs: Hemodialysis is ineffective because the drug is in the organs or bound to proteins, not free in the blood
- Low Vd / Low Protein Bound drugs: Hemodialysis is effective (drug is free in plasma)

Do hemodialysis	No role of hemodialysis
• **B**arbiturates • **L**ithium • **A**lcohol • **A**spirin (Salicylates) • **T**heophylline	• Amphetamine • Verapamil/Warfarin • Organophospahtes • Imipramine • Digoxin • Amiodarone • Benzodiazepines • Chloroquine

- Chloroquine:
  - Highest Vd (~15,000L); deposits in all organs
  - Retinal Deposits: Deposits in concentric rings or target-like shapes

- Interpretation: The image would show a "Target" or "Bull's eye" appearance on the retina
- Outcome: Bull's eye maculopathy → Permanent blindness



Redistribution

- Seen with highly lipid-soluble drugs like General Anesthetics (e.g., Thiopentone, Fentanyl)
- Process:
  - Drug enters the brain → Patient becomes unconscious
  - Most drugs end their action via elimination (urine)
  - Thiopentone exception: Drug moves from the brain/plasma and gets "redistributed" into fat
- Action of all drugs is terminated by: Elimination into the urine
- Action of Thiopentone is terminated by: Redistribution into the fats

Drug Metabolism/Biotransformation

- Definition: The conversion of a lipid-soluble drug (non-ionic, non-polar) into a water-soluble form (ionic, polar)
- Only water-soluble drugs can be excreted by the kidneys
- MC organ for metabolism is the Liver
- MC organ for excretion is the Kidney

Outcomes of Metabolism

- Active to Inactive: Most common (e.g., action ends)
- Active to Active: Drug remains active after metabolism
- Inactive to active: Prodrugs are inactive drugs and are converted to an active form
- **Active to Active form (Mnemonic: "FAT CP")**
  - Fluoxetine → Norfluoxetine - longest acting antidepressant
  - Allopurinol → Oxypurinol
  - Diazepam → Oxazepam
  - Codeine → Morphine
  - Primidone → Phenobarbitone
  - Spironolactone → Canrenone
  - Inactive to active
- **Inactive to active (Mnemonic: PLASMA CCD)**
  - Prednisone → Prednisolone
  - Levodopa → Dopamine
  - ACE Inhibitors (all ending in 'pril' except Captopril and Lisinopril)
  - Sulfasalazine
  - Mycophenolate Mofetil
  - Acyclovir
  - Carbimazole → Methimazole
  - Clopidogrel
  - Dipivefrine

Hepatic Metabolism

- Lipid-soluble drugs are broken down into smaller parts, then linked with a polar group
- Each broken part is linked with a water-soluble group

Phase 1 /Catabolic:	Phase 2 Reactions

• Drug becomes inactive or active
• A drug is broken into smaller parts
• Includes
  ○ Oxidation
  ○ Reduction
  ○ Hydrolysis
  ○ Cyclization
  ○ Decyclization
• Most drugs undergo oxidation and reduction, carried out by CYP450
• Location: Inside Smooth Endoplasmic Reticulum (SER), AKA microsomes (Microsomal reaction)
	• Drug becomes inactive only
	  ○ Exception: Morphine, minoxidil
	• A water-soluble group is attached to the drug
	• Includes
	  ○ Glucuronide conjugation
	  ○ Glycine
	  ○ Sulfate
	  ○ Methylation
	  ○ Glutathione
	  ○ Acetylation
	• Most drugs undergo Glucuronide conjugation
	• Location: Outside SER (Non-microsomal) (Exception: Glucuronide conjugation is a Phase 2 reaction, but occurs inside the microsomes)

CYP450 Enzyme System

- Shows genetic polymorphism

Substrates

- CYP1A2: Theophylline, Clozapine
- CYP2C9: Phenytoin, Warfarin (Zero-order/Saturation kinetics)
- CYP2C19: Clopidogrel (conversion to active form)
- CYP2D6: Propranolol, Anti-arrhythmics, Haloperidol, Fluoxetine, Codeine
- CYP2E1: Paracetamol
- CYP3A4 (max quantity): Most common; metabolizes >50% of drugs (e.g., statins like Atorvastatin)

Enzyme Inducers ("GRASS")	Enzyme Inhibitors ("COKE" + "IVC")

• Griseofulvin
• Rifampicin
• Anti-epileptics: Phenobarbitone, Phenytoin, Carbamazepine
• Alcohol
• Smoking
• St. John's Wort
	• Cimetidine
	• Omeprazole
	• Ketoconazole
	• Erythromycin
	• Isoniazid
	• Valproate
	• Ciprofloxacin
	• Others
	  ○ Grapefruit juice (Furanocoumarins)
	  ○ Acute Alcohol
	  ○ Ritonavir

- All anti-epileptics are inducers except Valproate
- Chronic alcohol- Inducer
- Acute alcohol- Inhibitor
- Isoniazid inhibits all CYP except- CYP2E1

Significant Drug Interactions

- Rifampicin + OCPs (estrogen): Rifampicin induces CYP3A4 → ↑ Degradation of Estrogen → Contraceptive failure
- "CAT" (Cisapride, Astemizole, Terfenadine) Drugs + Erythromycin/Ketoconazole → Inhibition of CYP3A4 → ↓ Metabolism → Drug accumulation
    - Accumulation → QT prolongation → Torsades de pointes (Fatal arrhythmia)
    - Note: CAT drugs are now banned
- Clopidogrel + Omeprazole: Omeprazole inhibits CYP2C19 → Clopidogrel (prodrug) cannot convert to active form → ↑ Risk of MI and Stroke

Drugs Metabolized by Acetylation

- "SHIP" Drugs: Sulfonamides, Hydralazine, Isoniazid, Procainamide, Dapsone
- Genetic Variation:
    - Fast Acetylators: High NAT enzyme levels (common in Americans)
    - Slow Acetylators: Low NAT enzyme levels (common in Indians/low protein diets)
- Outcome: Slow acetylators → Accumulation of SHIP drugs → Toxicity causing DLE
    - Mechanism: NAT enzyme in the liver is responsible for acetylating drugs

Extrahepatic Metabolism

- Plasma Esterase Metabolism: Certain drugs are metabolized by enzymes in the plasma before reaching the liver
- Key Drugs:
    - Esmolol: Shortest-acting beta-blocker
    - Clevidipine: Shortest-acting Calcium Channel Blocker (CCB)
    - Remifentanil: Shortest-acting opioid
- Pseudo-cholinesterase Metabolism:
    - Succinylcholine: Shortest-acting Skeletal Muscle Relaxant (SMR)
    - Landiolol: A beta-blocker even shorter-acting than Esmolol

Hoffman Elimination

- Spontaneous inactivation of a drug in the body
- Characteristics:
    - Requires no enzymes
    - Requires no organ function (Liver/Kidney)
- Key Drugs
    - Atracurium and Cisatracurium
- Clinical Use: Safe for patients with hepatic or renal failure

Elimination and Excretion

01:03:15

- Elimination is the rate of removal of the drug from the body (mg/min)
- Elimination Process: Metabolism (Liver) → Water-soluble form → Excretion (Kidney/Urine)
- Excretion Routes:

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- MC route: Urine
- Minor: Bile, sweat, saliva, tears, and milk

- Enterohepatic Recirculation
  - Example: Oral Contraceptive Pills (OCPs) like Estrogen
  - Estrogen in Liver → Bile → Intestine → Reabsorbed into Liver via intestinal bacteria
  - Interaction: Antibiotics (e.g., Doxycycline, Ampicillin) kill intestinal bacteria → Estrogen is excreted in feces → Contraceptive failure
- Excretion in Breast Milk ("SMAL" mnemonic):
  - **S**ulfonamides: Displace bilirubin → Kernicterus in neonates
  - **M**ethotrexate: Anti-cancer drug.
  - **A**spirin: Causes Reye's syndrome (liver damage in neonates)
  - **L**ithium
- Urinary excretion
  - Glomerular filtration
    → A passive process
    → High plasma protein binding → ↓ Filtration
    → Podocytes (Glomerulus) are negatively charged → Repel basic drugs → Basic drugs are filtered less than acidic drugs
  - Active tubular secretion
    → An active process using transporters/pumps (requires ATP)
    → OATP (Organic Anion Transport Protein) → Excretes acidic drugs (e.g., Penicillin).
    → OCTP (Organic Cation Transport Protein) → Excretes basic drugs (e.g., Curare/Tubocurarine).
    → P-Glycoprotein → Excretes neutral drugs (e.g., Digoxin)
    → Drug Interaction: Probenecid inhibits OATP → ↓ Penicillin excretion → Penicillin becomes longer-acting

Forced Diuresis

- Principle: Only water-soluble (ionized) drugs are excreted

Forced Alkaline Diuresis	Forced Acidic Diuresis
• Used for Acidic drug poisoning (Aspirin, Paracetamol, Methotrexate, Barbiturates). • Make urine alkaline using Sodium Bicarbonate → Acidic drug becomes water-soluble → ↑ Excretion	• Used for Basic drug poisoning (Amphetamine, Morphine, Atropine, Quinine). • Make urine acidic using Ammonium Chloride → Basic drug becomes water-soluble → ↑ Excretion

Important Information

- Antidote for:
  - Aspiring poisoning- Sodium bicarbonate
  - Amphetamine- Ammonium chloride

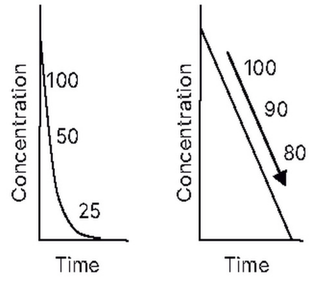
Clearance

- Clearance capacity: The power of the body to excrete out the drug

First-Order Kinetics

- Good clearance capacity

- High clearance capacity (constant fraction removed per unit time, e.g., 100 to 50 to 25 to 12.5)
- Elimination rate is proportional to the plasma concentration
- Half-life is constant
- Most drugs follow first-order kinetics



Zero-order (Saturation) Kinetics

- Low/Poor clearance capacity; easily saturated
- Constant amount removed per unit time (e.g., 100 to 90 to 80 to 70)
- Half-life is proportional to plasma concentration
- Only a few drugs follow zero-order kinetics
- Drugs showing zero-order kinetics(Mnemonic- WHATSAPP)
    - Warfarin
    - Heparin
    - Alcohol
    - Theophylline
    - Salicylates (Aspirin)
    - Phenytoin (Shows mixed/Pseudo-zero order kinetics)
    - Alcohol: Pure zero-order at all doses

Pharmacokinetic Formulas

01:14:10

Loading Dose (I.V)

- **Vd × Target Plasma Concentration**
- Depends on Volume of Distribution (D-D relation)

Maintenance Dose (I.V)

- ***Clearance × Target Plasma Concentration***
- Depends on Clearance

Note: If loading and maintenance doses need to be calculated for other routes, like oral, the formulas need to be divided by bioavailability

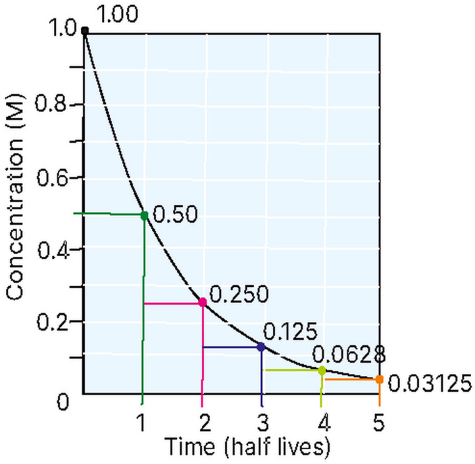
Half Life

- Time required to reduce plasma concentration by 50% after the drug is absorbed
- Half-life is not dependent on absorption

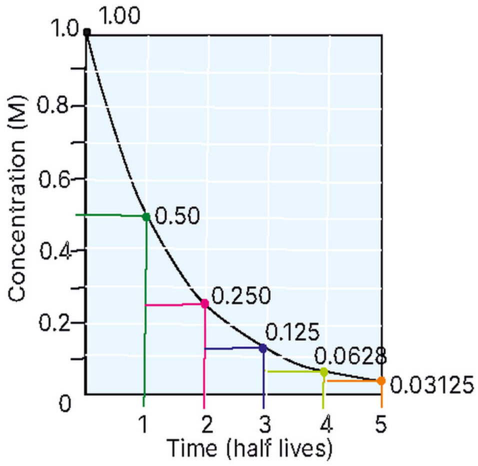
- $T\frac{1}{2} = 0.693\ \frac{Vd}{CL} = \frac{0.693}{0.693}$
    - $K = \frac{CL}{Vd}$
    - K = Elimination rate constant

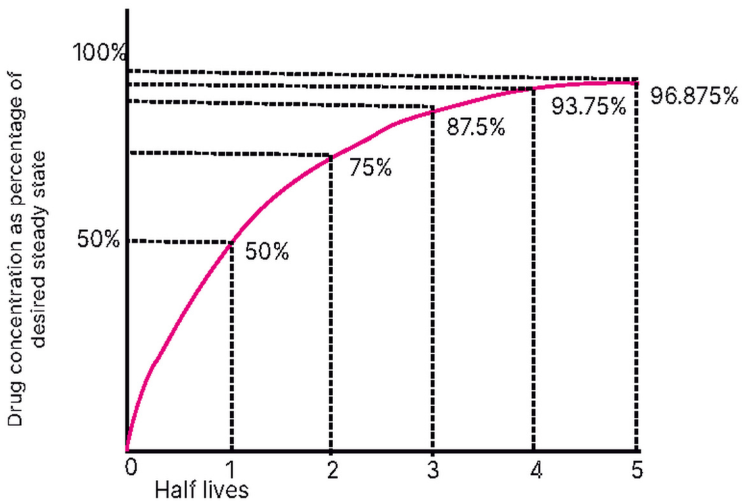
Half life	Plasma conc.	Elimination
0	100	0
1	50	50

2	25	75
3	12.5	87.5
4	6.25	93.125
5	3.125	96.875



- 90% elimination of the drug occurs in 3.3 half-lives
- 95% elimination of the drug occurs in 4-5 half-lives
  - Complete elimination of the drug is assumed if 95% of the drug is removed
  - Exception to this rule- Hit and run drugs
- 100% elimination of the drug occurs in ∞ half-lives





- Steady State Concentration: Reached after 4-5 half-lives of continuous administration
  - The action of the drug starts

Hit and Run Drugs

- AKA suicide inhibitors
- Irreversibly attached to target organs; action continues after the drug is cleared from the blood
- Substrates ("RAMP"):
  - Ritonavir (HIV protease inhibitor; irreversible)

- Aspirin (COX inhibitor; irreversible)
- MAO Inhibitors
- PPIs (e.g., Omeprazole; inhibits H^+K^+ ATPase irreversibly)

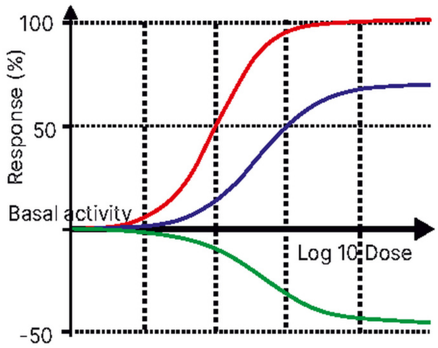
PHARMACODYNAMICS

01:22:20

- Drugs produce an effect when they bind to a receptor
  - Types of ligand- Agonist & antagonist
  - Receptors
  - Effect- measured by DRC

Ligand Types

- Agonist: Produces an effect
  - Full Agonist: 100% (Maximum) effect
  - Partial Agonist: Produces an effect <100%
- Antagonist: Produces no change in basal activity; blocks receptors
- Inverse Agonist: Produces a negative/opposite effect to the agonist



Types of Antagonism

Physical

- Binds an agonist physically to prevent absorption from the GIT (e.g., Activated Charcoal in poisoning)

Chemical

- Directly neutralizes the agonist via chemical bonding
  - Protamine Sulfate (Basic): Antidote for Heparin (Acidic)
  - Chelators: Used in metal poisoning
  - Sugammadex: Neutralizes Vecuronium and Rocuronium

Physiological/Functional

- Binds different receptors to produce opposite physiological responses
  - Histamine (H1; bronchoconstriction) vs Adrenaline (Beta-2; bronchodilation)
  - PTH (Hypercalcemia) vs Calcitonin (Hypocalcemia)
  - Beta-blockers (Bradycardia) vs Glucagon (Tachycardia)
  - Insulin (Hypoglycemia) vs Glucagon/Growth Hormone (Hyperglycemia)
  - Prostacyclin (Anti-platelet) vs Thromboxane A2 (Pro-platelet)

Pharmacological

- Blocks the agonist's own receptor
- E.g., Adrenaline (alpha and beta receptors), Phenoxybenzamine (alpha blocker), propranolol (beta blocker)

Competitive Pharmacological Antagonist

- Competes for the same site; similar structure to agonist; usually reversible
- Surmountable effect- Overcome the effect by increasing the dose of the agonist
- Exceptions (Competitive Irreversible/Uncompetitive): Methotrexate (inhibits DHFR), Organophosphates (inhibit Cholinesterase)

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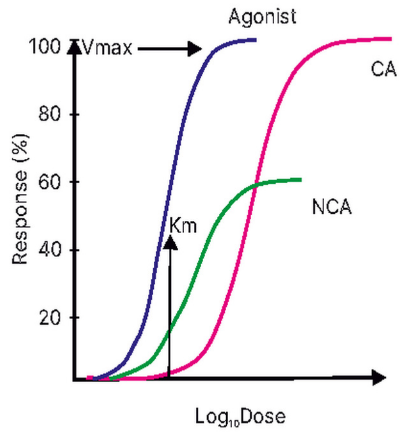
Non-Competitive Pharmacological Antagonist

- Binds allosteric/neighboring site; different structure. Non-surmountable; usually irreversible
- Exception (Non-competitive Reversible): Acetazolamide (inhibits Carbonic Anhydrase)

Dose Response Curve



- Shape: Sigmoid
- Parameters:
  - Vmax: Maximum response/effect produced by an agonist.
  - Km: The dose at which a drug produces 50% of the maximum response.

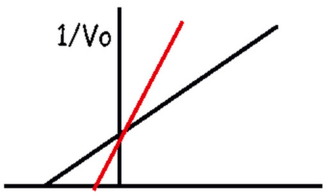
Competitive Antagonism

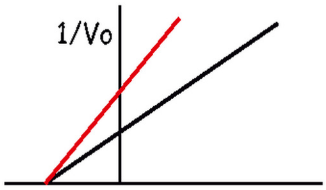
- Increasing the agonist dose can overcome the effect
- Shift: Rightward shift in DRC
- Result: Vmax remains unchanged; ↑ Km (dose required)
- Interpretation in Image: The curve moves horizontally to the right, but reaches the same peak

Non Competitive Antagonism

- An agonist dose increase cannot overcome the effect.
- Shift: Downward shift in DRC.
- Result: Vmax ↓; Km remains unchanged.
- Interpretation in Image: The curve peak is lower compared to the agonist alone.

Line Weaver Burk Plot /Reciprocal Plot





- Shape: Straight line graph
- Axes: Y-axis is Response (1/V); X-axis is Dose (1/K)
- Competitive Antagonism:
  - Lines cross in the plot
  - Vmax is the same for both
- Non-Competitive Antagonism:
  - Lines do not cross
  - They share the same origin point
  - Km is the same for both

Q. True about competitive antagonism is:

a. Vmax is unchanged, but Km increases

b. Vmax is reduced, but Km increases

c. Vmax & Km increases

d. Vmax & Km reduced

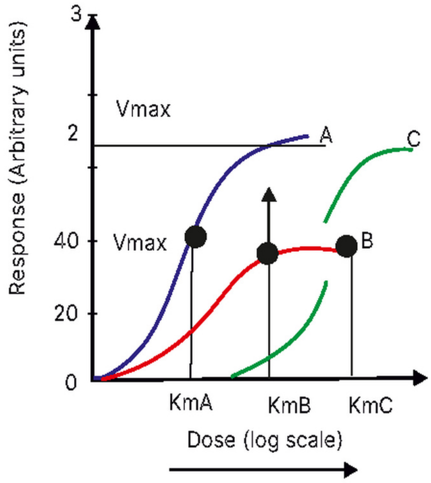
Answer: a

Efficacy and Potency

01:35:30

- Performed on a single individual to check drug response
- Uses a Log-dose of the drug

- Efficacy:
  - Maximum response (Vmax) produced by the drug.
  - Independent of dose.
  - Height of curve → Efficacy
  - Higher curve = More efficacious drug
- Potency:
  - Dose required to produce 50% of maximum response (Km)
  - Depends on the dose
  - Left-sidedness of curve → Potency
  - Drug requiring lower dose (more to the left) = More potent/powerful
- Clinical Selection: Choice of drug depends primarily on Efficacy, not Potency



Quantal DRC

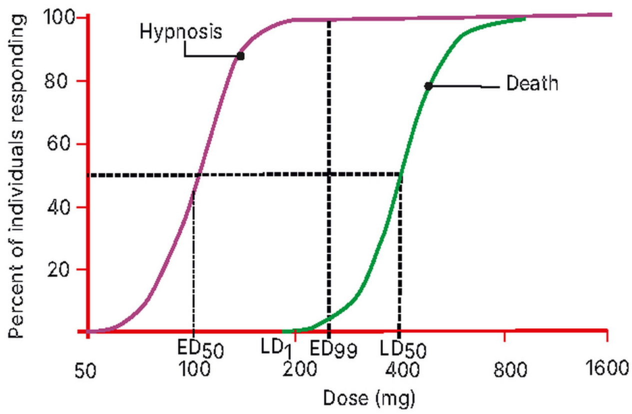
- Measures response in a percentage of the population
- ED50 (Effective Dose 50): Dose producing a therapeutic effect in 50% of the population
- TD50 / LD50 (Toxic/Lethal Dose 50): Dose producing toxic/lethal effect in 50% of the population
- Therapeutic Range: The area between ED50 and TD50, where the drug is beneficial without being toxic
  - Example: Phenytoin therapeutic range is 10-20 mg/dL

Therapeutic Index

- Formula: $TI = \frac{TD\ 50}{ED\ 50}$
- Function: Measures safety margin
- Low value of TI- Unsafe drugs (Narrow TI drugs)

Q. Calculate the Therapeutic index of a drug whose DRC is plotted as shown below:

- LD50= 400
- ED50= 100
- $TI = \frac{TD\ 50}{ED\ 50} = \frac{400}{100} = 4$



Narrow Therapeutic Index

- Drugs are unsafe and require Therapeutic Drug Monitoring (TDM).
- Drugs Requiring Monitoring:
  - "DAT"
    - → Digoxin
    - → Anti-arrhythmics
    - → Aminoglycoside
    - → Theophylline (Asthma).
  - CNS Drugs

→ Lithium (Bipolar)
→ Anti-epileptics
→ Anti-psychotics
→ Tricyclic Antidepressants (TCA)
→ Immunosuppressants→Cyclosporine, Tacrolimus
→ Cancer Drugs→ Methotrexate

Antidotes for Specific Poisoning

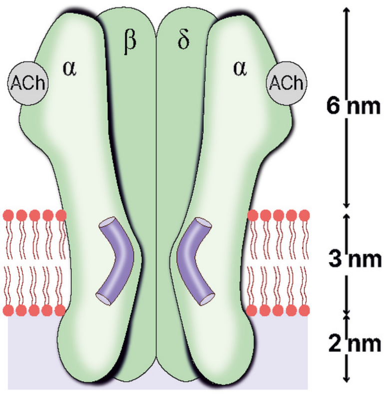
01:43:00

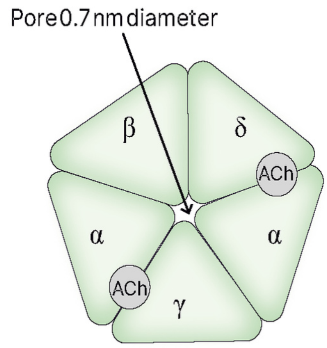
- Digoxin: Digibind or DigiFab (Antibodies against Digoxin)
- Local Anesthetics (e.g., Lignocaine): 20% Intralipid emulsion (traps the drug)
- Aspirin: Sodium Bicarbonate
- Paracetamol: N-Acetylcysteine
- Opioids (Morphine, Fentanyl, Heroin): Naloxone
- Amphetamine: Ammonium Chloride
- TCA: Sodium Bicarbonate
- Organophosphate: Atropine + Pralidoxime
- Carbamate: Atropine (Pralidoxime is not given)
- Atropine (Belladonna, Datura): Physostigmine
- Methanol / Ethylene Glycol: Fomepizole
- Benzodiazepines (Diazepam, Lorazepam): Flumazenil
- Calcium Channel Blockers (Verapamil): Calcium gluconate
- Propranolol (Beta Blocker): Glucagon hormone

Receptor Types

Ionotropic Receptors

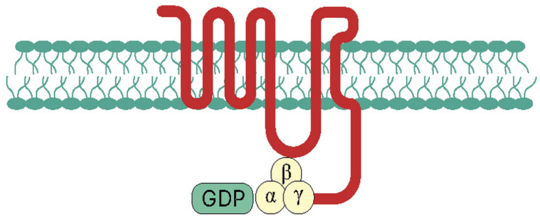
- Shape: Pentameric Rosette (5 subunits)
- Mechanism: Open to conduct ions directly
- Excitatory (Conduct Sodium → Depolarization):
  - Nicotinic receptors (ACh)
  - 5HT3 receptor (Serotonin)
  - NMDA receptor (Glutamate)
- Inhibitory (Conduct Chloride → Hyperpolarization):
  - GABA-A receptors
  - Glycine receptors





G-Protein Coupled Receptors

- Shape: Serpentine, Helical, 7-transmembrane turns
- Mechanism: Tail has a G-protein (GDP-bound) that activates second messengers
- Examples: Muscarinic (ACh), Serotonin (except 5HT3), Alpha, Beta, Histamine, Opioid, Angiotensin
- Hormone Exceptions: All Hypothalamic/Pituitary hormones use GPCR except Growth Hormone (GH) and Prolactin



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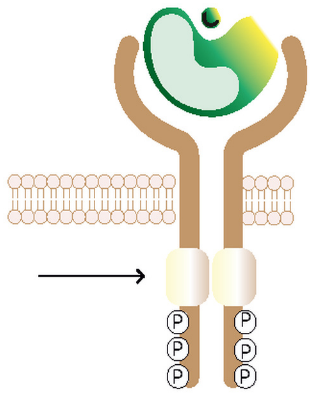
Types of G-Proteins

- Gq: Activates Phospholipase C → ↑ IP3/DAG → Cell excitation
- Gi: Inhibits Adenyl Cyclase → ↓ Cyclic AMP (cAMP)
- Gs: Activates Adenyl Cyclase → ↑ Cyclic AMP (cAMP)
- List of 2nd messengers
  - IP3- Inositol triphosphate
  - DAG- Diacyl glycerol
  - cAMP- Gs (↑); Gi (↓)
  - Cyclic GMP (cGMP):
    - → Levels ↑ by Nitric Oxide gas → Stimulates Guanylyl Cyclase
    - → Causes vasodilation
- Phosphodiesterase (PDE): Enzyme that degrades cAMP and cGMP
- PDE Inhibitors (e.g., Sildenafil/Viagra):
  - ↑ cGMP levels → Vasodilation
  - Used for: Erectile Dysfunction, Pulmonary Artery Hypertension

Q. Gq type of GPCR receptor acts by activation of:

a. Adenylyl cyclase
b. Phospholipase C
c. Guanylyl cyclase
d. Tyrosine kinase

Answer: b



Protein Kinase Receptors

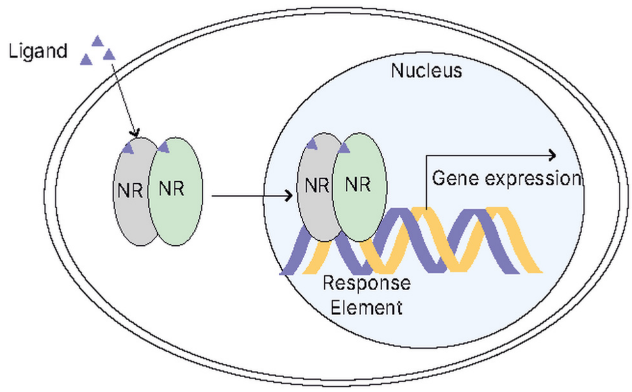
- Known as an enzyme-linked receptor
- Mechanism: Contains a kinase enzyme; activation leads to cell division and growth.

Tyrosine Kinase

- Used by Insulin, Insulin-like Growth Factor (IGF-1), VEGF, EGF

JAK-STAT Receptors

- Used by Growth Hormone (GH) and Prolactin
- Used by Cytokines: Erythropoietin, Thrombopoietin, Interleukins, Interferon
- Used by Leptin (Satiety hormone)



Intracellular Receptors

- Mechanism: Affects DNA transcription

Intracytoplasmic

- Vitamin D (Calcitriol)
- Steroid hormones
  - Glucocorticoids

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- Mineralocorticoids
- Testosterone
- Progesterone

Intranuclear

- Thyroid receptors (T3, T4)
- Vitamin A (Retinoic Acid)
- PPAR receptors
- Estrogen receptors (Note: Estrogen is intranuclear; other steroids are cytoplasmic)

Drug Development and Clinical Trials

01:56:45

- Drug discovery → Animal and lab testing → Human testing → Market
  - Clinical trials (done in phases)- Human testing
  - Pre-clinical trials- Animal and lab testing

Clinical Trial Phases

NEET PG 2024

Clinical trial phases	Number & type of volunteers	Design of trial	Purpose	
Phase 0	Microdosing Trial	5-10 Healthy humans	Very low dose (100 mg), radio- labeled	Pharmacokinetics & Target Binding
Phase 1	Safety & Pharmacology Trial	50-100 Healthy humans	Unblinded	Find the Maximum Tolerated Dose (MTD) and safety limits Check ADME Not for: Efficacy
Phase 2	Therapeutic Exploratory Trial	500-1000 Patients	Randomized Controlled Trial (RCT) with blinding/placebo	Explore if the drug is effective (Efficacy: Yes/No). Note: Highest failure rate occurs here.
Phase 3	Therapeutic Confirmatory Trial	5000-10,000 Patients Heterogenous population	Randomized Controlled Trial (RCT) with blinding/placebo	Confirm efficacy, compare with Gold Standard treatment, and find the actual dose Most expensive

Phase 4	Post-Marketing Surveillance.	Unknown	Unblinded	Done after market approval. Detects rare or missed adverse effects. Banning: Drugs are banned from the market in this phase.

Q. Phase 1 trial is not done for:

a. Efficacy
b. Safety
c. Max tolerable dose
d. Pharmacokinetics

Answer: a

Q. Phase 1 trial is mainly done for:

a. Efficacy
b. Safety
c. Max tolerable dose
d. Pharmacokinetics

Answer: c

- Best data on safety: 3 > 2 > 1
- Best data on safety: 3 > 2
- Phase 0 is not mandatory

Q. A drug that is already in Europe has to be marketed in India. Which phase of the clinical trial must be done for its approval in India?

a. Phase 1
b. Phase 2
c. Phase 3
d. Phase 4

Answer: c

- Bridging Trials: A Phase 3 trial conducted in a new country to gain approval for a drug already approved elsewhere (e.g., approved in Europe, seeking approval in India).

TYPES OF DRUGS

INICET 2022 02:07:05

- Placebo: Dummy drug; inert substance with the same look/taste as the test drug to maintain blinding; used in RCT blinding
- Sham Surgery: A fake surgery used as a control to compare the effect of an actual surgery.

Counterfeit and Illegal Drug

- Drugs are made with the intention to cheat consumers or harm patients.
- These are illegal and punishable by law

Spurious Drugs

- Contains no active ingredient
- Label, color, and company name match the original drug exactly
- Example: 500 mg Paracetamol label containing zero paracetamol upon testing

Misbranded Drugs

- Low-quality or poor-quality drugs
- The manufacturer provides a lower dose than labeled to increase profit margins
- Example: 500 mg Paracetamol label containing only 200 mg

Adulterated Drugs

- Contains harmful chemicals or excipients
- Example: Presence of ethylene glycol (neurotoxic alcohol) in cough syrups causing pediatric fatalities

Orphan Drugs

- Drugs used for rare diseases
- Prevalence of the disease is <1 per 5 lakh population
- Economic Status
  - Usually not profitable for companies to manufacture
  - Government provides financial support and incentives for their production

Examples

- Deferoxamine: Chelator for iron poisoning
- Digibind (Digifab): Antidote for digoxin poisoning
- Fomepizole: Antidote for methanol and ethylene glycol poisoning
- Vigabatrin: Anti-epileptic for infantile spasms

Drug Nomenclatures

Generic Names

- Also known as the non-proprietary name
- Not the property of any specific company; it can be used by everyone
- Example: Aspirin

Brand Names

- Known as the proprietary name
- Property of the manufacturing company
- Example: Ecosprin

Pharmacopea Symbols

- IP: Indian Pharmacopoeia (manufactured in India).
- USP: United States Pharmacopoeia (manufactured in the USA).

Expiry Date

- Has legal significance.
- Manufacturer is not responsible for quality assurance after the expiry date.

Essential Drugs

- Drugs used for highly prevalent diseases (e.g., Hypertension, Diabetes, Tuberculosis)

Requirements

- Must be cost-effective and affordable.
- Should be available in all doses (adult and pediatric).
- Should be available in all formulations (e.g., injections, oral syrups).
- Avoid combining essential drugs with others as Fixed-Dose Combinations (FDCs) to prevent unnecessary price increases

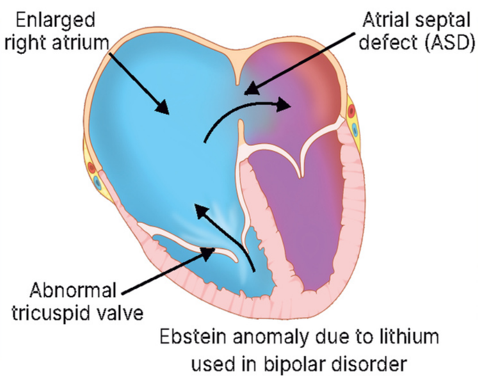
Drug Storage

- Storage Temperatures
  - Freeze: -10°C to -20°C
  - Cold: <5°C
  - Cool and Dry: 8°C to 15°C (most commonly asked)
  - Warm: 30°C to 40°C
  - Excessive Heat: >40°C

Teratogenic Drugs

- Drugs causing fetal malformations in pregnancy
- Category H drugs
- Key Examples and Effects
  - Thalidomide → Phocomelia (Short limbs; "Phoco" = short, "Melos" = limbs)
  - Lithium → Ebstein's anomaly (Cardiac defect involving the tricuspid valve)
  - ACE Inhibitors (Prils) and ARBs (Sartans) → Renal agenesis
  - Warfarin → Bone and cartilage defects
  - Carbimazole and Methimazole → Aplasia cutis (Absence of skin in the newborn)
  - Tetracycline → Bone and cartilage defects
  - Valproate and Methotrexate → Anti-folate action → Neural tube defects (e.g., Spina bifida)
  - Phenytoin → Cleft lip and cleft palate

Phocomelia



Ebstein Anomaly

Aplasia cutis

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DRUG MANAGEMENT IN PREGNANCY

02:16:25

Epilepsy

- Safest: Levetiracetam, Lamotrigine
- Most teratogenic: Valproate

Bipolar Disorders

- Safest: Antipsychotics (e.g., Clozapine, Quetiapine)
- Most teratogenic: Valproate

Hypertension

- Safest
  - Labetalol (DOC for Pregnancy-Induced Hypertension - PIH)
  - Hydralazine
  - Methyldopa
  - Calcium Channel Blockers (Nifedipine)
- Contraindicated: ACE Inhibitors and ARBs (Prils and Sartans)

Hyperthyroidism

- 1st Trimester DOC: Propylthiouracil (PTU).
- 2nd and 3rd Trimester: Carbimazole or Methimazole.
- PTU is contraindicated in the 2nd/3rd trimester; Carbimazole/Methimazole is contraindicated in the 1st trimester

Anticoagulants

- DOC: Heparin (Safe in all trimesters)
- Contraindicated: Warfarin in 1st trimester (up to 12 weeks)

SCHEDULES OF DRUGS

02:29:20

Schedule H

- Prescription drugs
- Carry the symbol "Rx" (Latin for "Take thou")
- Example: Insulin

Schedule X

- Narcotic and psychotropic drugs with high addiction potential
- Carry the symbol "X" in red
- Examples: Morphine, Ketamine

Schedule G

- Administered under medical supervision in the presence of a doctor
- Example: Vaccines (Hepatitis B, Polio)

Schedule Y

- Governed rules for clinical trials in India
- Now replaced by NDCTR 2019 (New Drugs and Clinical Trial Rules)
- Distinction between Category X and Schedule X

Q. Which of the following is schedule X drug?
a. Thalidome
b. Enalapril
c. Methotrexate
d. Ketamine

Answer: d

- Category X: Teratogenic drugs (e.g., Thalidomide, ACEi)

ADVERSE DRUG REACTION

02:21:40

- Pharmacovigilance: The branch of pharmacology that monitors ADRs.

Type A
- Augmented
- Occurs at high doses
- Predictable (Toxicity)
- Example: High dose Insulin → Hypoglycemia.

Type B
- Bizzare
- Unpredictable; can occur at any dose
- Also known as Idiosyncratic reactions
- Genetically determined
- Example: Penicillin allergy

Type C
- Continuous
- Due to long-term use.
- Example: Chronic Aspirin use → Peptic ulcers

Type D
- Delayed onset
- Occurs long after stopping the drug
- Example: Teratogenic effects seen months after 1st-trimester drug exposure.

Type E
- End of treatment
- Due to the sudden stoppage of the drug (Withdrawal reactions).
- Example: Sudden stoppage of Opioids or Corticosteroids.

Type F
- Failure
- Drug has not produced its own effect
- Example: Antimicrobial resistance

Q. Clozapine induced agranulocytosis is which type of ADR?

a. Type A toxicity
b. Type B dose independent idiosyncratic
c. Type C chronic use
d. Type D delayed onset

Answer: b

- Required for idiosyncratic reactions (Type B)
- Clozapine-induced agranulocytosis (bone marrow suppression) is Type B and requires HLA testing

PHARMACOGENETICS

02:25:25

- Warfarin: Test for Vitamin K-dependent enzymes (VKORC1) and CYP2C9
- Azathioprine / 6-Mercaptopurine: Degraded by Thiopurine Methyltransferase (TPMT)
  - Deficiency leads to bone marrow suppression/zero blood count
- 5-Fluorouracil: Degraded by Dihydropyrimidine Dehydrogenase (DPD)
- Succinylcholine: Degraded by Pseudocholinesterase. Checked via Dibucaine number
  - Deficiency leads to respiratory depression/apnea.
- Irinotecan (anti-cancer) & Atazanavir (anti-HIV): Contraindicated in Crigler-Najjar syndrome due to Glucuronide enzyme deficiency
- Abacavir (anti-HIV): Requires HLA-B*5701 testing to prevent allergic reactions

Drugs Contraindicated in G6PD Deficiency

- Avoid drugs producing free radicals (Nitro and Sulfa drugs)
- Contraindicated: Nitroprusside, Nitrates, Sulfonamides, Aspirin, Dapsone, Metronidazole, Fluoroquinolones, Anti-malarials (Primaquine, Proguanil, Quinine)

1. AUTONOMIC NERVOUS SYSTEM (ANS)

Sympathetic nervous system (sns)	Parasympathetic nervous system (pns)
• Emergency system (Flight or Fight response) • Physiological effects ○ Heart Rate → ↑ ○ Bronchus → Dilates (to increase oxygen intake) ○ Pupil → Dilates (Mydriasis) ○ Bladder → Relaxes (inhibits urination) ○ Stomach → ↓ HCl production ○ Intestine → Relaxes (leads to constipation) ○ Adipose Tissue → Lipolysis (fat burning) ○ Sexual Activity → Penile erection is a function of the Sympathetic system	• Rest-and-Digest system (Relaxation) • Physiological effects: ○ Heart Rate → ↓ ○ Bronchus → Constricts ○ Pupil → Constricts (Miosis) ○ Bladder → Contracts (↑ urination) ○ Stomach → ↑ HCl production ○ Intestine → Contracts (defecation/diarrhea) ○ Adipose Tissue → Lipogenesis (fat storage) ○ Sexual Activity → Penile ejaculation is a function of the Parasympathetic system

RELEVANT ANATOMY OF THE ANS

00:03:05

Sympathetic System (Thoracolumbar Outflow)

- Origin: Spinal nerves T1 to L2
- Synapse structure:
  - Pre-ganglionic nerve releases Acetylcholine (ACh)
  - ACh acts on Nicotinic Neuronal (Nn) receptors in the ganglia
  - Post-ganglionic nerve releases Norepinephrine (NE) at most sites
  - Minor Neurotransmitter: Dopamine (released only at the Kidney and the GIT)
- Adrenal Medulla:
  - Pre-ganglionic fibers act on Nn receptors
  - Releases Adrenaline into the blood
  - Receptors at end organs
    - → Alpha (α)
    - → Beta (β)
- Also known as the Adrenergic Nervous System
- Norepinephrine, adrenaline, and dopamine are known as Catecholamines

Parasympathetic System (Craniosacral Outflow)

- Origin: Cranial nerves (3, 7, 9, 10) and Sacral nerves (S2 to S4)
- Synapse structure:
  - Pre-ganglionic nerve releases Acetylcholine (ACh)
  - ACh acts on Nn receptors in the ganglia
  - Post-ganglionic nerve releases Acetylcholine (ACh)
  - Receptors at end organs
    - → Muscarinic (M) receptors
- Also known as the Cholinergic Nervous System

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Important Information

- Cholinergic drugs- Increase the parasympathetic activity
- Anti-cholinergic drugs- Decrease the parasympathetic activity

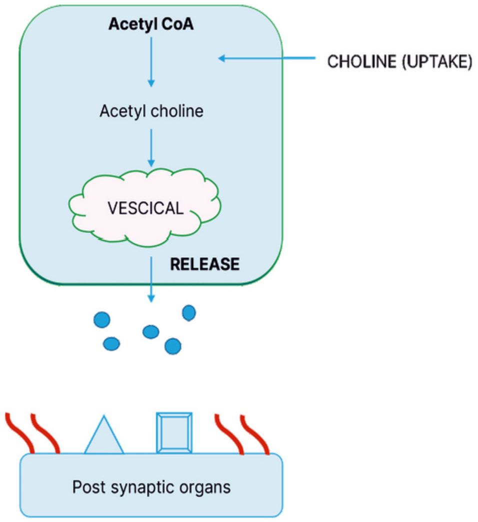
ACETYLCHOLINE (ACH) METABOLISM

00:08:15

Synthesis And Release

INICET 2019

- Components: Acetyl-CoA + Choline
- Choline Uptake: The rate-limiting step
  - Inhibited by Hemicholinium
- Vesicle Entry: ACh enters vesicles for storage
  - Inhibited by Vesamicol
- Release Mechanism
  - Nerve depolarization → Na^+ entry → Ca^{2+} release → Vesicle fusion → ACh release
  - Drugs inhibiting the release of ACh:
    - → Botulinum Toxin: Blocks Ca^{2+} release/SNARE proteins
    - → Puffer Fish Toxin: Blocks Na^+ channels



Degradation Of Ach

- Choline-esterase enzyme degrades choline into acetate and choline

Endogenous Degradation

- Degraded by Acetylcholinesterase (AChE / "Achhe" enzyme) at the post-synaptic organ

Exogenous Degradation

- Exogenous ACh (Drugs): Degraded by Butyrylcholinesterase or Pseudocholinesterase in the blood/plasma

Toxins Affecting The Release Of Ach

Botulinum Toxin

- Produced by Clostridium botulinum
- Inhibits the release of ACh by blocking the Ca^{2+} channel
- Mechanism: Inhibits ACh release → Muscle relaxation

Clinical Use

- Treat Muscle rigidity/spasm
  - Achalasia
  - Blepharospasm
  - Squint
  - Torticollis (sternocleidomastoid contraction)
- Hyperhidrosis→ Reduces excessive sweating
- Cosmetic→ Treats wrinkles by relaxing facial muscles (Botox)
  - Preparation: Botulinum Toxin Type A (BTXA) administered via injection

Tetanus Toxin (Clostridium Tetani)

- Produced by Clostridium tetani
- Mechanism: Inhibits inhibitory neurotransmitters (GABA and Glycine)
- Effect→ Leads to muscle contraction/spasm (Tetanospasmin)

CHOLINERGIC RECEPTORS

00:16:50

Nicotinic Receptors (N)

- Type: Ionotropic (conducts Na^+)
- Shape: Pentameric Rosette
- Excitatory receptors

Subtypes

- Nn (Neuronal): Found in postganglionic neurons (SNS & ANS) and the Adrenal Medulla
- Nm (Muscle): Found in skeletal muscles→ stimulation → muscle contraction
  - Agonist: Nicotine
  - Antagonists:

    → Nn Blockers: Ganglionic blockers (e.g., Trimethaphan)

    → Nm Blockers: Non-depolarizing muscle relaxants (e.g., Tubocurarine, Atracurium, Vecuronium)

Muscarinic Receptors (M)

- Type: G-Protein Coupled Receptors (GPCR)
- Shape: Serpentine (7-pass)

Subtypes

- M1, M3, M5: Gq type (Excitatory)
- M2, M4: Gi type (Inhibitory)

Receptor Locations And Clinical Correlations

Brain Locations

- Hippocampus: Predominantly M1 receptors; stimulation → Memory enhancement
  - Alzheimer's Disease: Characterized by ↓ ACh; treated with Cholinergic drugs
- Basal Ganglia: ACh reduces the effect of Dopamine
  - Parkinson's Disease: Treated with Anticholinergic drugs to balance reduced Dopamine

Peripheral Locations

- M1 (Stomach): Increases HCl production
- M2 (Heart): Inhibit SA/AV nodes → ↓ Heart rate (Bradycardia)
- M3 (Rest of body): Controls all body secretions and smooth muscle contraction

Summary Of Cholinergic Effects (Dumbbelss)

FMGE 2020

- **D**iarrhea (Intestinal contraction)
- **U**rination (Bladder contraction)
- **M**iosis (Pinpoint pupil)
- **B**ronchospasm
- **B**radycardia (M2 effect)
- **E**xcess HCl (M1 effect)
- **L**acrimation
- **S**alivation
- **S**weating (M3 effect)

Specific Drug Agonists And Antagonists

- M1 Antagonists: Pirenzepine, Telenzepine (used for Peptic Ulcers)
- M2 Agonist: Methacholine
- M3 Agonist: Bethanechol
- M3 Antagonists: Solifenacin, Darifenacin (used for Urinary Incontinence)

Cholinergic Drugs (Parasympathomimetics)

00:27:50

Directly Acting Drugs

NEET PG 2023
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Esters

- Acetylcholine: Shortest acting; rapidly degraded by Pseudocholinesterase
- Bethanechol: Resistant to degradation by Pseudocholinesterase; M3 specific
  - DOC for Post-operative urinary retention (POUR)
  - DOC for Post-operative paralytic ileus (POPI)
- Methacholine: M2-specific
  - Used inhalationally for the Asthma Challenge Test

Alkaloids (Natural)

- Pilocarpine
  - Used as eye drops (0.5-4%) for Miosis and Glaucoma
  - Treats xerophthalmia & xerostomia in Sjögren's syndrome
- Cevimeline
  - Modification of Pilocarpine
  - Used for Sjögren's syndrome
- Nicotine
  - Used for smoking cessation
- Muscarine
  - Found in poisonous mushrooms

SMOKING CESSATION DRUGS

00:32:15
FMGE 2022

- First-line drugs **(Mnemonic: Nicotine Very Bad)**

- Nicotine
  - → Available as patches
  - → Nasal sprays
  - → Gums
  - → Lozenges
- Contraindication
  - → Never given sublingually (excessive absorption)
- Varenicline:
  - → Partial agonist at nicotinic receptors
  - → Side Effects: Depression, suicidal risk
- Bupropion
  - → An antidepressant approved for smoking cessation

- Common Side Effects of first-line drugs (All three)
  - Seizures
  - Hypertension
  - Angina
  - Contraindicated in CNS and Heart disease patients
- Second-line: Clonidine (Safe for heart/CNS disease)
- Most Effective: Varenicline.

MUSHROOM POISONING

00:35:30

FMGE 2021, INICET 2022

Early Type

- Species- Inocybe
- Toxin: Muscarine.
- Symptoms: DUMBBELSS
- Treatment: Atropine (blocks M receptors).

Late Type (Amanita Phalloides)

- Species- Amanita phalloides
- Toxin: Amatoxin
- Symptoms: Hepatotoxicity (Liver damage)
- Treatment: Thioctic acid and Silybin (Hepatoprotective)

Hallucinogenic Type (Amanita Muscaria)

- Species- Amanita muscaria
- Toxin: Muscimol
- Symptoms: Hallucinations and Seizures
- Treatment: Supportive care; no antidote; Atropine is absolutely contraindicated (can worsen hallucinations)

INDIRECTLY ACTING CHOLINERGIC DRUGS

00:37:48

FMGE 2022, 2023

- Mechanism Inhibit Cholinesterase enzymes (AChE and BChE) → ↑ endogenous ACh
- Also called Anticholinesterases

Classification

- Reversible: Carbamates (Tertiary and Quaternary amines), Clinically safer to use in patients
- Irreversible: Organophosphates (used as poisons)

Yourwish

Carbamates

- Carbamates are reversible inhibitors used clinically in patients
- Divided into two chemical classes based on nitrogen bonds: Tertiary amines & Quaternary amines

Tertiary Amines

- Nitrogen has 3 bonds
- Properties:
  - Lipid-soluble due to lack of charge
  - Cross the Blood-Brain Barrier (BBB)
  - Can be administered as eye drops
- Clinical Significance
  - Increase Acetylcholine (ACh) levels in the brain to improve memory
  - Useful in Alzheimer's disease

Drugs

- **Physostigmine**
  - Drug of Choice (DOC) for Atropine poisoning (crosses BBB)
  - Acts as a miotic drug (causes miosis)
  - Used in the treatment of Glaucoma
- **Alzheimer's Disease Drugs (Mnemonic: T-DAGGER):**
  - Tacrine
  - Donepezil
  - Galantamine
  - Rivastigmine

Quaternary Amines

- Nitrogen has 4 bonds, resulting in a positive charge.
- Properties
  - Water-soluble due to the presence of a charge
  - Cannot cross the Blood-Brain Barrier
- Clinical Significance
  - Ineffective for memory improvement or Alzheimer's disease
  - Example: Neostigmine

Drugs

- **Neostigmine:** Acts only outside the brain
- **Edrophonium (Tensilon):** Shortest-acting carbamate
- **Pyridostigmine:** Longest acting carbamate (distinct from Physostigmine)

Drugs Used In Alzheimer's Disease

FMGE 2021

- Memory improvement requires ↑ ACh levels in the brain.
- Improve memory by increasing ACh levels in the brain.
- Used for Alzheimer's/Dementia

Drugs

- Tacrine: Banned due to hepatotoxicity
- Donepezil: Longest acting and most effective; considered the DOC for Alzheimer's
- Galantamine
- Rivastigmine: Available as a transdermal patch (helps patients who forget to take oral tablets)
- **Memantine:**
  - Mechanism: NMDA receptor antagonist (blocks Glutamate receptors).
  - Glutamate causes memory loss; Memantine prevents this.
    Mnemonic: MEM (Memory) and A (Alzheimer's)
- Monoclonal Antibodies:
  - Targets Beta-1 Amyloid protein deposits (which cause neuronal degeneration)
  - Aducanumab: Approved for AD (Alzheimer's Disease)
  - Lecanemab
  - Donanemab

Neostigmine Uses (Mnemonic: Ccm)

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Cobra Bite Poisoning

- Cobra venom blocks Nm receptors at the neuromuscular junction
- Leads to muscle paralysis and potential death via respiratory paralysis
- Neostigmine ↑ ACh levels → stimulates Nm receptors → prevents muscle paralysis

Curare Reversal

- Curare-like drugs (e.g., Tubocurarine) are skeletal muscle relaxants used during surgery
- They block Nm receptors
- Neostigmine is given after surgery to reverse the block and restore muscle function

Myasthenia Gravis

FMGE 2024

- Autoimmune disease where antibodies block Nm receptors
- Leads to muscle weakness/paralysis
- Neostigmine/Pyridostigmine are used for symptomatic treatment

Neostigmine Limitations

- Problem: Neostigmine stimulates both Nicotinic (desired) and Muscarinic (undesired) receptors
- Muscarinic stimulation → Side effects (DUMBBELSS: Diarrhea, Urination, Miosis, Bradycardia)
- Always combine Neostigmine with Atropine
  - Atropine blocks Muscarinic receptors to prevent DUMBBELSS
  - Atropine does not affect the nicotinic muscle contraction

Myasthenia Gravis Management

- Autoimmune disease, where Nm receptors are blocked, leading to muscle paralysis

Treatment Strategy

- Stimulate muscle contraction(symptomatic treatment)
  - Neostigmine
  - Pyridostigmine combined with Atropine

- Definitive treatment
  - Reduce antibody production.
  - Prednisolone (DOC): Corticosteroid used for induction.
  - Azathioprine: Used for maintenance to avoid long-term steroid side effects (Cushing's)
- Surgical
  - Thymectomy (removal of the thymus gland) if a thymoma (thymus tumor) is present
- Emergency (Myasthenic Crisis):
  - Involves respiratory muscle depression
  - Plasmapheresis: Removes antibodies from plasma.
  - Intravenous Immunoglobulin (IVIG): Neutralizes auto-antibodies.
  - Applicable to other autoimmune emergencies (e.g., Guillain-Barré, Kawasaki)
- **Diagnosis**
  - Edrophonium (Tensilon Test)
    → The shortest-acting drug used to diagnose MG
    → Ptosis (drooping eyelid) is common in MG → Injection of Edrophonium → Immediate opening of eyes (positive result)
    → Key takeaway: Rapid improvement confirms MG diagnosis

Drugs To Avoid In Mg (Mnemonic: Abc)

- Antibiotics:
  - Aminoglycosides (e.g., Streptomycin, Gentamicin) block Nm receptors
  - Fluoroquinolones (e.g., Ciprofloxacin)
  - Macrolides (e.g., Erythromycin)
- Beta Blockers: e.g., Propranolol
- Curare-Like Drugs: e.g., Tubocurarine, Atracurium (block Nm receptors)

Snake Bite

00:53:00

Cobra

- Neurotoxic venom blocks Nm receptors
- Treatment: Polyvalent Antivenom (DOC) + Neostigmine/Atropine

Krait

- Neurotoxic venom inhibits the presynaptic release of ACh
- Treatment: Neostigmine/Atropine are ineffective; only Antivenom is used

IRREVERSIBLE ANTICHOLINESTERASES (POISONS)

00:53:30

Classes

Organophosphates	Carbamates
• Malathion, Parathion • TIK-20 • Nerve gases: Tabun, Sarin (common in warfare), Soman.	• Aldicarb, Carbaryl, Propoxur. • BAYGON: Combination of Tik 20 (OP) + Propoxur (Carbamate)

Clinical Features

- Inhibition of AChE + BChE → massive ↑ in ACh
- Symptoms (DUMBBELSS):
  - Pinpoint pupils (Miosis)
  - Increased body secretions (diarrhea, lacrimation, salivation, sweating).

Treatment

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- Atropine (DOC): Controls the Muscarinic symptoms (DUMBBELSS)
- Oximes:
  - Mechanism: Reactivate the AChE enzyme
  - Examples: Pralidoxime (PAM), Obidoxime, DAM
  - Restriction: Used ONLY for Organophosphate (OP) poisoning; ineffective for Carbamates

ANTICHOLINERGIC (ANTIMUSCARINIC) DRUGS

00:57:20

General Effects - Opposite Of Dumbbelss

- Constipation
- Urinary retention
- Mydriasis (dilated pupils)
- Tachycardia
- Dry eyes and dry mouth

Drug Types

- Atropine and Hyoscine (Scopolamine)
  - Derived from Datura (Belladonna/Beautiful lady).
- Other classes with anticholinergic action:
  - Tricyclic Antidepressants (TCA): e.g., Imipramine
  - Antihistamines: e.g., Diphenhydramine.

Atropine / Datura Poisoning

00:59:30

Clinical Features

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- Hot as Hare - Hyperthermia (Hot skin) due to ↓ sweating
- Red as Beat - Flushing (Red skin) via vasodilation for heat loss
- Dry as a bone - Dry eyes, dry mouth
- Blind as a bat - Mydriasis and Cycloplegia: Lens paralysis leads to loss of accommodation and blindness
- Mad as a hatter - CNS effects: Acute confusional state (Delirium), Hallucinations, Seizures
- Full as a flask - Tachycardia, constipation, urinary retention

Antidote

Physostigmine (Doc)

- Crosses BBB to control CNS symptoms (seizures, delirium)
- Note: Neostigmine is not the DOC because it cannot cross the BBB

Clinical Uses Of Anticholinergics

01:02:06

Cortex - Hyoscine (Scopolamine)

- Decreases cognition/memory (Truth Serum)

Yourwish

- Used in Narco-analysis for criminal interrogation
- Thiopental (Barbiturate) is also a DOC for Narco-analysis

Basal Ganglia- Drug-Induced Parkinsonism

- Antipsychotics can ↓ Dopamine, leading to muscle rigidity/dystonia
- Treatment: Benzhexol (DOC), Benztropine, Biperiden
- Antihistamines (Promethazine, Diphenhydramine) are also used

Vestibular System (Motion Sickness)

- Motion → Endolymph movement → M1/H1 receptor stimulation in vestibular nerve → CTZ → Nausea/Vomiting
- Treatment
  - Scopolamine (Hyoscine): Antimuscarinic
  - First-generation Antihistamines (cross BBB): Diphenhydramine, Promethazine, Cyclizine, Meclizine, Cinnarizine
  - Identification: Drugs ending in "-amine" or "-zine"
- Administration:
  - Oral or Transdermal patch (behind the pinna)
  - Taken 30 minutes before the journey for prevention
  - Ineffective once vomiting has started
- Side Effect: Sedation/Sleepiness

Heart- Atropine

- Blocks M2 receptors on the SA and AV nodes
- DOC for Bradycardia due to SA node block, and AV node block
- ECG Findings:
  - Bradycardia: ↑ RR interval
  - AV block: ↑ PR interval
- Limitation: Ineffective in Transplanted hearts (denervated)

Respiratory Tract- Glycopyrrolate

- Reduces mucus/saliva
  - Used pre-anesthesia to keep the airway dry and prevent aspiration
- Bronchodilators
  - Ipratropium, Tiotropium, Umeclidinium, Aclidinium
  - Used via inhaler for COPD and Asthma

Eye

- Cycloplegia: Paralysis of the ciliary muscle (loss of accommodation)
- Mydriasis: Paralysis of the iris circular muscle
- Eye Drops (Mnemonic: ACTH):
  - Atropine
  - Cyclopentolate
  - Tropicamide
  - Homatropine
- Uses

- Cycloplegics: For refractive error testing
- Mydriatics: For fundoscopy (retina examination)

- Atropine 1% ointment
  - Strongest acting
  - DOC for fundoscopy in children
  - Avoided in refractive error testing due to a 14-day recovery period

Urinary Bladder

M3 receptors	Beta-3 receptors
• Located on the detrusor muscle • Activation → Contraction of detrusor → Urination • Part of the parasympathetic nervous system	• Opposite effect of M3 • Activation → Relaxation of the detrusor muscle → Inhibition of urination • Part of the sympathetic nervous system

Vesicoselective Drugs

- Block M3 receptors on the detrusor muscle
- Relaxation of the bladder
- Clinical Use
  - Treatment of Overactive Bladder (OAB) and urinary incontinence.
- Specific Drugs:
  - Oxybutynin:
    - → Given to relax the bladder in OAB
    - → Least vesicoselective; acts on other muscarinic receptors
    - → Result → Significant side effects
  - Solifenacin & Darifenacin:
    - → Specific M3 blockers
    - → Highly vesicoselective
  - Trospium:
    - → A quaternary amine.
    - → Does not cross the blood-brain barrier (BBB).
    - → Benefit → Does not reduce memory in the brain.
    - → Preferred drug for OAB in patients with Alzheimer's or dementia.
- New drug for OAB:
  - Mirabegron:
    - → Beta-3 agonist
    - → Stimulates Beta-3 receptors → Detrusor relaxation

Gastrointestinal Tract

Stomach receptor	Intestinal receptors
• M1 Receptors: Located in the stomach→ increase HCl production	• M3 Receptors: Cause muscle contraction in the intestine

M1 Blockers

- Pirenzepine and Telenzepine
- Clinical Use: Treatment of peptic or stomach ulcers

Effects Of Overactivity

- Contraction → Increased motility (diarrhea) and spasm of sphincters → Abdominal colicky pain.

Antispasmodic drugs (m3 blockers):

- Dicyclomine and Glycopyrrolate: Quaternary amines; do not cross the BBB
- Hyoscine (Brand: Buscopan): Tertiary amine

Non-anticholinergic alternative:

- Drotaverine: Phosphodiesterase 4 (PDE4) inhibitor; relaxes intestinal muscles.

Pain Management Warning

- Morphine/Opioids: Avoided in colicky pain
- Reason → Increase spasm of GI sphincters → Worsen colicky pain

Contraindications For Anticholinergics

- Alzheimer's disease→ Anticholinergics reduce memory in the brain
- Benign Prostate Hypertrophy (BPH):
  - The bladder outlet is already narrowed
  - Anticholinergics relax the detrusor → Aggravate urinary retention
- Glaucoma:
  - These drugs produce mydriasis
  - Contraindicated; glaucoma requires miotic drugs

GANGLIONIC BLOCKERS

01:20:50

- Block Nicotinic Nn receptors in sympathetic and parasympathetic ganglia

Side Effects

- Parasympathetic block → Atropine-like side effects
- Sympathetic block → Reduced sympathetic discharge → Hypotension

Drugs

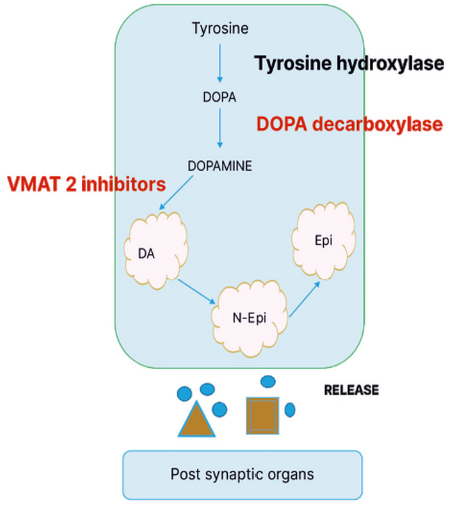
- Hexamethonium (HMT)
- Mecamylamine
- Trimethaphan
  - Used during arterial repair surgery
  - Example: Aortic dissection surgery → Maintains stable blood pressure and prevents vessel constriction/ relaxation

ADRENERGIC (SYMPATHETIC) NERVOUS SYSTEM

01:20:00

Catecholamine Synthesis

Components



- Dopamine
- Noradrenaline (Norepinephrine)
- Adrenaline (Epinephrine)
- Precursor → Tyrosine (amino acid)

Synthetic pathway:

- Tyrosine → Dopa (Enzyme: Tyrosine Hydroxylase)
- Tyrosine Hydroxylase is the rate-limiting step
- Dopa → Dopamine → Norepinephrine → Epinephrine

Drugs

- Metyrosine
  - Inhibits Tyrosine Hydroxylase → Stops all catecholamine synthesis
  - Drug of choice for Pheochromocytoma (tumor releasing excess catecholamines)
- Cocaine
  - Local anesthetic that increases catecholamine release
  - Leads to ↑ blood pressure and vasoconstriction

Adrenergic Receptor Specific Drugs

Agonist	Receptors	Antagonist
Phenylephrine	Alpha-1	Prazosin
Clonidine	Alpha-2	Yohimbine
Dobutamine	Beat-1	Metoprolol (cardioselective beta-blocker)
Salbutamol	Beta-2	Butaxiamine
Merabegron	Beta-3	-

Adrenergic drugs

Noradrenaline (norepinephrine)

- Acts on Alpha-1, Alpha-2, Beta-1, Beta-3
- Does not act on Beta-2 (no bronchodilation or vasodilation)
- Drug of choice for Shock
  - Cardiogenic shock (Acute heart failure + hypotension)
  - Septic shock
  - Neurogenic shock (Bradycardia + hypotension)

Mechanism In Shock

- Beta-1 stimulation → ↑ Cardiac contractility and heart rate
- Alpha-1 stimulation → Vasoconstriction → ↑ Blood pressure

Important Information

- Norepinephrine and dopamine are ineffective in anaphylactic shock as they lack Beta-2 action

Adrenaline (Epinephrine)

- Acts on all receptors (Alpha-1, Alpha-2, Beta-1, Beta-2, Beta-3)

Uses

- Anaphylactic Shock
  - Drug of choice; provides Beta-2 mediated bronchodilation
  - 0.5 ml of 1:1000 I.M
- Acute Asthma
  - Used in emergencies
  - 0.5 ml of 1:1000 I.M/S.C
- Cardiac Arrest
  - Used during CPR.
  - 1 ml of 1:10000 I.V
  - Route: Intraosseous (IO) via the tibia bone if the veins are collapsed.
- Local Anesthesia Adjuvant
  - Added to cause vasoconstriction → ↓ Absorption of anesthetic into blood → ↑ Duration of local action
  - 1:200000

Dopamine

- Does not act on Beta-2
- Low Dose (1-2 mcg/kg/min) → Acts on D1, D2 → Renal vasodilation → ↑ GFR → ↑ Urine production.
  - DOC: Acute Renal Failure (ARF) or Oliguria
  - Side effect: Hypotension
- Medium Dose (2-10 mcg/kg/min) → Acts on Beta-1 on the heart → ↑ Force of contraction
  - Use: Acute heart failure
  - Max. Risk: Arrhythmias
- High Dose (>10 mcg/kg/min) → Acts on Alpha-1 → Vasoconstriction → ↑ Blood pressure
  - Use: Shock (similar to Noradrenaline)
  - Low dose of dopamine in shock worsens hypotension

Synthetic Catecholamines

Dobutamine:

- Specific Beta-1 agonist.
- DOC for Acute Heart Failure
- DOC for Stress Echocardiography

Fenoldopam

- D1 agonist
- Used in ARF or Oliguria to increase urine production

Summary Of Drugs For Shock And Heart Failure

- Anaphylactic Shock→ Adrenaline (0.5 ml of 1:1000 IM)
- Cardiac Arrest→ Adrenaline (1 ml of 1:10,000 IV)
- Septic / Neurogenic / Cardiogenic Shock (with Hypotension)→ Noradrenaline
- Acute Heart Failure (without Hypotension)→ Dobutamine

Yourwish

- Cardiogenic Shock (with Acute Renal Failure)→ Dopamine
- Resistant Shock→ Vasopressin

Non-Catecholamine Adrenergics

Vasopressors (Alpha-1 Agonists)

- Alpha-1 stimulation → Vasoconstriction → ↑ Blood pressure

Clinical Uses

- Hypotension in Pregnancy→ Ephedrine
- Hypotension during Spinal Anesthesia→ Phenylephrine
- Postural Hypotension→ Midodrine

Midriatics (Eye Drugs)

- Radial muscle
  - Stimulation → Contraction → ACTIVE MIDRIASIS
  - Drug: Phenylephrine (Alpha-1 agonist)
- Circular muscle: Blockade → Paralysis → PASSIVE MIDRIASIS
  - Drugs (Antimuscarinics- Block M3): Atropine, Cyclopentolate, Tropicamide, Homatropine
- Clinical Use→ FundoscopyContraindication→ Glaucoma

Nasal Decongestants

- Alpha-1 mediated vasoconstriction → ↓ Plasma leakage

Drugs

- Nasal drops: Oxymetazoline (Otrivin), Xylometazoline, Phenylephrine
- Oral tablets: Ephedrine, Pseudoephedrine, Phenylephrine

Complications

- Atrophic Rhinitis→chronic use → Ischemia → Mucosal atrophy
- Rhinitis Medicamentosa→ Sudden stoppage → Rebound vasodilation → Rebound running nose

Tocolytics (Uterine Relaxants)

- Delay pre-term labor (before 37 weeks)

Drugs

- Atosiban: Oxytocin receptor blocker
- Ritodrine and Isoxsuprine: Beta-2 agonists
- Nifedipine: Calcium channel blocker

Beta 3 Agonists

- Relaxes the detrusor muscle in the bladder
- Vebergon, Miraberon→ Overactive bladder Rx

Indirect And Mixed Acting Adrenergics

- Increase the release of Norepinephrine from nerves

Drugs (Mnemonic: Mat Me)

- Modafinil
- Amphetamine
- Tyramine
- Mephentermine
- Ephedrine

Central Effects (Amphetamine/Modafinil)

- Cross BBB
- ↓ Appetite.
- ↓ Sleep
- ↑ Attention span/Alertness
- Tachyphylaxis→ Rapid loss of effect (tolerance) due to depletion of Norepinephrine stores

Clinical Uses

Narcolepsy (daytime sleepiness):

- DOC: Modafinil.
- New Drug: Tiprolisant, AKA Pitolisant (H3 inverse agonist)
- Sometimes seen in OSA → Rx modafinil

Attention Deficit Hyperactivity Disorder (Adhd)

- First line: Behavioral therapy.
- DOC (Stimulant): Methylphenidate (NDRI - Norepinephrine Dopamine Reuptake Inhibitor).
- Amphetamine can be given, but it is easy to abuse
- If Tics/Tourette's present→ Atomoxetine (NRI) or Clonidine; Non-stimulant drugs

Obesity (Weight Loss Drugs)

- SLIT (also used in diabetes mellitus)
  - Semaglutide
  - Liraglutide
  - Tirzepatide (GLP-1 analogues)
- Topiramate and Zonisamide (Anti-epileptics)
- Bupropion (Anti-depressant)
- Orlistat and Cetilistat (Lipase inhibitors)

Effects Of Epinephrine & Norepinephrine On Blood Pressure And Heart Rate

Blood Vessel Receptors	• Alpha-1: Vasoconstriction (A-Constriction) → ↑ BP • Beta-2: Vasodilation (B-Dilation) → ↓ BP
Heart Receptors	• Beta-1: Direct stimulation → Tachycardia
Reflex Heart Rate	• Controlled by the brain based on BP • ↑ BP → Reflex Bradycardia • ↓ BP → Reflex Tachycardia

Adrenergic Drug Effects On Blood Pressure And Heart Rate

- Norepinephrine (NE) vs. Epinephrine (Epi)

Epinephrine

- Acts on all receptors, causing Biphasic BP changes
  - ↑ BP initially due to Alpha-1 vasoconstriction.
  - ↓ BP follows due to Beta-2 mediated vasodilation
- Increases HR (Beta-1 action)
  - Produces tachycardia due to direct action on the heart.
- Minimal change in reflex as BP both increases and decreases.

Non Epinephrine

- Acts on all receptors, except Beta-2, increasing BP d/t vasoconstriction by Alpha-1
- Increases HR (Beta-1 action)
- Produces reflex bradycardia due to Alpha-1 mediated vasoconstriction
  - Direct effect: Produces tachycardia (Beta-1 action on the heart)
  - Reflex effect: Leads to reflex bradycardia (stronger than direct effect)
  - Net effect on heart: Bradycardia d/t more stronger reflex effect by the brain
- Transplanted Heart:
  - Reflex nerves from the brain are absent
  - Norepinephrine produces tachycardia (no reflex bradycardia)

Vasomotor Reversal Of Dale

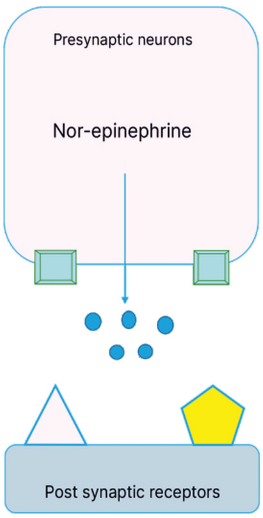
- Epinephrine + Alpha blocker (e.g., Prazosin, Phentolamine)
- Alpha-1 receptor is blocked → Upward wave of BP increase is inhibited
- Beta-2 receptor remains active → Results in an unopposed fall in BP.
- This unopposed fall in BP with Epinephrine + Alpha blocker is the "Vasomotor Reversal of Dale."

Anti-Adrenergic Drugs (Sympatholytics)

01:54:55

General Mechanism

- Nerve releases Norepinephrine → Acts on postsynaptic Alpha and Beta receptors
- Presynaptic neurons contain Alpha-2A receptors
- Stimulation of Alpha-2A receptors → Inhibits the release of Norepinephrine



Classification

- Alpha-2A Agonists (Centrally Acting Sympatholytics)
  - Act in the CNS to ↓ Norepinephrine release

Drugs (Mnemonic: Cd-Tag)

- Dexmedetomidine
  - IV drug used as a sedative during anesthesia or surgery
  - Reduces alertness by ↓ sympathetic activity
- Tizanidine- Centrally acting muscle relaxant
- Alpha-methyldopa
  - Drug of choice for HTN in Pregnancy
  - Side effects: Drug-induced SLE, RBC damage (Hemolytic anemia)

Yourwish

- Guanfacine- Longest acting
- Clonidine Clinical Applications **(Mnemonic: PHC)**
  - P: Post-menopausal symptoms (e.g., hot flushes)
    → Hormone Replacement Therapy (HRT) is the primary drug of choice for hot flushes
  - H: Hypertensive crisis
  - C: Control of withdrawal symptoms
    → Used in smoking (cravings), alcohol, and opioid withdrawal, where sympathetic activity is increased

Clonidine Rebound Hypertension

- Clonidine stimulates presynaptic Alpha-2A → ↓ Norepinephrine release.
- Long-term inhibition of Norepinephrine causes postsynaptic Alpha-2B receptors to increase in number and sensitivity
- Sudden stoppage of Clonidine → Sudden massive release of Norepinephrine
  - Norepinephrine acts on super-sensitive Alpha-2B receptors on blood vessels
    → Outcome: Massive vasoconstriction → Hypertensive crisis
    → Treatment: Fentolamine (Alpha blocker) to block Alpha-2B receptors

NON-SELECTIVE ALPHA BLOCKERS

02:00:10

- Block Alpha-1 And Alpha 2
- Action: Vasodilation → ↓ BP
- Phenoxybenzamine:
  - Used to control Hypertension in Pheochromocytoma.
  - Side effect: Reflex tachycardia
    → Management of reflex tachycardia→ Add Beta blocker (Propranolol)
    → Sequence: Give an alpha blocker first, then a beta blocker.
- Phentolamine:
  - Drug of choice for Clonidine rebound hypertension
  - Drug of choice for Cheese Reaction
    → Cheese contains Tyramine
    → Tyramine + MAO inhibitors → ↑ absorption of Tyramine
    → Tyramine causes massive Epinephrine/Norepinephrine release → Hypertensive crisis
- Tolazoline:
  - Used as a vasodilator during angiography to help the dye move forward.

Selective Alpha-1 Blockers

- Drugs ending in "-zosin": Prazosin, Terazosin, Doxazosin, Alfuzosin
- Mechanism: Block Alpha-1A and Alpha-1B
  - Alpha-1A block → Opens internal urethral sphincter (IUS) → Treats BPH
  - Alpha-1B block → Vasodilation → Treats Hypertension
- Drug of choice for BPH with Hypertension: Prazosin
  - Side effect: First-dose effect (Postural hypotension) due to vasodilation
- Drugs ending in "-osin" (No 'z'): Tamsulosin, Silodosin
  - Selective for Alpha-1A only
  - Used for BPH only
  - No risk of hypotension

Yourwish

Benign Prostatic Hypertrophy (Bph) Management

02:05:25

Treatment Goals

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- Open the urethral sphincter: Tamsulosin or Silodosin
- Reduce prostate size: 5-Alpha Reductase Inhibitors

5-Alpha Reductase Inhibitors

- Drugs: Finasteride, Dutasteride
- Mechanism
  - Inhibit conversion of Testosterone to Dihydrotestosterone (DHT).
    → DHT normally ↑ prostate size and causes male pattern baldness (Androgenic Alopecia)
    → These drugs ↓ prostate size and treat baldness
  - Baldness Treatment: Finasteride/Dutasteride combined with Minoxidil cream (2-5%)

Scorpion Sting

- Scorpion venom stimulates Alpha-1 receptors → Vasoconstriction → Hypertension and Pulmonary edema
- Treatment for HTN/Pulmonary edema: Prazosin
- If sting causes Hypotension (Anaphylactic shock): Treatment is Adrenaline

BETA BLOCKERS

02:08:30

Classification

- 1st Generation (Non-selective): Block B1, B2, B3 equally
  - Mnemonic: "Pyari Sotan" (Propranolol, Sotalol, Timolol, Nadolol)
- 2nd Generation (Cardio-selective): Mainly blocks B1
  - Mnemonic: "BEAMA" (Bisoprolol, Esmolol, Atenolol, Metoprolol, Acebutolol)
- 3rd Generation (Vasodilatory Beta Blockers)
  - Nebivolol: Produces Nitric Oxide (NO) → Vasodilation
  - Celiprolol: Beta-2 Agonist action → Vasodilation
  - Labetalol: Alpha-blocking action
  - Betaxolol: Calcium channel blocking action
  - Carvedilol: Alpha-blocking and Calcium-blocking action
  - Tilisolol: Opens Potassium channels → Vasodilation

Pharmacokinetic Properties

- Longest acting: Nadolol
- Shortest acting: Landiolol > Esmolol
  - Esmolol is degraded by plasma esterase
  - Landiolol is degraded by pseudocholinesterase
- Avoid in Renal Failure **(Mnemonic: ANS)**: Atenolol, Nadolol, Sotalol
- Most Cardio-selective: Nebivolol
- Potassium Channel Effects
  - Tilisolol: Opens K+ channels
  - Sotalol: closes K+ channels → prolongs QT
- Partial Agonist Action (Intrinsic Sympathomimetic Activity - ISA)
  - Drugs: Pindolol, Bopindolol, Acebutolol
  - Advantage: No risk of causing bradycardia

- Local Anesthetic Effect (Membrane Stabilizing Activity)
  - Mechanism→ Block Sodium channels on nerves
  - Drug: Propranolol
  - Benefit: Provides pain relief for conditions such as migraine

Propranolol As Doc

- Hypertrophic Obstructive Cardiomyopathy (HOCM)
- Thyroid Storm: Controls symptoms (tachycardia/tremors) and inhibits T4 to T3 conversion
- Essential Tremors
- Performance Anxiety (Stage fright)
- Migraine Prevention
- Hemangioma (Only approved drug)

Side Effects And Contraindications

Mnemonic: BARD

- B: Bradycardia (B1 block on the heart)
- A: Asthma/Bronchospasm (B2 block)
- R: Raynaud's Disease (B2 block causing vasoconstriction)
- D: Diabetes Mellitus (B2 block inhibits insulin release)

Drug Specifics

- Propranolol (Non-selective): Absolutely contraindicated in BARD
- Cardio-selective (Atenolol/Metoprolol): Contraindicated in Bradycardia, but can be used with caution in Asthma, Raynaud's, and Diabetes

Drug Interactions

- Never combine Beta blockers with Verapamil or Diltiazem (Calcium Channel Blockers).
  - Both cause severe bradycardia
- Antidote for beta-blocker toxicity: Glucagon
  - Glucagon acts on the heart to ↑ heart rate (tachycardia)

Beta Blockers In Diabetes

- Cause "Hypoglycemic Unawareness"
  - Mask symptoms of hypoglycemia: Palpitations/Tachycardia (B1 block) and Tremors (B2 block)
  - Exception: Sweating is NOT masked
- Sweating is mediated by Acetylcholine (Muscarinic), not Beta receptors

DRUGS FOR GLAUCOMA

02:18:26

FMGE 2023

Pathophysiology

- ↑ Aqueous humor volume → ↑ Intraocular Pressure (IOP) → Damage to retinal neurons
- Aqueous humor is produced in the Ciliary Process (between the iris and the lens)
- Drainage occurs via Uveoscleral outflow and Trabecular outflow

Drugs To Decrease Aqueous Production

- Alpha Agonists: Stimulate Alpha receptors

- Beta Blockers: Inhibit B2 receptors
- Carbonic Anhydrase Inhibitors (CAIs): Inhibit Enzyme C

Important Information

- Mydriatics are never given in Glaucoma as they close the iridocorneal angle and reduce the trabecular outflow

Drugs To Increase Drainage

- Prostaglandin F2-Alpha Agonists: ↑ Uveoscleral outflow
- Alpha Agonists: Also, ↑ Uveoscleral outflow
- Miotics (Pilocarpine):
  - Produce miosis (constrict pupil)
  - Open the Iridocorneal (IC) angle → ↑ Trabecular outflow

Doc For Glaucoma (Open-Angle And Angle-Closure)

- Prostaglandin F2-Alpha Agonists (e.g., Latanoprost, Bimatoprost)
- Side effects of Prostaglandins:
  - Inflammation (Anterior Uveitis)
  - Heterochromia iridis (Change in iris color)
  - Cystoid Macular Edema (Retinal edema)
  - Hypertrichosis (↑ eyelash/eyebrow growth)

    → Bimatoprost is used for Hypotrichosis (slow hair growth)



Doc For Acute Congestive Glaucoma (Medical Emergency)

- Symptoms: Sudden ↑ IOP, swollen eyes, risk of blindness
- Treatment:
  - IV Acetazolamide (CAI)
  - IV Mannitol (to rapidly ↓ IOP)
  - Surgery: Iridotomy (to prevent further attacks)

Specific Glaucoma Side Effects

- Apraclonidine: Causes maximum allergy
- Betaxolol / Timolol: Avoid in Asthma (causes bronchospasm)
- Acetazolamide / Dorzolamide: CAIs; can cause secondary angle-closure glaucoma due to ciliary edema
- Dipivefrin
  - Prodrug of Epinephrine
  - Side effect → Dark/Black eye (due to the black color of Epinephrine)
- Pilocarpine: Highly painful eye drops due to iris/ciliary muscle spasm
- Brimonidin
  - Contraindicated in children <2 years (causes respiratory depression/apnea)
  - Safest drug in Pregnancy

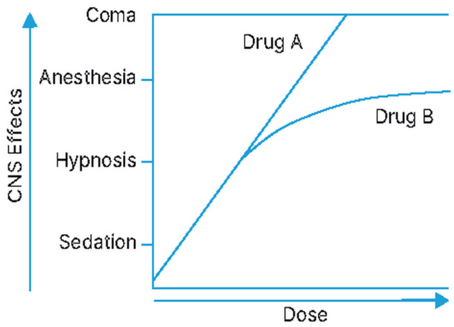
1. CENTRAL NERVOUS SYSTEM

SEDATIVES AND HYPNOTICS

- Sedative → Calms and removes anxiety
- Hypnotic → Induce sleep
- As the dose increases, the effect moves through the following stages:
  - Sedation → Hypnosis → Muscle relaxation → Anaesthesia → Respiratory depression/Coma
- Classification:
  - Barbiturates
  - Benzodiazepines (BZDs)
  - Atypical Benzodiazepines (Z-Drugs)
  - Melatonin
  - Alcohols

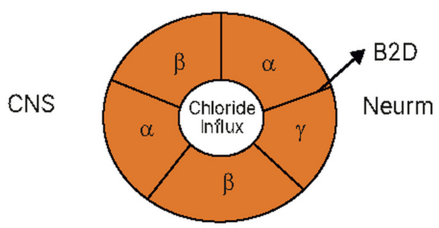
Dose Response Curve

- Drug A → Barbiturates & Drug B → Benzodiazepines
- Barbiturates → Steep DRC → high-risk.
- Benzodiazepines → Flat DRC
- BZDs are considered safer than barbiturates



Barbiturates & Benzodiazepines

00:03:22

<table>
<tr><th>Barbiturates</th><th>GABA-A Chloride Channel Agonist</th><th>Benzodiazepines</th></tr>
<tr><td>• Acts on multiple sites
• Low dose: GABA facilitatory
• High dose: GABA mimetic (Direct open)</td><td>GABA-A Chloride channel Agonist

</td><td>• Acts on α-γ subunit
• GABA facilitatory</td></tr>
</table>

- Benzodiazepines (diazepam, lorazepam) act on the α-γ subunit of the GABA-A channel
- Flumazenil is a Competitive Antagonist of the α-γ subunit of the GABA-A channel
- Beta carboline is an inverse agonist of the α-γ subunit of the GABA-A channel → not used
- Treatment of Benzodiazepine (Diazepam, Lorazepam, etc.) toxicity → Flumazenil
- Treatment of Barbiturate (Thiopentone, Phenobarbitone) toxicity → Forced Alkaline diuresis
  - If insufficient → Hemodialysis
  - No antidote

Barbiturates

00:07:33

Ultrashort acting	Short acting	Long acting
Redistribution into fats (lipid soluble) • Thiopentone (Sodium Pentothal) • Methohexitone	• Butabarbitone • Amobarbitone • Pentobarbitone • Secobarbitone	• Phenobarbitone • Primidone

- Thiopentone is used in
    - General Anesthesia
    - Truth serum (NARCO-Analysis)
        → Hyoscine is also used in NARCO- Analysis
- DOC during ECT: Methohexitone (decreases seizure threshold)
    - ECT in depression: Ketamine
- The active form of Primidone is Phenobarbitone
- Primidone and Propranolol are first-line drugs for Essential Tremors
- DOC for Neonatal seizures is Phenobarbitone
- DOC for Neonatal jaundice (Criggler-Najjar, Gilbert syndrome) is Phenobarbitone
    - Phenobarbitone is an enzyme inducer - Induces UDP-GT
- Drug contraindicated in Criggler-Najjar, Gilbert syndrome: Irinotecan, Atazanavir
- Barbiturates are C/I in Acute Intermittent Porphyria
    - Barbiturates are CYP inducers - contain Heme

Benzodiazepines

00:12:40

Anti-Seizures	Anti-Anxiety	Insomnia
Diazepam	Diazepam	Flurazepam
Lorazepam	Clonazepam	Temazepam
Clonazepam	Oxazepam	Estazolam
Clobazam	Lorazepam	Quazepam
Midazolam	Alprazolam	Triazolam

Pre-Anaesthetic medication:

- Causes sedation, ↓ Anxiety, and anterograde amnesia
- Drugs used:
    - Diazepam
    - Lorazepam
    - Midazolam → 2nd shortest acting BZD
    - Remimazolam → Shortest acting BZD

Automatism: Barbiturates & BZDs → Anterograde amnesia → repetitive self-medication

- Muscle relaxant:
    - Diazepam: Acts via GABA-A in the brain
    - Baclofen: Acts via GABA-B Agonist in the spinal cord (No addiction, No sedation)
- Management of Anxiety:
    - Acute anxiety (PANIC): BZD

- Anxiety disorder (maintain): SSRI
- Performance anxiety: Propranolol

Bzds Safe In Liver Disease

- Most BZDs are metabolised by CYP3A4 in the liver into other active forms
- Diazepam → CYP3A4 → Oxazepam → excreted in the urine after metabolism
- Drugs not metabolised by the liver:
  - Triazolam
  - Oxazepam
  - Temazepam
  - Estazolam
  - Lorazepam

Date Rape Drugs

- Alcohol
- Ketamine
- Barbiturates
- **GHB** (Gamma-hydroxybutyrate)
- Flunitrazepam (Rohypnol)
  - Status: Banned.
  - Tasteless & colourless (making it easy to lace into drinks like wine).

Atypical Benzodiazepines (Z-Drugs)

00:19:52

- Act only on α1-Gamma subunit: Primarily responsible for sedation
- Do not act on α2 → Lacks muscle relaxant effects
- Drugs:
  - Zopiclone (Longest)
  - Zolpidem
  - Zaleplon (Shortest)
- Addictive
- DOC for Insomnia
  - Only reduce sleep latency time (time taken to fall asleep).
  - Causes the least distortion of the natural sleep cycle
- Antidote → Flumazenil

α- (GABA-A receptor)

- α1 → Sedation activity → Treatment of insomnia
- α2 → Muscle relaxant activity → Anti-seizure

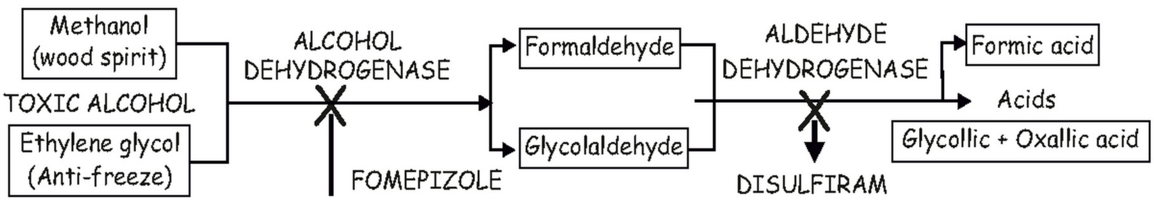
Melatonin Agonist (Mt_1/Mt_2 Agonists)

00:22:46

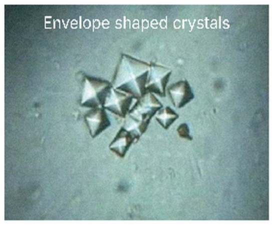
- Melatonin maintains sleep-wake cycle (circadian rhythm)
  - Dark → pineal gland → ↑melatonin → sleep
  - Lighlt → ↓melatonin → wakefulness
- Drugs:
  - Ramelteon: T/t of Jet lag, Old age insomnia, Shift workers
  - Agomelatin: MT_1/MT_2 agonist + 5-HT_{2C} antagonist
    → Indication: Insomnia + Depression
  - Tasimelteon: Maintains circadian rhythm in blind people

Other Drugs for Insomnia:
- Orexin antagonist → Suvorexant, Lemborexant
- Sedating Antidepressants → Mirtazapine, Mianserin

ALCOHOLS
- Metabolised by non-specific dehydrogenase enzymes in the liver



- Effect of toxic acids:
  - Neurotoxic effects → Respiratory depression
  - Blindness
  - Oxalate crystals in urine: Specifically associated with Ethylene glycol poisoning
- Management:
  - Sodium bicarbonate: Used to treat High Anion Gap Metabolic Acidosis
  - Hemodialysis: Best
  - Antidote: Fomepizole → Inhibits Alcohol Dehydrogenase (Orphan Drug)
  - Folinic acid
  - Ethanol: Used to saturate ADH



Ethanol (Alcohol Addiction)

00:30:16

Acute Withdrawal (Emergency)
- Delirium Tremens: IV Diazepam (Liver failure → Lorazepam/Oxazepam)
- Korsakoff Psychosis: Thiamine + Haloperidol.

↓

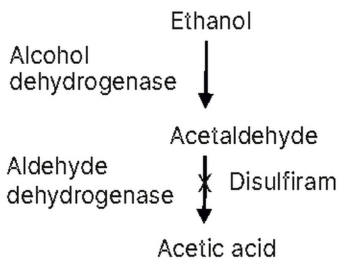
Maintenance phase (To prevent withdrawal)

Oral Chlordiazepoxide (taper slowly): Liver failure → Lorazepam/Oxazepam

↓

Prevent relapse (Abstinence/Aversion therapy)
- Anti-craving: Naltrexone + Acamprosate (NMDA Antagonist).
- Deterrent: Disulfiram (Antabuse).
- Off-label:
  - Anti-craving → Topiramate, Gabapentin
  - Deterrent → Metronidazole

Disulfiram
- Inhibits Aldehyde dehydrogenase
- Acetaldehyde accumulates:
  - Vomiting, Headache, Abdominal pain, Flushing, Hypotension (death)
- Disulfiram is C/I in Active drinkers



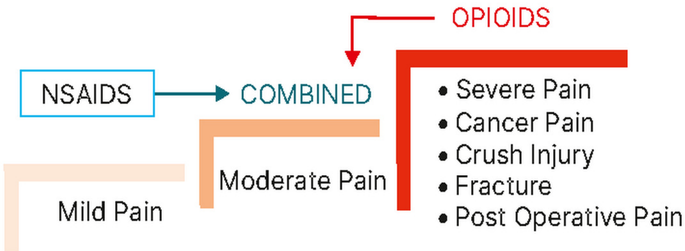
- Drugs with Disulfiram-Like Reaction: (Avoid in active drinkers)
  - Chlorpropamide
  - Griseofulvin
  - Metronidazole
  - Procarbazine
  - Cephalosporins (Cefoperazone, Cefamandole, Cefotetan)
    → Due to MTT (Methyl Thio Tetrazol ring)

OPIOIDS

00:37:13

- Alkaloids from Opium (Papaver somniferum) - Poppy plant
- Natural opioids are known as Opiates (Morphine & Codeine)
- Most effective analgesics

Who Stepladder Of Pain



Opioid Receptors

Receptor Type	Endogenous Ligand	Key Characteristics
Mu (μ)	Endorphins	Morphine → Full agonist at μ
Kappa (k)	Dynorphins	Does not produce euphoria; leads to dysphoria/psychosis.
Delta (δ)	Enkephalins	Lead to convulsions.

Mu (μ) RECEPTOR

Mnemonic: SACRUM NO GAP

- S - Sedation
- A - Analgesia: Pain relief at both spinal and supraspinal levels.
- C - Constipation & Cough suppression
- R - Respiratory depression → Common cause of death (Bradypnea)
- U - eUphoria
- M - Miosis: "Pin-point pupils" via stimulation of the Edinger-Westphal nucleus.
- NO - Nausea / Vomiting: Due to stimulation of the CTZ in the brain.
- G - Gallstones: Presents as biliary colic.
- A - Abdominal colic: Caused by the spasm of smooth muscle sphincters.
- P - Prolactin release

Important Information

- Opioids (morphine) are not given for Colicky pain
- Opioids are not given for a head injury
  - Respiratory depression → ↑CO_2 → ↑CSF → ↑ICP

- Morphine eye drops do not produce miosis → No topical action
  - Oral/IV → produce miosis (Stimulation of EWN)

Morphine And Congeners (Mu Agonist)

- Morphine → used in Myocardial Infarction & Acute LVF (Pulmonary edema)
  - Reduces Heart Rate and Preload.
  - Reduces the overall oxygen demand of the heart.
  - Pethidine & Pentazocine → C/I in MI
    → Increases HR & Oxygen demand
- Morphine is metabolised into two key glucuronides, which are excreted in the urine:
  - Morphine-6-Glucuronide: Active metabolite → Analgesic
  - Morphine-3-Glucuronide: Minor metabolite. → S/e → Convulsions in children.

Opioids C/I in Renal failure

P- Pethidine

C- Codeine

M- Morphine

- Morphine triggers histamine release from Mast cells → Asthma/Pruritis

Antitussives

Anti-tussive: S/e → Addiction & Sedation

- Codeine
- Hydrocodone
- Oxycodone
- Pholcodeine
- Morphine
- Hydromorphone
- Oxymorphone
- Levorphanol

Non-Addictive Anti-tussives- No Addiction & Sedation

- Dextromethorphan: Acts as an NMDA antagonist.
- Noscapine: Acts as a sigma agonist.

OTHER DRUGS

$$\text{Codeine} \xrightarrow{\text{CYP2D6}} \text{Morphine}$$

- Codeine: 1/10th as potent as Morphine. Use → Antitussive (cough suppressant).
- Diacetylmorphine (Heroin): 10 times more potent than Morphine.
- Longest acting opioid: Methadone
- Shortest acting opioid: Remifentanil
- Most Potent opioid: Sufentanyl → 1000 times potent & max protein-bound opioid.
- Least Potent opioid: Pethidine.

Pethidine (Meperidine)	• Mu Agonist + Anticholinergic (↑HR) • Uses: Pregnancy (DOC), Post-Anaesthetic Shivering

	• Prodrug (Active component → Meperidine) • Avoid with MAO inhibitors → Increased risk of Seizures
Tramadol & Tapentadol	• Mu Agonist + SNRI action • Avoid with MAO inhibitors → Serotonin syndrome
Methadone	• Mu Agonist + NMDA Antagonist • Longest acting opioid (Half-life: 40 Hours) • Oral methadone → Action starts in 20-40 minutes • Use: Maintenance therapy to prevent opioid withdrawal • S/e → QT prolongation
Remifentanyl	• Shortest-acting opioid. • Degraded by plasma esterase. • Ideal for Daycare Surgery ○ Often used with Propofol.

Fentanyl	• Highly lipid soluble
	• Uses:
	  ○ Transdermal: Chronic Cancer pain.
	  ○ Epidural analgesic
	  ○ Sublingual and IV: Acute pain
	• Fentanyl is NOT given by the ORAL route
	  ○ High First Pass Metabolism in the liver
	• S/e: Wooden Chest Syndrome

Drugs For Day Care Surgery

- General Anesthetic: Propofol
- Analgesic: Remifentanil
- Muscle relaxant: Mivacurium

Mixed Acting Opioids

00:53:35

- Partial k agonist + μ antagonist: Side Effect → Psychosis (d/t k agonist activity)
  - Pentazocine
  - Nalbuphine
  - Butarphanol:
    → Only opioid available as a nasal spray
    → Used for the treatment of Migraine.
- Partial μ Agonist + k Antagonist:
  - Buprenorphine: Used to prevent opioid withdrawal
  - Dezocine
- Pure Antagonist → Competitive blockers of μ/k/δ receptors
  - Naloxone (IV): Used as the antidote for opioid poisoning.
  - Naltrexone (oral): Used to prevent relapse in opioid addiction.
    → Hepatotoxic.
  - Nalmefene: No hepatotoxicity
  - Others: Naldemedine, Naloxegol, Naloxol.

Tolerance does NOT develop to these 3 effects of opioids:
- Constricted Pupil (Miosis)
- Constipation
- Convulsion

Opioid Addiction

Acute Morphine/Opioid Poisoning
- Clinical Features: Respiratory depression and pinpoint pupil.
- Antidote: IV Naloxone → Requires repetitive injections

↓

Maintenance (Detoxification Phase): To prevent withdrawal symptoms
- Opioids: Oral Methadone, Buprenorphine, Tramadol (taper slowly)
- Non-opioids: Clonidine and Lofexidine (2 Agonists)

↓

Prevent Relapse (Abstinence, Aversion therapy)
- Oral Naltrexone.

Opioids Used In Diarrhoea

- Opioids reduce intestinal motility
- Loperamide:
  - μ agonist → Non-addictive: Cannot cross the Blood-Brain Barrier (BBB).
  - DOC for Diarrhoea
    → IBS
    → Drug-induced diarrhoea- Irinotecan.
  - Contraindicated in Children.
- Diphenoxylate:
  - μ agonist → Addictive
  - Often combined with Atropine specifically to reduce addiction
- Racecadotril → Encephalinase inhibitor → Preferred for Diarrhea in children.

Treatment of Opioid-Induced Constipation: Give an Opioid Antagonist in the GIT
- Alvimopan
- Naloxone
- Naldemedine
- Methyl-Naltrexone

ANTI-EPILEPTIC DRUGS

01:02:10

- Acute Seizure Attack (>5 min) → Status Epilepticus FMGE 2025
  - Drug of Choice (DOC): IV. Lorazepam or IM. Midazolam (and other Benzodiazepines).
  - Refractory Status Epilepticus (IV): Valproate, Fos-phenytoin, Levetiracetam, Phenobarbitone.
- Maintenance in Epilepsy → At least 2 years

Types Of Epilepsy & First Line Drugs

- GTCS (Grand mal epilepsy) → Valproate, Lamotrigine
- Absence Seizure (Petit mal epilepsy) → Ethosuximide (DOC), Valproate, Lamotrigine

- EEG Finding: 3 Hz wave spike pattern
- No convulsions occur

- Atypical absence, Myoclonic seizure, Atonic seizure, and Tonic seizures:
  - Valproate
  - Lamotrigine
  - Topiramate
- Focal seizures:
  - **L** - Lamotrigine
  - **O** - Oxcarbazepine
  - **C** - Carbamazepine
  - **P** - Phenytoin
  - **L** - Levetiracetam
- Febrile seizures
  - Rectal Diazepam (DOC)
  - Intranasal Midazolam
- Infantile spasm (West syndrome) → ACTH (DOC) → ↓CRH
- Infantile spasm + Tuberous sclerosis → Vigabatrin (Lifelong)
- Lennox-Gestaut syndrome → Myotonic, Atonic & Tonic seizure
  - Valproate (DOC), Lamotrigine, Topiramate
  - Valproate resistance → Felbamate
- Dravet syndrome → Severe myoclonic epilepsy of Infancy
  - Valproate(DOC), Lamotrigine, Topiramate
  - Valproate resistance → Stiripentol

CANNABIDIOL: Approved for

- Infantile spasm + Tuberous sclerosis
- Lennox-Gastaut syndrome
- Dravet syndrome

Epilepsy In Pregnancy

- Most teratogenic → Valproate
- Safest → Levitiracetam > Lamotrigine
- Never stop AED
  - Add → Folic acid (4000μg/4mg) + Vitamin K

Lactation (in Milk)	
Valproate	Least secreted in milk
Levitiracetam	Maximim secreted in milk

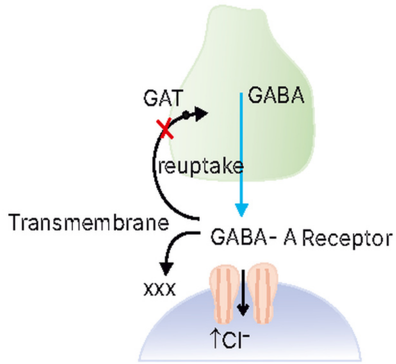
Classification Of Anti-Epileptics

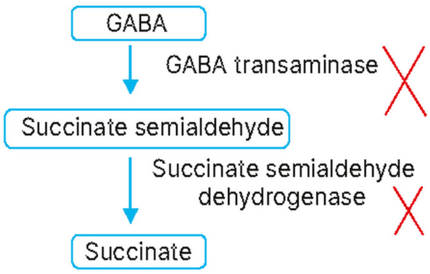
- Block Voltage-gated Na+ Channels: Used primarily for GTCS and Focal seizures.
  - PCV: Phenytoin, Carbamazepine, Valproate.
  - TOLL: Topiramate, Lamotrigine, Lacosamide, Zonisamide, Rufinamide.
  - Lacosamide works by prolonging the inactivation of the Na+ channel.

- Block "T" type Calcium Channels: Located in the Thalamus; used for Absence seizures.
    - VEL: Valproate, Ethosuximide, Lamotrigine.
    - Others: Zonisamide, Clonazepam.
- Ethosuximide → Not effective in GTCS, Focal Seizures. status epilepticus
    - D/t no effect on Na+ channels.
- Phenytoin and Carbamazepine → Not effective in Absence Seizures
    - D/t no effect on Ca++ channels.

Gabaergic Mechanisms Of Anti-Epileptics

- GABA receptor Agonists: Barbiturates, Benzodiazepines
- GABA Transaminase Inhibitors: Vigabatrin, Valproate
    - Blocks the degradation of GABA.
- GABA Transporter Inhibitor: Tiagabine
    - Blocks the reuptake of GABA
- Voltage-Gated Calcium Channel Blockers: Pregabalin, Gabapentin
    - Blockage of $\alpha 2\delta$ subunit of voltage-gated calcium channels
- Valproate inhibits GABA Transaminase and SSD → ↑ GABA





Vigabatrin

- **VI** → Visual field contraction (S/e)
- **GABA TRansaminase Inhibitor**
- Use → Infantile spasm + Tuberous sclerosis

Neuropathic Pain (DOC)
• Trigeminal Neuralgia → Carbamazepine • Post-herpetic Neuralgia → Pregabalin, Gabapentin • Diabetic Neuropathy → Pregabalin

Levitiracetam

- SV2A Inhibitor → Inhibits Glutamate release
- Nootropic: Increase memory
- Antioxidant → Neuroprotective

Brivaracetam → New AED

Piracetam → T/t of Alzheimer's Disease

Other Mechanisms

- NMDA Blocker: Felbamate (S/e: Aplastic Anaemia)
- AMPA Blocker: Perampanel, Telampanel

- Open K+ Channel: Ezogabine (Retigabine) (S/e: Blue Color Blindness)
- Cannabinoids: Cannabidiol
- Neurosteroids: Ganoxolone

Anti-Epileptics Requiring Eye Check-ups (VET)
- Vigabatrin (Visual field contraction)
- Ezogabine / Retigabine (Blue color blindness)
- Topiramate (Secondary Angle Closure Glaucoma)

Therapeutic Drug Monitoring In Anti-Epileptics

Therapeutic Range Values	
Phenytoin	10-20 mcg/ml
Valproate	50-100 mcg/ml
Phenobarbitone	15-40 mcg/ml
Carbamazepine	4-12 mcg/ml

Phenytoin (Phenyl Hydantoin)

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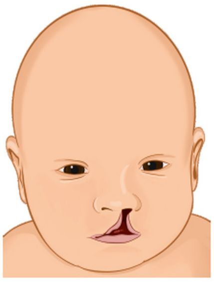

- Oral, Fosphenytoin (I.V): Status epilepticus
- Metabolism: CYP2C9
- Kinetics: Saturation kinetics or Zero-order kinetics
- Phenytoin and Carbamazepine:
  - Advantage: No Sedation/CNS Depression
  - Not effective in Absence seizure
  - Contraindicated in Myoclonic seizures
- Adverse Effects:
  - At high dose (Preventable): > 20
    - → Cerebellar toxicity: Ataxia, Nystagmus, Diplopia
    - → Cerebral toxicity
    - → Cardiac arrhythmia → Bradycardia (Class 1B Anti-Arrhythmic)
  - At normal dose (Non-Preventable): 10-20
    - → Hyperplastic gums (M/c)
    - → Hirsutism, Heavy weight, Hyperglycemia (DM) → PCOD
    - → Hamper Vitamin K, D Absorption → Osteomalacia
    - → Hamper folic acid absorption: Megaloblastic anaemia
    - → Hypersensitivity → Stop Phenytoin → Start Valproate
    - → Hodgkin-like pseudo-lymphoma

Carbamazepine

- **Side effects:**
  - Steven Johnson/Rash → HLA-B* 1502 → In children
  - Hepatotoxic
  - Aplastic Anemia

- Diplopia, Ataxia: Cerebellar Neurotoxic
- Enzyme Inducer → CYP ↑
- SIADH (excess ADH) → Hyponatremia → Old Age

Oxcarbazepine Vs Carbamazepine

FMGE 2021

	Oxcarbazepine	Carbamazepine
More Risk	Hyponatremia	Steven Jhonson
Avoided in	Old Age	Children

- Eslicarbazepine → Prodrug (Active form: Oxcarbazepine)
- All antiepileptics are CYP enzyme inducers except → Valproate
- All antiepileptics can cause Stevens-Johnson / Rashes except → BZDs (Diazepam, Lorazepam)

NEET PG 2025
INICET 2021, 2022

Valproate

01:31:46

- DOC:
  - BPD (Bipolar Disorder)
  - Epilepsy
  - Migraine prophylaxis
  - Syndenham's Chorea
- Side effects:
  - Vomiting (mc)
    → Divalproex: Less risk of vomiting
  - Alopecia
  - Liver Toxic (<2 Years): Children → Age specific S/E
  - Pancreatitis, PCOS: females → Gender specific S/E
  - Rashes
  - Obesity
  - Ammonia Increase → encephalopathy; T/t: L-CARNITINE
  - Tremors
  - Enzyme Inhibitor: CYP inhibitor
- Most teratogenic → Neural Tube Defects
- Sedative drug → Increase GABA levels

Topiramate/Zonisamide

- Carbonic anhydrase inhibitor
- Approved as anti-obesity drug → Causes weight loss
- Side effects: Angle closure glaucoma, Nephrolithiasis

PARKINSON DISEASE

01:35:30

- Neurogeneration of dopaminergic neurons in the Substantia nigra - Pars compacta of BG
- Toxin causing Parkinson → MPTP toxin

Levodopa (L-Dopa) →Cross Bbb
• Prodrug: Converted To Dopamine by DOPA Decarboxylase. • Inhibit peripheral DOPA Decarboxylase: Carbidopa, Bensarazide   ○ Combined with Levodopa (Syndopa) → ↑ Effectiveness. • Never combine Levodopa with Pyridoxine (Vit B6): ↑ Peripheral conversion. • C/I → Angle Closure Glaucoma, Melanoma.

Adverse effects of levodopa:

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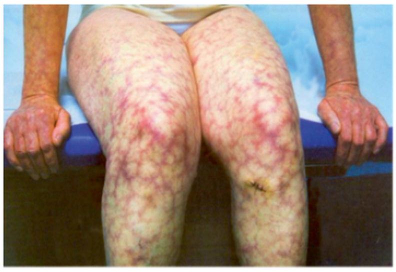
- Peripheral side effects: (Can be reduced by combining with Carbidopa)
  - Nausea/vomiting (M/c): Due to D2+ on CTZ
    → T/t of Levodopa induced vomiting → Domperidone (D2 Blocker)
  - Postural hypotension:
  - D2 → Vasodilation
  - Mydriasis: $\alpha1$ +
  - Arrhythmia: $\beta1$ +
- CNS side effects:
  - Dyskinesia (Basal Ganglia): T/t → Amantadine, Levetiracetam
  - Psychosis (Cortex): T/t → Antipsychotics (Clozapine, Quetiapine)
- On-off phenomenon with Levodopa:
  - Prolong On Phase:
    → MAO inhibitor
    → COMT inhibitor
    → Istradefylline (Adenosine (A2) Blocker)
  - Rescue Off phase: Inj. Apomorphine
- Levodopa cannot control Resting Tremor in Parkinson's disease.
- Levodopa is not used for Drug-induced Parkinsonism
- Drug-induced Parkinsonism:
  - Due to the blockage of D2 receptors.
  - Common agents:
    → Antipsychotics: Haloperidol, Risperidone
    → Antiemetic: Metoclopramide
  - Treatment: Anticholinergics are the DOC for drug-induced Parkinsonism & also for the treatment of resting tremors.
    → Benzhexol (Trihexyphenidyl) – DOC
    → Biperiden
    → Benztropine
    → Promethazine

Other Drugs

Drug Class	Specific Medications	Features
MAO-B Inhibitors (Irreversible)	Selegiline, Rasagiline	Only Neuroprotective drugs.
MAO-B Inhibitors (Reversible)	Safinamide	

COMT Inhibitors	Entacapone, Opicapone	Do not cross the Blood-Brain Barrier
	Tolcapone	Crosses BBB; Hepatotoxic (Drug of last resort).
NMDA Antagonist > D2 Agonist, Anticholinergic	Amantadine	Also: Antiviral (Influenza). Side Effect: Livedo Reticularis. 
Dopamine Agonist	Ropinirole, Pramipexole	Oral administration.
	Rotigotine	Transdermal / Cranial Patch.
	Apomorphine	Only Injectable drug DOC as Emetic Agent.

Other Movement Disorders

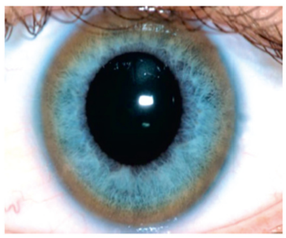
Condition	Primary Treatment / DOC	Alternative
Restless Leg Syndrome	Pregabalin / Gabapentin	
Huntington's Chorea	Dopamine Depletors: Valbenazine, Tetrabenazine	In resistant cases: Antipsychotics- Haloperidol, etc.
Tourette Syndrome (Tics)	2 Agonists: Clonidine, Guanfacine	
Sydenham's Chorea (Rheumatic Chorea)	Valproate	

Other Neurodegenerative Conditions

Wilson Disease

01:49:20

- Copper deposition in the liver, brain, and cornea (KF rings)
- DOC → Zinc (reduces absorption of Cu from GIT)
- Severe cases → Copper chelators
  - Penicillamine
  - Trientene
  - Tetrathiomolybdate



Amyotrophic Lateral Sclerosis (Loh Gehrig's Disease)

- Movement disorder
- Riluzole → NMDA Antagonist
- Edaravone → Antioxidant

Rett Syndrome → Trofinetide (Only approved drug)

Friedreich-Ataxia → Omaveloxolone

Progeria Syndrome → Lonafarib (Only approved drug)

Multiple Sclerosis 01:50:51

- Autoantibodies against the myelin sheath of neurons in the brain
- Relapsing Remitting MS (RRMS): Relapses followed by periods of remission.
  - T/t → Interferon-beta (DOC) + Glatiramer acetate
- Secondary Progressive MS: Initial relapsing-remitting phase followed by steady progression.
  - T/t → Mitoxantrone > Natalizumab
  - Maximum Improvement in EDSS Scale (Expanded Disability Status Scale).
  - Natalizumab S/e → Progressive Multifocal Leukoencephalopathy (PMLE)
    → Caused by the JC polyoma virus
- Primary Progressive MS: Characterised by continuous worsening of symptoms from the beginning without distinct relapses.
  - T/t → Ocrelizumab (anti-CD20)

DRUGS IN PSYCHIATRY 01:53:38

Psychosis				Neurosis
Insight → Absent				Present
Schizophrenia	**Mood disorder**			**Aka anxiety disorder**
Problem in thought	Mania	BPD	Depression- Unipolar	• GAD • PTSD • OCD • PMTS • Anorexia, Bulimia
T/t → Antipsychotics	T/t → Mood stabilizers • Lithium • Antipsychotics • Antiepileptics		T/t → Antidepressants → SSRIs (DOC)	

Anti-Psychotic Drugs

- MOA → Block Dopamine/Serotonin receptor
  - **Antiemetic** → Blockage of dopamine/serotonin receptors in the CTZ area
  - **Psychosis** → Blockage of dopamine/serotonin receptors in the cortex
  - D/t blockage in the basal ganglia:
    → **Chorea**
    → **Tics** (Tourette syndrome)

1st Generation: Typical Antipsychotics	2nd Generation: Atypical Antipsychotics (DOC)
Block Dopamine (D2) More	Block 5-HT 2 (Serotonin) More > Other action

Control Positive Symptoms only (Hallucination, Delusion, Aggression)	Control Positive + Negative Symptoms (Hallucination, Delusion, Aggression + Anhedonia, Apathy, Amnesia, Depression)
More Risk Of: Parkinson's Disease & ↑ Prolactin	More Risk Of: ↑ Appetite → Metabolic Syndrome

Typical Antipsychotics (Neuroleptics)

FMGE 2024
INI CET 2025 02:00:25

Class	Suffix	Examples	Features
Phenothiazine	-Azine	Chlorpromazine, Thioridazine, Fluphenazine, Perphenazine, Prochlorperazine	**Least Dopamine Blockage:** Chlorpromazine & Thioridazine have the least risk of Parkinsonism.
Thioxanthenes	-THIX-	Thiothixene, Flupenthixol, Zuclopenthixol	
Butyrophenone	-RIDOL	Haloperidol, Droperidol, Benperidol, Penfluridol	**Maximum Dopamine Blockage:** Max risk of Parkinson's Disease & ↑ Prolactin.

- Droperidol + Fentanyl → Neurolept Analgesia
- Droperidol + Fentanyl + N2O (GA) → Neurolept Anesthesia

Atypical Antipsychotics

FMGE 2021, 2024

Receptors	Drugs		Features
$5\text{-}HT_{2A} >> D_2$ antagonist	**- PINE** Clozapine Olanzapine Zotepine Asenapine Quetiapine	**- DONE:** Ziprasidone Risperidone Ilaperidone Sertindone Paliperidone Lurasidone	**Clozapine:** Least risk of Parkinsonism **Risperidone:** Maximum risk of Parkinsonism and ↑ Prolactin
D_1/D_2 Partial agonist + $5HT_2$ antagonist	-PIPRAZOLE: Aripiprazole Brexipiprazole		S/e: ↑ Vomiting
$D_2 + D_3$ antagonist	Sulpiride Amisulpiride Levosulpiride		Sulpiride: Prokinetic (↑GIT motility) → T/t of GERD.
$5\text{-}HT_{2A}$ inverse agonist	Pimavanserin		No Risk of Parkinson's disease. Indicated for Psychosis in Parkinson's disease.

Q. Which antipsychotic does not act on Dopamine (D2) receptors?
Ans: Pimavanserin

Yourwish

Q. Overall, the least risk of Parkinson's / Prolactin elevation?

Ans: Pimavanserin > Clozapine

Q. Least risk of Prolactin elevation / Parkinson's among typical antipsychotics?

Ans: Chlorpromazine & Thioridazine

Q. Maximum risk of Prolactin elevation / Parkinson's among atypical antipsychotics?

Ans: Risperidone

- New antipsychotic drug: Xanomeline
  - Muscarinic receptor agonist
  - Does not act on the dopamine receptor
  - No risk of drug-induced Parkinson's disease

Route Of Administration

- **Oral:** All drugs
  - Poor compliance → Intramuscular Depot (Z Technique)

Intramuscular Depot (Z Technique)	
Typical Antipsychotics	**Atypical Antipsychotics**
Haloperidol Fluphenazine Zuclopenthixol Perphenazine	Paliperidone Aripiprazole Risperidone Olanzapine

- **Intranasal:** Loxapine
- **Sublingual:** Asenapine

Specific Drugs & Notable Effects

- Chlorpromazine: DOC for Intractable Hiccups.
- Thioridazine: Banned → d/t Retinal degeneration.
- Cataract: Clozapine > Quetiapine
- QT prolongation: Ziprasidone, Sertindole, Quetiapine
- Max weight gain/obesity: Olanzapine
- Least weight gain: Aripiprazole, Ziprasidone

Adverse Effects of Dopamine Blockage

- Prolactin Increase: ↑
  - Mechanism: Dopamine blockage in the HPA (Hypothalamic-Pituitary Axis).
  - C/f: Galactorrhea, Amenorrhea, Infertility.
- Extrapyramidal Symptoms (EPS) → Dopamine blockage in the BASAL ganglia.

Extrapyramidal Symptoms (Eps)

- Mnemonic: (Never - A P A R T)

EPS	Features	Treatment
Neuroleptic Malignant Syndrome - Emergency	Rigidity, Hyperthermia, Rhabdomyolysis, Myoglobinuria (Fatal) → Cola Cola urine	Dantrolene (DOC) • Muscle Relaxant Bromocriptine (D2+)
Acute Muscle Dystonia 1st Dose (First EPS)	Spasm of muscles of the tongue, face, Uprolling of eyes (oculogyric crisis)	Anticholinergic agent (inj.) • Benzhexol • Benztropine • Promethazine
Parkinsonism Weeks	Bradykinesia, rigidity, tremor.	Anticholinergic agent (oral): Benzhexol etc
Akathisia - Months	Restlessness, inability to sit (Anxiety)	Propranolol (DOC)
Rabbit Syndrome Months	Perioral Tremors	Anticholinergic agent (oral): Benzhexol etc
Tardive Dyskinesia Years/Last EPS Permanent EPS	Chorea	Dopamine Depletors • Valbenazine • Tetrabenazine

Dantrolene (Muscle Relaxant) 02:16:16

- Ryanodine receptor antagonist (RyR-1 blocker)
  - Present in Smooth ER → Blocks the release of Calcium
  - Given for Neuroleptic Malignant Syndrome
- DOC for Malignant Hyperthermia

Drugs Causing Malignant Hyperthermia

- Succinyl choline
- Halothane (Max) > Fluranes
- Atropine
- Lignocaine

Clozapine INICET 2023

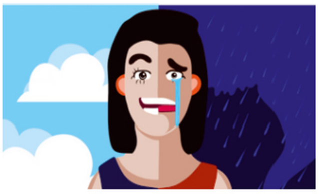
- Most effective antipsychotic + Anti-suicidal drug
  - Anti-suicidal → Clozapine & Lithium

Adverse Effects:

Non-Serious	Serious
Hypersalivation - Wet Pillow Syndrome Obesity Type II DM Sedation → d/t chemical structure ○ Di-Benzodiazepine	Seizures Agranulocytosis (↓WBC/Neutropenia) • Dose independent S/e of clozapine • Stop clozapine if: ○ WBC < 3000 ○ Neutrophils < 2000 Myocarditis

Mood Stabilizers

INI CET 2022 02:20:38


Bipolar Disorder

- T/t of BPD
- Off-label use (Not approved for BPD)
  - Topiramate
  - Oxcarbazepine

Drugs	
Low	**Lithium**
V	Valproate
O	Oxcarbazepine, Carbamazepine
L	Lamotrigine
T	Topiramate
A	**Antipsychotics**
Ge	Gabapentin

Bipolar Disorder (Bpd) Treatment

FMGE 2023

- Acute mania: i/v Lithium, Valproate, Antipsychotics
- Maintenance of BPD: Oral Lithium (DOC)
- Rapid Cycling BPD (>3 Attacks/year): Valproate
- BPD in Pregnancy
  - Most teratogenic: Valproate
    → Never started in pregnancy
  - Safest: Antipsychotics
- Anti-Depressants (AD) in BPD:
  - ADs are not mood stabilisers
  - They can precipitate MANIA ↑ → Never used alone in BPD

Lithium

02:25:00

FMGE 2023, 2024
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- T/t of Bipolar disorder
- Anti-suicidal drug (Also Clozapine)
- C/I → During breastfeeding
- Lithium stopped → 24 Hours before surgery

Lithium citrate/carbonate	
Route	Oral → 100% BA, IV
Half life	24 Hours
Metabolism	No
Excretion	Urine (95%)>Sweat, Saliva, Milk

Lithium Serum Level Monitoring

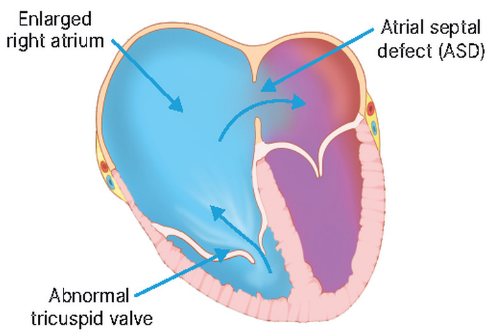
- Blood sample taken 12 Hours after the last dose

Lithium Serum Level	Clinical
0.6 - 1.0 meq/L	Maintenance of bipolar disorder
1.0 - 1.5 meq/L	Acute mania
> 1.5 meq/L	Toxicity
> 4 meq/L	Start Hemodialysis

- Management of Lithium Toxicity:
  - Saline: NaCl (Hydration)
  - Mannitol (Diuretic)
  - Amiloride (Diuretic)
  - C/I → Thiazides
- ECG Changes with Lithium:
  - T wave flattening/T-inversion → Characteristic
  - Inhibit SA node → Increase R-R interval
  - Inhibit AV node → Increase P-R interval
  - QT shortening

Adverse effects of lithium:

- Leucocytosis: ↑ WBC
- Increase weight
- Tremor:
  - Normal dose: Fine tremors
  - Toxic dose: Coarse tremors
- Hypothyroid Goitre
  - Inhibit T3/T4 synthesis → ↑ TSH
- Increase nausea, vomiting, diarrhoea: M/c → GIT
- Urination: Nephrogenic diabetes insipidus
  - Block ADH → Polyuria
- Mental: Ataxia, tinnitus, seizures
- Skin: Acneiform eruption
- Teratogenic → Ebstein Anomaly (Cardiac Anomaly)

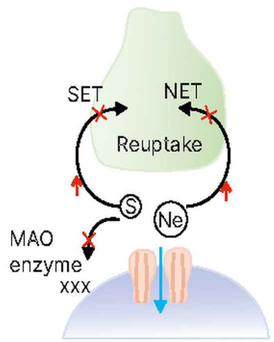


Ebstein anomaly due to lithium used in bipolar disorder

ANTI-DEPRESSANT DRUGS

- ↑ Serotonin & NE in the brain
- Drugs:
  - SSRI: Selective Serotonin Reuptake inhibitor
  - SNRI: Serotonin Nor-epinephrine Reuptake inhibitor
  - NRI: Nor-epinephrine Reuptake inhibitor
  - TCA: Tricyclic Antidepressants
  - MAO inhibitor
  - Atypical Antidepressant: Other MOA

02:31:42



Yourwish

- Synaptic action:
  - SERT & NET Blockage: Inhibits the Reuptake of Serotonin & NE
  - MAO enzyme block: Prevents the breakdown of neurotransmitters.

Treatment of depression & anxiety (gad, ocd, ptsd, phobia, pmts, anorexia):

- Acute phase:
  - Depression → ECT (Electroconvulsive Therapy)
  - Anxiety → Benzodiazepines
- Maintenance phase → SSRI — NEET PG 2024, FMGE 2021
  - In resistant cases → SNRI

Ssri	Snri	Nri
Fluvoxetine Fluvoxamine Paroxetine Dapoxetine Escitalopram Citalopram Sertraline	Venlafaxine Milnacipran Duloxetine **Other uses of Duloxetine:** 1. Diabetic neuropathy 2. Urinary (stress) incontinence	Atomoxetine (Used for: ADHD + Tourette syndrome)

- **Longest:** Fluoxetine
- **Shortest:** Paroxetine (SSRI), Venlafaxine (SNRI)
- **Safest:** Escitalopram (Heart Disease)

Side Effects Of Ssri

- Nausea/vomiting (M/c)
- Secretions Reduced: Dry Eyes And Mouth
- Seizures, Vivid dreams
- Sexual Dysfunction: Anorgasmia, Delayed Ejaculation
  - SSRI (DOC) for Premature Ejaculation
- Antidepressants in pregnancy → In Fetus → Pulmonary artery hypertension

Drug Discontinuation Syndrome: (Rebound Anxiety, Insomnia, Suicides)

- **Maximum risk:** Paroxetine, Venlafaxine
- **Least risk:** Fluoxetine

Tricyclic Antidepressants (Tca)

02:39:30

NEET PG 2022, 2024

-Pramine	Others
Imipramine Des imipramine Clomipramine Trimipramine	Doxepin Amoxapine Reboxetine Dothepin
-triptylline	
Amitriptyline Nortriptyline	

Mechanism Of Action

- SNRI + "Block unwanted receptor"
- Block Histamine → H1 receptor → Sedation
- Block Muscarinic Ach (Atropine like) → Hyperthermia, mydriasis, urinary retention
  - C/I: Glaucoma
  - Imipramine: (T/t of Nocturnal enuresis)
- α block → Hypotension
- Na+Block → QT prolongation
- TCA requires monitoring: YES (unsafe)
  - SSRI: Safe / No monitoring
- Antidote of TCA Poisoning: Sodium Bicarbonate

Mao Inhibitors

Irreversible	Reversible
Hit & Run drugs	• No QT prolongation • Safe in Heart Disease
Tranylcipromine Phenelzine	Moclobemide Clorygyline

Atypical Antidepressants

02:43:30

Drug	Mechanism	Clinical
Bupropion	NDRI (NE Dopamine Reuptake inhibitor)	• Anti-smoking • Anti-obesity S/e: Seizure
Trazodone	Prolong penile erection → Priapism (S/e)	
Mirtazapine **Mianserin**	2 Blocker → Sedation	T/t → Insomnia + depression
Buspirone	$5HT_{1A}$ Agonist	Anti-Anxiety
Vortioxetine **Vilazodone**	New SSRI	
Ketamine (IV) **Esketamine (Nasal spray)**	Acute Depression	
Brexanolone **Zuranolone**	Progesterone derivative → T/t: Postpartum depression • Postpartum depression → DOC: SSRI	

2. AUTACOIDS

HISTAMINE

00:00:37

Production of Histamine

- Source: Histamine is produced from the histidine amino acid
- Synthesis: Histidine is converted to Histamine by Histidine decarboxylase enzyme
- Histamine receptors- H1, H2, H3, H4
- Receptor Type: All histamine receptors are G protein-coupled receptors (GPCR)

H1 receptor

- Type: Excitatory, Gq type of GPCR
- Location and Storage:
  - Present in the brain (CNS)
  - In the periphery: Histamine stored in mast cells → mast cells release histamine

H1 Receptor Actions in Brain	H1 Receptor Actions in the Periphery
• Neurons release histamine as a neurotransmitter: ○ Produces wakefulness ○ Increases memory ○ In the vestibule of the inner ear, Histamine causes vomiting and vertigo → Motion sickness → Seasickness → Morning sickness	• Function: Responsible for allergic reactions (Type 1 hypersensitivity) • Mechanism: Mast cells release histamine → Produce allergic reaction ○ Triple Response in Hypersensitivity: Redness, Wheal, Flare • Additional Effect: Can lead to vasodilation

Antihistaminic Drugs (H1 Receptor Blockers)

- Classification:
  - First-Generation Antihistaminics- Can cross the blood-brain barrier
  - Second Generation Antihistaminics- Do NOT cross the blood-brain barrier
    → Exception: Cetirizine

EFFECTS OF 1st GENERATION ANTIHISTAMINICS	EFFECTS OF 2nd GENERATION ANTIHISTAMINICS
• Effects of blocking H1 receptor in the Brain • Opposite effects occur: Memory loss • Used as antiemetic drugs for: ○ Motion sickness ○ Seasickness ○ Morning sickness • Used as anti-vertigo drugs • Additional Property: Also block acetylcholine receptors → have anti-cholinergic effect	• Action: Only block histamine outside the brain in the periphery (where it produces allergic reactions) • Use: Only as anti-allergic drugs • Properties they don't have: ○ Do not produce sedation ○ Do not produce memory loss ○ Doesn't have an antiemetic property ○ Doesn't have an anti-vertigo property

Contraindications of 1ST Generation Antihistaminics

- Absolutely contraindicated in Pilots, Drivers, & Machinery workers
- Reason: They are sedative drugs → can lead to accidents
- Not prescribed during the daytime to normal patients (can lead to accidents)
- Exception: Chlorpheniramine
  - Least sedative 1st generation antihistamine
  - Only 1st generation drug that can be given during the daytime

First Generation Antihistaminic Drugs

- Identification: Drugs ending with "-zine" or "-amine"

Promethazine	• Most sedative 1st-generation antihistaminic drug • Has maximum anti-cholinergic effect • Given in the treatment of drug-induced Parkinson's disease (EPS - Extrapyramidal Symptoms)
Diphenhydramine	• Available as a transdermal patch for motion sickness
Hydroxyzine	• Longest acting drug • Active form = Cetirizine (2nd generation antihistamine)
Doxylamine	• With Vitamin B6 (Pyridoxine) = Drug of choice for morning sickness (vomiting during 1st trimester of pregnancy)
Other Drugs	• Cyclizine • Meclizine • Cinnarizine • All these can be given in motion sickness and seasickness
Cyproheptadine	• Also blocks serotonin receptor → has anti-serotonin property • Given for the prevention of migraine (due to anti-serotonin property)
Chlorpheniramine	• Least sedative among 1st generation antihistaminic drugs • Can be prescribed during daytime

Second Generation Antihistaminic Drugs

- Use: Only for mild allergy (rashes, dry cough, urticaria)
- Not used for severe allergy
- Severe Allergy = Anaphylaxis:
  - The patient goes into shock
  - Drug of choice: Adrenaline intramuscular injection

Drugs

Terfenadine and Astemizole	• Reason to be banned: Increasing QT interval prolongation on ECG → increasing risk of Torsades de Pointes (arrhythmia)

Fexofenadine	• Ends with "-nadine"
	• Active form of Terfenadine
	• Advantages:
	  ○ No risk of QT prolongation
	  ○ Non-sedative antihistaminic drug
	• Brand name: Allegra
	• Used in allergic reactions

Cetirizine	• Sedative, 2nd-generation antihistaminic drug • Can cross the blood-brain barrier • From Cetirizine → made Levocetirizine (levo form) • Levocetirizine requires a half dose → less sedative compared to Cetirizine

Topical Preparations (Eye Drops & Nasal Drops)

- Used for Allergic rhinitis and allergic conjunctivitis

Azelastine	• Has maximum topical activity • Most effective drug
Ketotifen and Olopatadine	• Have additional mast cell stabilizing action • Additional anti-allergic effect

Special Antihistaminic Drugs

Betahistine	• Mechanism: NOT an antagonist of the H1 receptor, rather a partial H1 agonist
	• Does NOT completely block H1 receptor
	• Use: Treatment of vertigo
	• Brand Name: Vertin
	• Indications: Any type of vertigo (ENT):
	  ○ Benign positional vertigo
	  ○ Meniere's disease, etc.

Tiprolisant (Pitolisant)	• Mechanism: H3 receptor inverse agonist • Effect: Causes wakefulness • Approval: For the treatment of narcolepsy • Note: In narcolepsy, the drug of choice was Modafinil (previously)

Drug of Choice Summary

Motion Sickness and Seasickness	• Motion sickness: Vomiting when sitting in a car or bus
	• Seasickness: Vomiting when roaming on a ship
	• Drugs: End with "-zine" or "-amine"
	  ○ Scopolamine (an anti-cholinergic drug)
	  ○ Diphenhydramine
	  ○ Cyclizine
	  ○ Meclizine
	  ○ Cinnarizine
	• Note: Diphenhydramine and Scopolamine are also available as a transdermal patch
	• All above (including Diphenhydramine and -zine drugs): 1st generation antihistaminic drugs

Morning Sickness	• Definition: Vomiting in pregnancy
	• Drug of Choice: Doxylamine + Vitamin B6 (Pyridoxine)
	• First Treatment:
	  ○ Tell mother to take small amounts of frequent meals
	  ○ Stomach should not become full → no vomiting
	  ○ If doesn't work → start Doxylamine + B6

Mountain Sickness	• No vomiting in mountain sickness
	• Respiratory depression at very high altitude
	• Drug of Choice: Acetazolamide
	• First Treatment (NOT Acetazolamide):
	  ○ Check if the patient is going into hypoxia
	  ○ Check SpO_2 (saturation of oxygen)
	  ○ If falling → Rapid descent to a lower altitude

SEROTONIN

00:13:06

- Another Name: 5-Hydroxytryptamine (5-HT)
- Serotonin (Tryptamine) is produced from the Tryptophan amino acid
- Synthesis Pathway:

$$\text{Tryptophan} \xrightarrow{\text{Tryptophan Hydroxylase}} \text{5- Hydroxytryptophan} \xrightarrow{\text{Tryptophan Decarboxylase}} \text{Serotonin}$$

Serotonin Receptors

- Total Receptors: 7 receptors (5-HT1 to 5-HT7)
- Type: All are GPCR (G Protein Coupled Receptors)
- Exception: 5-HT3 receptor = Ionotropic receptor

5-HT1 receptor

5-HT1A Receptor	**BUSPIRONE (PARTIAL AGONIST)** • Use: Anti-anxiety drug for generalized anxiety disorder

5-HT1B and 1D Receptor	**TRIPTANS (SUMATRIPTAN) & ERGOTAMINE**
	• Drug of choice for an acute attack of migraine
	
	Migraine Pathophysiology
	• Brain neurons (trigeminal neurons) release inflammatory mediators:
	  ○ Serotonin
	  ○ CGRP (Calcitonin Gene-Related Peptide)
	• This leads to vasodilation → throbbing or pulsatile headache in migraine
	• Neurons contain: 5-HT1B and 1D receptors

	Triptans - Mechanism Of Action
	• Actions:
	  ○ Inhibits the release of serotonin and CGRP from neurons
	  ○ Act on blood vessels → produce vasoconstriction in migraine
	• Consequence of Vasoconstriction:
	  ○ Can lead to increased blood pressure
	• Contraindicated in:
	  ○ Hypertension patients (vasoconstriction → hypertension)
	  ○ Heart disease patients (angina, MI)
	  ○ Can cause coronary vasoconstriction

5-HT1F Receptor	**LASMIDITAN** • Mechanism: 5-HT1F Agonist • New drug for: Acute attack of migraine • Action: Only inhibits the release of serotonin (acts on 5-HT1B and 1D receptors) • Key Difference: Lasmiditan has no vasoconstrictive action • Advantage: Safe in heart disease patients (where Triptans are contraindicated)

Ergotamine

- Type: Non-specific drug
  - Also stimulates 5-HT1B and 1D receptors
  - Also has alpha-blocking action (alpha blocker)
- Hydrogenation: Ergotamine → Dihydroergotamine
  - Increases alpha-blocking action
  - Reduces the 5-HT1B and 1D action of Ergotamine

Triptan Drugs

- Mechanism: Specific 5-HT1B and 1D Agonists

Sumatriptan	• Routes of Administration: Oral, Injection, & Nasal spray
	• Nasal Spray:
	  ○ In migraine, the patient sometimes has vomiting
	  ○ Cannot give an oral drug in vomiting
	  ○ Can give a nasal spray

Eletriptan	• The most effective drug for acute migraine
Rizatriptan	• "Riza" means rapid • Fastest acting Triptan
Frovatriptan	• "Frova" means far • Longest Triptan
Zolmitriptan	• Available as a nasal spray

Ergotism

- Definition: Dry gangrene of fingers due to Ergotamine
- Mechanism
  - Triptans and Ergotamine produce vasoconstriction
  - If vasoconstriction occurs in fingers → ischemic necrosis of fingers
  - Dry gangrene of fingers
- Clinical Feature: Blackening of fingers (fingers will rot)
- Treatment of Ergotism:
  - Give vasodilator
  - Drug of choice: Nitroprusside

Migraine Prophylaxis

- Drug of Choice for Prophylaxis: Propranolol
  - Produces vasoconstriction
  - Beta blocker
    → Contraindicated in asthma patients
- If the patient has asthma, give other drugs **(Mnemonic: A C T)**
- A - Anti-epileptic Drugs (3 approved):
  - Valproate
  - Topiramate
  - Gabapentin
- C - Calcium Channel Blockers:
  - Flunarizine (approved for migraine prevention)
  - Verapamil
- T - TCAs (Tricyclic Antidepressants):
  - End with "-triptyline"
  - Amitriptyline
  - Nortriptyline
  - Can be given to asthmatic patients

CGRP Inhibitors (New Class)

- CGRP: Calcitonin Gene-Related Peptide (inflammatory molecule causing migraine)
- For Acute Attack
- Drugs: End with "-gepant"
  - Ubrogepant
  - Rimegepant (recently asked)
  - Atogepant
- Use: Acute attack of migraine
- Advantage: Do NOT produce vasoconstriction → Safe in heart disease patients (unlike Triptans)
- For Prophylaxis
  - Drug: Erenumab (Monoclonal antibody)
  - Blocks the CGRP receptor
  - Given for prophylaxis/prevention of migraine

Yourwish

Migraine In Pregnancy

- Important Rule: Never give any drug for prophylaxis
- Only treat: Acute attack of migraine in pregnancy
- Drug of Choice: Paracetamol (safest drug)

5-HT2 receptor

00:23:32

5-HT2C RECEPTOR	• Mnemonic: 2C = Too much Calorie
	• Agonist Action: Suppresses calorie intake/suppresses appetite
	• Drug: Lorcaserin
	  ○ Approved as an anti-obesity drug (reduces appetite)
	  ○ Later BANNED
	  ○ Reason: Increasing risk of GIT cancers

5-HT2 A, B, C RECEPTOR ANTAGONISTS	• Drugs: Atypical antipsychotics
	  ○ Olanzapine
	  ○ Clozapine
	• Effect (since blocking 5-HT2):
	  ○ Increase appetite
	  ○ Can increase the risk of obesity
	  ○ Which causes maximum obesity: Olanzapine

5-HT2 to 5-HT4 ANTAGONISTS	• Block all subtypes → known as Anti-serotonin drugs
	• Drugs:
	  ○ Ketanserin
	  ○ Ritanserin
	  ○ Cyproheptadine
	• Cyproheptadine:
	  ○ Drug of choice for Serotonin Syndrome (excessive serotonin in the body)
	• Ketanserin and Ritanserin:
	  ○ Previously used in migraine prophylaxis

5-HT3 Receptor

00:25:33

- Only have: Blockers/Antagonists
- Drugs: End with "-setron"

ALOSETRON	• Action in GIT:
	  ○ Normally, serotonin increases GIT motility, → causes diarrhea
	  ○ Blocking 5-HT3 receptor → anti-motility drug
	  ○ Reduces GIT motility
	• Use: Treatment of diarrhea in Irritable Bowel Syndrome (IBS)
	• Important:
	  ○ Only given in FEMALES
	  ○ Feminist drug
	  ○ Contraindicated in MALE patients
	  ○ Gender-specific drug
	  ○ Reason: In males, it can lead to ischemic colitis

SETRONS AS ANTI-EMETIC DRUGS	• Location: CTZ (Chemoreceptor Trigger Zone) area of the brain = vomiting center • Action: Blocking 5-HT3 receptor in CTZ → decrease vomiting • Indications (Drug of Choice): ○ CINV: Chemotherapy-Induced Nausea and Vomiting (anti-cancer drugs) ○ RINV: Radiotherapy-Induced Nausea and Vomiting ○ Nausea and vomiting due to GIT infections (gastroenteritis) • Drugs: ○ Ondansetron ○ Granisetron ○ Tropisetron ○ Ramosetron ○ Palonosetron (longest acting) • Main Side Effect of Ondansetron: ○ Reduces GIT motility → constipation ○ On heart: QT prolongation • Important: Ondansetron-like drugs are NOT effective in motion sickness • In motion sickness → give antihistaminic drugs

Chemotherapy-induced Nausea and Vomiting (Detailed)

- Mechanism:
  - Anti-cancer drugs kill GIT cells (rapidly dividing)
  - Inflammatory molecules released → Go to the brain → stimulate CTZ area → vomiting
- Anti-cancer drug with maximum risk: Cisplatin

Treatment Strategy

1. Early Phase Treatment

- First Drug of Choice: Setrons
  - Ondansetron
  - Granisetron
  - Palonosetron
  - Block: 5-HT3 receptor of serotonin (5-HT3 antagonist)
- Drawback:
  - Only effective up to 24 hours
  - This is the early phase of nausea and vomiting
- If vomiting continues beyond 24 hours: Delayed Phase

2. Delayed Phase Treatment

- Drug of Choice: Aprepitant (Pitants)
- Mechanism:
  - Block NK1 receptor (Neurokinin-1 receptor)
  - Receptor of Substance P (released from the GIT)
- Drugs: End with "-pitant"
  - Aprepitant
  - Fosaprepitant

- Rolapitant
- Netupitant
- In Resistant Cases:
    - Add Corticosteroid: Dexamethasone
    - Still resistant → Give CB1 (Cannabinoid-1) receptor AGONISTS

3. Cannabinoid Drugs

- Mechanism: Stimulate cannabinoid receptor (NOT antagonists - rather AGONISTS)
- Drugs: Contain "-nab-" word
    - Dronabinol
    - Nabilone
- Action: Also suppresses nausea and vomiting
- What are Cannabinoids: Bhang, Charas, Ganja, Marijuana
- Effect: Increases appetite
- Which antiemetic drugs stimulate appetite:
    - Dronabinol and Nabilone
- Additional Use: Treatment of Cachexia
    - Cachexia = severe weight loss
    - Seen in AIDS patients
    - Seen in cancer patients
    - Given for AIDS-related weight loss, cancer-related weight loss/cachexia

4. Palonosetron

- Longest setron
- Can be given in the delayed phase also
- Other setrons only given up to 24 hours (early phase)

Prokinetic Drugs

00:31:53

- Pro = increase
- Kinetic = GIT motility
- Increase GIT motility/muscle contraction

Uses of Prokinetic Drugs

- Constipation (increased intestinal contraction → food passes forward)
- Gastroparesis (stimulates stomach motility when the stomach is not contracting)
- GERD (Gastroesophageal Reflux Disease)
    - Contract LES (Lower Esophageal Sphincter)
    - Food won't move upward from the stomach to the esophagus

Principle of Prokinetic Drugs

- Serotonin and Acetylcholine → INCREASE GIT motility (stimulate their receptors)
- Dopamine → REDUCES GIT motility (blocks dopamine receptor)

Classes of Prokinetic Drugs

SEROTONIN 5-HT4 AGONISTS	• Drugs: End with "-pride"
	  ○ Cisapride
	  ○ Mosapride
	  ○ Renzapride
	  ○ Itopride
	  ○ Prucalopride:
	    → Acts on 5-HT4 Agonist
	    → Approved for treatment of constipation
	• Banned Drugs: Cisapride and Tegaserod
	• Reason: Causing QT prolongation → increasing risk of Torsades de Pointes (arrhythmia)

DOPAMINE RECEPTOR BLOCKERS	• Drug: Domperidone
	  ○ Blocks dopamine → prokinetic action
	  ○ Method: Inhibit cholinesterase enzyme → Increase Acetylcholine Levels
	• Drug: Neostigmine (Anticholinesterase)
	  ○ Given for POPI (Post-Operative Paralytic Ileus)
	  ○ After the operation → person suffers from constipation

ERYTHROMYCIN	• Antibiotic with Prokinetic Effect • Erythromycin (increases GIT motility) ○ Sometimes given in the treatment of gastroparesis

METOCLOPRAMIDE	• 5-HT4 Agonist
	• Dopamine D2 Blocker
	  ○ Increases Acetylcholine levels
	• Drugs that Block Dopamine:
	  ○ Domperidone
	  ○ Metoclopramide

Dopamine D2 Antagonists

- Effects of Dopamine Blockers:
  - Prokinetic effect (in GIT)
  - Antiemetic action (in the CTZ area of the brain)
- Key Difference:
  - Domperidone: CANNOT cross the blood-brain barrier
  - Metoclopramide: CAN cross the blood-brain barrier
- Consequence:
  - Metoclopramide enters the brain → blocks dopamine receptors
  - Causes Drug-Induced Parkinson's Disease (by blocking dopamine in the brain)
  - NOT seen with Domperidone
- Drug-Induced Parkinsonism:
  - Also known as muscle dystonia or muscle rigidity
  - Treatment of Drug-Induced Parkinsonism: Give an anti-cholinergic drug
    → Drug: Benzhexol (for drug-induced Parkinson's disease)

Domperidone

Metoclopramide

Yourwish

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PROSTAGLANDINS

00:37:00

Prostaglandin E1

- Drugs: M-A-L
- Misoprostol
  - Drug of Choice for: Medical Abortion (MTP - Medical Termination of Pregnancy)
  - Can be given in 1st trimester of abortion
    → Up to 63 days of pregnancy
  - Additional Use: NSAID-induced peptic ulcer
  - Most Common Side Effect: Diarrhea
    → Increases chloride secretion in the intestine
  - Teratogenic Effect: If an incomplete abortion occurs
    → Mobius Syndrome- Malformation/defect in the 6th and 7th cranial nerves
- Alprostadil
  - Drug of Choice: To open the Ductus Arteriosus
- Lubiprostone
  - Type: Laxative (causes diarrhea)
  - Mechanism: Causes chloride secretion (like Misoprostol)
  - Use: Treatment of constipation in IBS (Irritable Bowel Syndrome)

Prostaglandin E2 Analog

- Mnemonic: "2" word coming → 2nd trimester abortion
- Drug: Dinoprostone (Prostaglandin E2)
  - Formulation: Available as a vaginal cream
  - Action: Only dilates the lower segment of the uterus (cervix)
  - Use: Drug of choice for cervical ripening

Prostaglandin F2-Alpha

- Mnemonic: "2" → 2nd trimester abortion
- Drugs:
  - Dinoprost (Prostaglandin F2-alpha) - NOT Dinoprostone
  - Carboprost
  - Latanoprost
  - Bimatoprost
  - Travoprost
- Formulation: Injection
- Carboprost is available as an intramuscular injection
- Action: Act on the upper part of the uterus
  - Contract the upper part of the uterus → child delivery
  - After delivery → contract the uterus to control PPH (Postpartum Hemorrhage)
- Uses:
  - 2nd trimester abortion
  - Control PPH (Postpartum Hemorrhage)
- Important Note:
  - Dinoprostone (E2) is NOT available as an injection
    → Cannot act on the upper uterus
    → NOT given to control PPH

- Only Dinoprost and Carboprost are given for PPH control
- Carboprost
  - Contraindication: Absolutely contraindicated in asthma
  - Dose for PPH:
    - → 250 microgram intramuscular injection
    - → Maximum 8 injections in one day
    - → Maximum dose = 2000 micrograms/day

Prostaglandin F2-Alpha (Eye Drops)

- Drugs:
  - Latanoprost
  - Bimatoprost
  - Travoprost
- Use: Drug of choice for the treatment of Glaucoma

Prostaglandin I2 (Prostacyclin)

- Also Known As: Prostacyclin
- Drugs:
  - Treprostinil
  - Iloprost
  - Epoprostenol
- Use: Drug of choice for PAH (Pulmonary Artery Hypertension)
- Mechanism: Vasodilatory action + antiplatelet effect

Thromboxane A2

- Opposite of PGI2
- Actions:
  - Produces vasoconstriction (opposite of PGI2)
  - Causes platelet aggregation and platelet-rich thrombus
  - Formation of platelet-rich thrombus
- Relationship: Prostaglandin I2 and Thromboxane A2 produce opposite effects
- Definition: Molecules producing opposite action = Physiological Antagonists

Medical Abortion - Guidelines

Day 1 **(First Visit)**	• Give Mifepristone 200 mg • Mifepristone is an anti-progestin (blocks progesterone receptor) • Kills fetus (fetus requires progesterone hormone) • Send the female/mother back home
Day 3	• Call her back • Prescribe Misoprostol ○ Misoprostol contracts the uterus → contraction expels the fetus → medical abortion

	Dose of Misoprostol:
	• Up to 49 days of gestation:
	  ○ 400 microgram
	  ○ Route: Sub-buccal OR Sublingual
	• Beyond 49 days to 63 days:
	  ○ Double the dose → 800 microgram
	  ○ Route: Vaginal cream OR Sublingual

Ductus Arteriosus

- Maintain Patency
  - Drug of Choice: Alprostadil (Prostaglandin E1)
  - Maintains patency of the ductus arteriosus
- Closure of Patent Ductus Arteriosus (PDA)
  - Normally, after a child is born, the ductus arteriosus must close
  - Drugs: NSAIDs (decrease prostaglandin synthesis)
  - Drug of Choice: Ibuprofen
  - Most Commonly Used: Indomethacin

UTERINE STIMULANTS AND RELAXANTS

00:45:00

Uterine Stimulants (tocometry)

- Definition: Drugs that contract the uterus → the child comes outside
- **Oxytocin**
  - Drug of Choice for: Induction of Labor
    - → Induce labor and facilitate childbirth
  - After Child Delivery:
    - → Still give Oxytocin
    - → To control PPH (Postpartum Hemorrhage)
  - Contract uterus → bleeding stops
- **Carbetocin**
  - Ending: "-tocin"
    - → Injectable drug (IV or IM)
    - → Longer-acting form of Oxytocin
  - Uses:
    - → Induction of labor
    - → Control of postpartum hemorrhage
- **Other Drugs (Resistant Cases Only)**
  - For resistant cases of controlling PPH:
    - → Carboprost (Prostaglandin F2-alpha)
    - → Misoprostol (Prostaglandin E1)
    - → Ergometrine and Methylergometrine
      - Methylergometrine brand name: Methergin
      - Contract the myometrium (uterus)
- **New Guideline:**
  - Ergometrine and Methylergometrine are NOT used to control PPH

Tocolytic Drugs (uterine Relaxants)

- **Definition:** Drugs that relax the uterus
- **Indication: Premature Labor**
  - Delivery occurring before 37 weeks
  - Fetal lungs are not mature
  - Delay labor → do fetal lung maturation

Mnemonic: ABC

- A - Atosiban
  - Mechanism: Blocks the oxytocin receptor
- B - Beta-2 Agonists
  - Mechanism: Beta-2 receptor relaxes the uterus
  - Drugs:
    → Ritodrine (commonly asked)
    → Isoxsuprine (for reference)
- C - Calcium Channel Blockers
  - Mechanism: Calcium is required for muscle contraction
  - Drug: Nifedipine
  - Identification of Tocolytic Drugs:
    → Atosiban → "TO" word
    → Ritodrine → "T" word
    → Tocolytic → "TO" word coming

Halothane

- Halothane
  - Has a uterine relaxant effect
  - "TO" word coming in Halothane

Nsaids and Labor

- NSAIDs decrease prostaglandin synthesis
- Prostaglandins are required for uterine contraction
- NSAIDs have a tocolytic effect → can delay labor

ANTI-INFLAMMATORY DRUGS

00:49:30

INFLAMMATION PATHWAY

- The cell membrane contains Phospholipids
- Phospholipase A2 enzyme breaks down Phospholipids to Arachidonic Acid
- Arachidonic Acid can enter:
  - COX pathway (Cyclooxygenase pathway):
    → Produce Prostaglandins and Thromboxane
    → Lead to inflammation
  - LOX pathway (Lipoxygenase pathway):
    → Produce Leukotrienes
    → Lead to inflammation

Yourwish

Anti-Inflammatory Drugs (blocking Pathways)

- Block Phospholipase A2: Corticosteroids
  - Have anti-inflammatory action
  - Best anti-inflammatory drug
  - Steroidal drug → can lead to Cushing Syndrome
- Block COX Enzyme: NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)
  - Inhibit the COX enzyme
  - Reduce prostaglandin and thromboxane production
- Block LOX Enzyme: Zileuton
  - Given in the treatment of asthma (anti-inflammatory)
- Dual Inhibitor (COX + LOX): Licofelone
  - Inhibits BOTH COX and LOX enzymes
  - Approved to control inflammation in Osteoarthritis

Nsaids (Non-steroidal Anti-inflammatory Drugs)

Mechanism of Action

- Inhibit the cyclooxygenase enzyme
- Decrease production of prostaglandins and thromboxane A2 from arachidonic acid

Aspirin

- First NSAID made: Aspirin
- Unique Property: The only NSAID that is an irreversible COX inhibitor
  - Rest all NSAIDs are reversible COX inhibitors
- Also Known As:
  - Suicide Inhibitor (irreversible inhibitor of the enzyme)
  - Hit and Run drug

Doses And Uses of Aspirin

- Low Dose (Anti-Platelet)
  - Dose: 40-325 mg
  - Action: Only reduces Thromboxane A2 production in platelets
  - Use: Drug of choice for MI and Stroke patients
- Medium Dose (Antipyretic + Analgesic)
  - Dose: Up to 2 grams
  - Effects: Antipyretic (reduces fever), Analgesic (reduces pain)
- High Dose (Anti-Inflammatory)
  - Dose: More than 2 grams to 5 grams
  - Effect: Anti-inflammatory (reduces inflammation)
  - Drug of choice for Kawasaki Disease (in children)
  - Drug of choice for Rheumatic Heart Disease/Rheumatic Carditis

Side Effects of All Nsaids

- Most common side effect:
  - Allergic reactions: Rashes, Stevens-Johnson Syndrome, allergy
- Aspirin specific:

- Can cause a peptic ulcer
- Treatment: Proton Pump Inhibitor (drug of choice) or Misoprostol
- Long-Term use:
  - Can cause kidney damage (reduce GFR)
  - Disease: Analgesic Nephropathy
  - Don't take painkillers like NSAIDs for long-term use

Aspirin Poisoning

- Aspirin: Acidic drug
- Antidote: Sodium Bicarbonate (basic drug)
- Sodium Bicarbonate Resistant Cases: Hemodialysis

Reye Syndrome

- Definition: When aspirin is given in the presence of viral fever
  - Can lead to acute liver failure or fulminant hepatic failure
- Why it happens: Unknown
- Consequence:
  - Aspirin is NEVER given in any viral infection (like COVID infection)
  - Aspirin is contraindicated in children <18 years of age
- ONLY 2 CONDITIONS where Aspirin is given in children:
  - Kawasaki Disease (very dangerous disease → risk vs benefit ratio → still prescribe)
  - Rheumatic Heart Disease/Rheumatic Carditis
- Safest Analgesic in Children: PARACETAMOL
  - Does NOT produce Reye Syndrome

Samter's Triad

- Definition: Triad means 3 things
- Components:
  - Aspirin
  - Asthma
  - Nasal Polyp (ethmoid polyp in the nose)
  - Note: Both asthma and nasal polyps are allergic diseases (Type 1 hypersensitivity)
- Pathway: COX inhibition by Aspirin → LOX activation → Leukotrienes lead to allergic diseases (asthma, nasal polyp)--> Asthma + Nasal Polyp

Cox Inhibitors

Cox Enzymes

- COX-2 Inhibition → Controls inflammation (only COX-2 responsible for inflammation)
- COX-1 Inhibition → Side effect of peptic ulcer/stomach ulcer

Ideal Nsaid

- To make an anti-inflammatory drug, it should inhibit only COX-2
  - No peptic ulcer side effects
- Non-Selective COX Inhibitors (inhibit both COX-1 and COX-2)
  - Had the side effect of a peptic ulcer

- Preferential COX-2 Inhibitors (inhibit more COX-2 than COX-1)
- Selective COX-2 Inhibitors (don't block COX-1)
    - Advantages of Selective COX-2 Inhibitors:
      → Least risk of causing a peptic ulcer
      → Identification: End with "-coxib"

Non-Selective Cox Inhibitors

- Drugs:
    - Piroxicam
    - Tenoxicam
    - Ending: "-cam" or "-oxicam"
- Property: Longest acting drugs
- Reason: Undergoes entero-hepatic circulation
- Ketorolac:
    - Can be given intravenously
    - Sometimes given for post-operative pain
    - Note: In post-operative pain, the drug of choice is Opioid
- Ibuprofen and Indomethacin:
    - Drug of choice for closure of PDA (Patent Ductus Arteriosus)
- Two NSAIDs got banned:
    - Phenylbutazone:
      → Causing a dangerous allergic disease
      → Bone marrow suppression or agranulocytosis
    - Phenacetin:
      → Highly nephrotoxic drug
      → Causing analgesic nephropathy

Preferential Cox-2 Inhibitors

- Drugs:
    - Nimesulide
    - Meloxicam
    - Diclofenac
    - Aceclofenac
    - Etodolac
    - Nimesulide:
- Nimesulide Side effect: Stevens-Johnson Syndrome
    - Also hepatotoxic
    - Banned in many countries (available in India)
- Diclofenac:
    - Available as a spray or a cream
    - Brand names: Volini cream, Moov cream
    - Has the best topical action (best skin penetration)
    - Given as a cream/spray for arthritis and muscle pain

Selective Cox-2 Inhibitors (Coxibs)

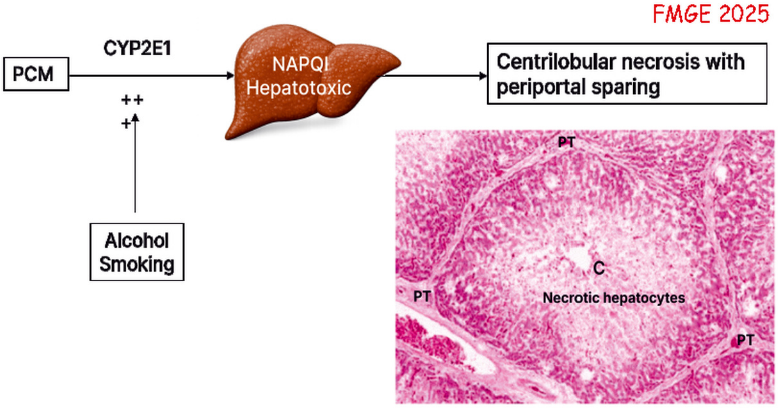
- Drugs:
  - Celecoxib
  - Etoricoxib
  - Parecoxib
- Advantage: Least risk of causing a peptic ulcer
- Banned Coxibs:
  - Rofecoxib
  - Valdecoxib
- Reason for Ban:
  - Increasing platelet attachment to the blood vessel
    → Causes thromboembolism
    → Causes MI and Stroke

Paracetamol (Acetaminophen)

01:02:04

FMGE 2025

- AKA Acetaminophen
- Safest Drug Overall
- Safest in:
  - Renal Failure (not nephrotoxic)
  - Children (no risk of Reye Syndrome)
  - Pregnancy (won't interact with the uterus)
- Least Risk of: Gastric ulcer
  - Does NOT act on COX-1 and COX-2



Mechanism Of Action

- Acts on: COX-3 Inhibitor
  - Location: COX-3 enzyme present in the brain
- In the brain:
  - COX-3 enzyme causes fever and pain sensation
  - Inhibiting COX-3 → analgesic (pain-relieving)
  - Inhibiting COX-3 → antipyretic (fever reducing)
  - No Action on COX-2: Has very poor anti-inflammatory action
- Additional Action:
  - Stimulates the TRPV1 receptor in the brain (related to cannabinoids)
  - Recently asked question

Paracetamol Toxicity

- Main Side Effect: If given >4 grams per day → risk of liver damage/hepatotoxicity
- Mechanism:
  - Paracetamol enters the liver and produces a toxic form: NAPQI
  - Higher dose → more NAPQI produced
  - NAPQI causes liver damage
  - Pattern of Liver Damage:
    → Damages cells around the central vein
    → Cells around the portal triad are spared
    → Called: Centrilobular Necrosis with Periportal Sparing

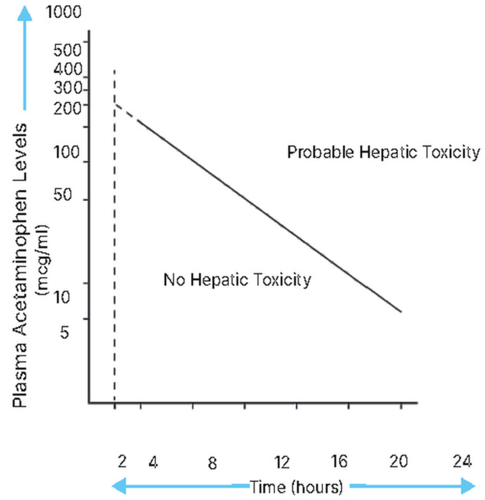
Yourwish

Antidote of Paracetamol Poisoning

- Antidote: N-Acetylcysteine
- Mechanism:
  - Increases the amount of Glutathione in the liver
  - Glutathione removes NAPQI from the liver

Monitoring Paracetamol Toxicity

- Method: Nomograms (graphs monitoring plasma levels of the drug in toxicity)
- For Paracetamol: Rumack-Matthew Nomogram
- Monitor paracetamol levels until they return to normal
- Other Nomograms:
  - Vancomycin: Matzke Nomogram
  - Aminoglycoside (Gentamicin): Hartford Nomogram



01:06:18

GOUT

Pathophysiology

- Increased uric acid levels in blood (Hyperuricemia) → Uric acid goes into joint cavities → Arthritis
- Most commonly involved joint: Toe joint (Metatarsophalangeal joint)
- Patient comes with an acute attack of joint pain, redness, swelling (arthritis)

Treatment of Acute Gout Attack

- Goal: Reduce inflammation in the joint
- Drug of Choice: NSAIDs (Anti-Inflammatory drugs)
- Can give all NSAIDs except:
  - Aspirin (increases the uric acid level itself)
  - Paracetamol (very poor anti-inflammatory effect)
- NSAID-Resistant Cases: Colchicine (2^{nd} drug)
- Colchicine-Resistant Cases: Corticosteroid
- Advantages of Colchicine and Corticosteroid:
  - Renal safe drugs (not nephrotoxic)
  - NSAIDs, if given long-term → nephrotoxic

Colchicine - Mechanism of Action

- Given in: Acute attack of gout
- Mechanism:
  - Microtubule Inhibitor
  - Microtubules = skeleton of the cell (WBC)
  - WBCs move/migrate with the help of microtubules
  - By inhibiting microtubules → inhibits the migration of WBC
  - WBC can't come to the joint → no inflammation
- Additional Effect:
  - Microtubules make spindle fibers → cell division
  - Colchicine inhibits cell division
- Side Effects:
  - Rapidly dividing cells affected:
    → Bone marrow suppression
    → GIT cells → diarrhea

Chronic Gout Treatment

- Goal: Reduce blood uric acid level (long-term treatment)
- Uric Acid Production Pathway:
    - Purine (from DNA degradation) = Hypoxanthine
    - Hypoxanthine → Goes to liver → (Xanthine Oxidase enzyme) → Uric Acid
    - Uric acid is excreted in urine through the kidneys

Xanthine Oxidase Inhibitors

- Drugs:
    - Allopurinol (contains "-purinol")
    - Oxipurinol (contains "-purinol")
    - Febuxostat (XO-stat)
- Mechanism:
    - Competitive inhibitors of the Xanthine Oxidase enzyme
    - Inhibit the production of uric acid from hypoxanthine
- Febuxostat:
    - "XO" word = Xanthine Oxidase
    - "Stat" = Inhibitor
    - Preference: Nowadays, prefer Febuxostat
    - Can be given in Allopurinol allergic cases
    - Allopurinol can cause a dangerous hypersensitivity reaction
- Drug of Choice for Chronic Gout: Allopurinol and Febuxostat
- To reduce the blood uric acid level
- Important Causes of Chronic Gout:
    - CKD (Chronic Kidney Disease) → blood uric acid increases
- Tumor Lysis Syndrome:
    - Anti-cancer drugs given → cancer cells die
    - Purines released → production of uric acid → gout

Uric Acid Oxidase Enzymes

- Mechanism:
    - Oxidize uric acid (in blood) into a harmless molecule: Allantoin
    - Drugs: End with "-ase" (enzymes)
      → Pegloticase (mammalian enzyme)
      → Rasburicase (bird enzyme)
- Birds Don't Get Gout: Birds have the Uricase enzyme
- Indication:
    - Given in Allopurinol-resistant cases of gout
    - Especially Tumor Lysis Syndrome

Uricosuric Agents

- Mechanism:
    - Increase excretion of uric acid in urine
    - Inhibit URAT (Uric Acid Transporter) or OATP transporter
    - Causes excretion of uric acid in urine

- Drugs:
  - Probenecid (very famous)
  - Sulfinpyrazone
    - → Additional NSAID-like activity
    - → Can be given in both acute and chronic gout
  - Benzbromarone (renal safe drug)
- New Drugs:
  - Lesinurad
  - Verinurad
  - (Contains "-urad" = excrete uric acid)

Drugs That Increase Risk of Gout

- Mnemonic: PANT
  - P - Pyrazinamide > Ethambutol (TB drug)
  - A - Aspirin (in low dose <2 grams)
  - N - Niacin (hypolipidemic drug)
  - T - Thiazide and Loop Diuretics
- Additional TB Drug:
  - Ethambutol also causes gout
  - Can Increase Blood Uric Acid Level

Drugs Beneficial in Gout

- Mnemonic: FALLS
  - F - Fenofibrate (hypolipidemic drug)
  - A - Aspirin (in high dose >5 grams - good for gout)
  - L - Losartan (Angiotensin Receptor Blocker)
  - L - Lipid-lowering drugs
  - S - Statins (another hypolipidemic drug)
- Have Uricosuric Effect: Increase uric acid in urine

Important Questions

- TB drug has the maximum risk of causing gout: Pyrazinamide
- Aspirin in low doses: Bad for gout
- Aspirin in very high doses is good for gout
- A hypolipidemic drug causes gout Niacin
- Hypolipidemic drugs are good for gout: Fenofibrate, Statins

RHEUMATOID ARTHRITIS

01:13:45

Pathophysiology

- Type: Type 3 and 4 Hypersensitivity
  - Unwanted inflammation → arthritis
- Mainly Affects: Females (middle-aged)
- Most Commonly Involved Joint:
  - Metacarpophalangeal and Interphalangeal joints
  - Wrist and finger joints

ACUTE ATTACK TREATMENT

- First Line Drug: Anti-Inflammatory Drugs
- Start with: NSAIDs
  - Can give ALL NSAIDs EXCEPT Paracetamol
- Reason: Poor anti-inflammatory effect
  - NSAID-Resistant Cases:
  - Give Corticosteroid
- Benefits of Corticosteroids:
  - Intra-articular injection of corticosteroid

Definitive/long-term Treatment

- Treatment: DMARDs
- DMARD: Disease-Modifying Anti-Rheumatic Drug
- Mechanism:
  - Reduce the body's immunity
  - By killing lymphocytes
  - Have immunosuppressive effect
- In the long term:
  - Reduce immunity
  - Definitive treatment

Conventional DMARDS

- First Class: Older drugs = Conventional DMARDs
- Mnemonic: MALIKA SHERAWAT PAGAL C

Drugs:

- Methotrexate
  - Overall, the drug of choice for Rheumatoid Arthritis
  - Most effective drug
  - Mechanism of Action:
    - → Inhibits Dihydrofolate Reductase enzyme
      - Inhibits lymphocyte division → kills lymphocytes
    - → Causes efflux of Adenosine
- Adenosine also kills lymphocytes
  - Most Effective: DMARD for Rheumatoid Arthritis
- Sulfasalazine
  - Type: Prodrug
  - Two Active Forms:
    - → Sulfapyridine:
      - Effective in Rheumatoid Arthritis
    - → 5-ASA (5-Aminosalicylic Acid):
      - Effective in UC (Ulcerative Colitis)
  - Uses: Two diseases
    - → Rheumatoid Arthritis
    - → Ulcerative Colitis
    - → In UC: Made a drug containing only 5-Aminosalicylic Acid (Mesalazine & Olsalazine)

Yourwish

- Penicillamine
  - Dual Function:
    → Copper Chelator
    → Given in Wilson's Disease
  - Immunosuppressive Drug
    → Given in Rheumatoid Arthritis
  - Side Effect:
    → Highly nephrotoxic drug
- Gold
  - Side Effect:
    → Highly nephrotoxic
  - No longer used
  - Both Penicillamine and Gold:
    → Highly nephrotoxic
    → No longer used
- Leflunomide
  - Dose: 100 mg
  - Mechanism:
    → Inhibits DHODH enzyme (Dihydroorotate Dehydrogenase)
    → This enzyme inhibits Pyrimidine synthesis
    → Lymphocyte count falls
- Chloroquine and Hydroxychloroquine
  - Type: Malaria drug
  - Longer Acting Form: Hydroxychloroquine
  - Also have: Immunosuppressive effect
  - Mechanism:
    → Decreases Interleukin-1 and Interleukin-6 production
  - Use: Also given in Rheumatoid Arthritis

Methotrexate in Pregnancy

- Most Effective DMARD: Methotrexate
- Inhibits: Folic acid synthesis (Antifolate drug)
- Absolutely contraindicated in pregnancy:
  - Category X drug
  - Can lead to Neural Tube Defects
- Safest DMARD in Pregnancy:
  - Chloroquine or Hydroxychloroquine
  - DMARD of choice in pregnancy

Biologics (New Class of DMARDS)

- In Methotrexate Resistant Cases: Give Biologics
  - Contain biological molecules (like monoclonal antibodies)

TNF-ALPHA BLOCKERS

- Mnemonic: I-G-A-T

- Drugs: Monoclonal antibodies blocking TNF-alpha
  - Infliximab
  - Golimumab
  - Adalimumab
  - Certolizumab
  - Etanercept
- Route:
  - Infliximab: IV injection
  - All others: Subcutaneous injection

Infliximab

- Inhibits TNF-alpha:
  - Immunity reduces
  - Can cause reactivation of Tuberculosis (inside macrophage)
- Before Giving Infliximab:
  - Always do the Mantoux Test
  - Rule out latent TB
- Uses (Apart from Rheumatoid Arthritis):
  - Mnemonic: RUPA
    → R - Rheumatoid Arthritis
    → U - Ulcerative Colitis
    → P - Psoriatic Arthritis
    → A - Ankylosing Spondylitis
  - Given in: Methotrexate resistant cases (add Infliximab)

Other Biologics

- Interleukin-6 Blockers:
  - Tocilizumab
  - Sarilumab
- CD20 Receptor Blocker (on B lymphocytes): Anti-CD20
  - Rituximab
- Interleukin-1 Blocker: Anti IL 1
  - Anakinra
- Recombinant CTLA-4 Receptor:
  - Abatacept
  - Directly suppresses lymphocytes

Jak Inhibitors (janus Kinase Inhibitors)

- Drugs: End with "-tinib"
- Tofacitinib - JAK 1 and 3 Inhibitor
  - "One and 3" → "Tofa"
- Baricitinib - JAK 1 and 2 Inhibitor
  - "2" → "Bari"
- Upadacitinib - Only JAK 1 Inhibitor
  - "Upa" means "one" → only JAK 1

- Important:
  - Among all biologics, only JAK Inhibitors are ORAL drugs
  - Rest all given by injection

Common Drugs For Both Ra and Ibd

- Mnemonic: SIT
  - S - Sulfasalazine
  - I - Infliximab-like drugs
  - T - Tofacitinib
- Important Question:
  - Tofacitinib approved for both Inflammatory Bowel Disease AND Rheumatoid Arthritis

5. CARDIOVASCULAR PHARMACOLOGY

RENAL: DIURETICS

00:00:26

- Drugs that increase excretion of sodium or water in urine

Carbonic Anhydrase Inhibitors

- MOA
  - Act at PCT of nephron
  - Inhibits carbonic anhydrase enzyme
  - Loss of sodium and bicarbonate in urine
- Drugs include
  - Acetazolamide
  - Methazolamide
  - Dichlorphenamide
- Drugs are derivatives of sulphonamide
- Drugs are noncompetitive and reversible inhibitors of carbonic anhydrase enzyme

Clinical Uses

Mnemonic: GAME Plan

- Glaucoma
- Alkalinization of urine
  - As they cause bicarbonate loss in urine
  - T/t of Acidic stones (Uric acid stone, Cysteine stone)
  - They can lead to calcium phosphate stones
- Metabolic acidosis
  - Increased H+ ions in blood → Stimulates respiratory centre
  - Acetazolamide → DOC for mountain sickness
  - Best treatment for hypoxia → Rapid descent
- Epilepsy treatment
- Plan: Periodic muscle paralysis
  - Occurs due to imbalance in potassium level
  - Given for hyperkalaemic / Hypokalemic periodic muscle paralysis

Side Effects

Mnemonic: BASE

- Bone marrow suppression
  - Acetazolamide like drugs can cause bone marrow suppression
- Ammonia level in blood is increased
  - Contraindicated: Liver diseases (ammonia not converted to urea → encephalopathy)
- Stones in the kidney: Calcium phosphate stone
- Electrolyte imbalance
  - Hyperchloremic + hypokalemia + metabolic acidosis

Osmotic Diuretics

- Act at the loop of Henle
- Drug: Mannitol
  - Given only I/V as 20% osmolar solution
- MOA
  - Increase plasma osmolarity in blood vessels
  - Due to ↑ osmolarity → fluid from organs comes back into intravascular compartment/blood vessel
  - CSF production ↓ → Reduce ICP
  - Aqueous humor production in eye ↓ → Reduce IOP

Clinical Uses

- Cerebral oedema (Drug of choice)
  - Decreases CSF production → ↓ intracranial pressure (ICP)
- Acute attack of glaucoma
  - Decreases aqueous humor → ↓ intraocular pressure
- Dialysis disequilibrium syndrome
  - During dialysis → plasma osmolarity ↓ → ↑ chances of cerebral oedema
  - Mannitol maintains plasma osmolarity → prevents cerebral oedema
- Mannitol excretes metals:
  - Lithium toxicity (Treatment of choice)
  - Cisplatin toxicity

Absolute Contraindications:

- Heart failure
  - ↑ Preload → worsen heart failure
- Renal failure / End-stage renal disease

Loop Diuretics

00:08:20

- Site of Action: TAL (Thick Ascending Limb) of Loop of Henle
- MOA
  1. Inhibit Na+K+2Cl- transporter on TAL
  2. Increase prostaglandin synthesis → vasodilation → ↑ blood supply to nephron → ↑ GFR → ↑ urine production
- Most effective diuretics / High ceiling diuretics

Drugs

- Mercury-containing (not used now):
  - Mersalyl → highly ototoxic → permanent deafness
- Sulfa -containing: Furosemide, Torsemide (longest-acting drug), Bumetanide (most potent drug)
  - Also ototoxic but less compared to mercury
  - Can cause sulpha allergy
- Non-mercury, Non-sulphur containing:
  - Ethacrynic acid

Clinical Uses

- Hypertensive crisis
- Pulmonary oedema (Drug of choice)

Drug Interaction

- Aspirin + loop diuretic:
  - Aspirin is a NSAID
  - All NSAIDs→ decreases prostaglandin synthesis → ↓ GFR
  - Aspirin reduces effect of loop diuretics

Thiazide Diuretics

00:11:03

- Site of Action: DCT (Distal Convoluted Tubule)
- MOA: Inhibit Na+Cl- symporter on DCT

Drugs

- Simple thiazides
  - Chlorothiazide
  - Hydrochlorothiazide
- Thiazide-like drugs
  - C = Chlorthalidone
    → Most potent thiazide-like drug
  - M = Metolazone
    → Only thiazide safe in renal failure, when GFR < 45
  - I = Indapamide

Clinical Uses

MNEMONIC: HORD

- H = Hypertension (DOC)
  - For hypertensive crisis → use loop diuretics
  - For hypertension → use thiazide
- O = Osteoporosis
  - Decrease risk of osteoporosis
  - Thiazides preserve calcium → ↑ bone mineral density
- R = Renal stones (calcium stones - Treatment of choice)
  - Preserve calcium → given for calcium renal stones
- D = Diabetes insipidus
  - Have antidiuretic action

Adverse Effects Of Loop And Thiazide Diuretics

00:13:20

- Hyponatraemia → hypotension
- Hypokalaemia → ↑risk of digoxin toxicity
- Hypomagnesemia
- Hyperglycemia
- Hyperlipidaemia
- Hyperuricemia
- Note: Both loop and thiazide diuretics are contraindicated in individuals with: Diabetes mellitus, Gout, Dyslipidaemia

Difference: In Calcium Handling

Aspect	Loop Diuretics	Thiazide Diuretics
Effect on Ca2+	Loses calcium in urine	Retains calcium (takes back into blood)
Blood Ca2+ level	Hypocalcaemia	Hypercalcaemia
Clinical use	DOC for hypercalcaemia	DOC for hypercalciuria
Note	-	• ↑Risk of Calcium citrate stones • But used in the treatment of calcium phosphate/oxalate stones

Potassium-sparing Diuretics

00:16:07

- Site of Action: Collecting duct (last part of nephron)
- The aldosterone hormone acts its receptor on collecting duct → produces ENaC protein (Epithelial Sodium Channel)→ Na+ absorption (back into blood) + K+ excretion (into urine)
- MOA: Block aldosterone receptor
  - ↓ Na^+ reabsorption → ↑ Na^+ excretion (diuresis)
  - ↓ K^+ excretion → ↑ K^+ retention (potassium-sparing)

Types

ALDOSTERONE RECEPTOR ANTAGONISTS	ENaC INHIBITORS
• Act from the basolateral side • Spironolactone • Eplerenone	• Act from luminal side • Amiloride • Triamterene

Important Information

- Potassium sparing diuretic: Only class of diuretics that produce hyperkalaemia (all others cause hypokalaemia)

Spironolactone

- Active form: Canrenone
- It also blocks testosterone receptors (not just aldosterone)
  - Can cause gynecomastia in males
  - Can treat hirsutism in PCOS females
- Clinical Uses: Spironolactone and Eplerinone are used in
  - Chronic Heart Failure → cardioprotective
  - Chronic Liver Disease → hepatoprotective

Finerenone

- Newer drug
- Nephroprotective
  - Given for Tx of diabetic nephropathy

- Less risk of gynecomastia
- Less risk of hyperkalaemia compared to spironolactone

Amiloride

- **Uses**:
  - Liddle syndrome (genetic excess of ENaC channel) → block ENaC by amiloride
  - Lithium toxicity → lithium absorbed from ENaC channel → block ENaC → lithium excreted in urine

Edema: Diuretic Of Choice

00:20:08

	Heart failure	Renal failure	Liver failure	Cerebral oedema
Type of Oedema	Pulmonary oedema	Periorbital oedema	Ascites	↑ ICP
Diuretic of Choice	Loop diuretic	Loop diuretic	Spironolactone	Mannitol

- Refractory oedema (spironolactone or Mannitol resistant) → Give Loop diuretic
- Important: Loop can be given in All types of oedema

Contraindications :

- Mannitol contraindicated in heart failure & renal failure

ANTIDIURETIC HORMONE (ADH) / VASOPRESSIN

00:21:12

Vasopressin Agonists

Natural Arginine Vasopressin	• Mechanism: "Presses" blood vessels • Administration: Injection • Outcome: ↑ Blood Pressure (BP). • Indications: Resistant shock (shock resistant to Epinephrine and Norepinephrine)
Terlipressin	• Mechanism: V1 agonist • Administration: Injection • Outcome: Vasoconstriction • DOC for: ○ Bleeding esophageal varices (dilated vessels seen in liver disease or portal hypertension) ○ Hepatorenal syndrome (Chronic liver disease → ↓BP → Acute renal failure)
Desmopressin	• Mechanism: V2 agonist. • Administration: Oral or Nasal spray • DOC for: ○ Neurogenic Diabetes Insipidus (ADH deficiency) ○ Nocturnal Enuresis (Bed-wetting in children) • Other use: Hemophilia A ○ V2 stimulation → ↑ Clotting Factor 8

Yourwish

Vasopressin Antagonists (Vaptans)

- Mechanism: Block ADH receptors.
- Drugs:
  - Conivaptan (Injectable).
  - Tolvaptan (Oral).
- Indications: Syndrome of Inappropriate ADH Secretion (SIADH).
  - SIADH → Excess ADH → Water reabsorption → Dilutional Hyponatremia
  - Common causes: Head injury, brain tumors, Heart failure (CHF), or Autosomal Dominant Polycystic Kidney Disease (ADPKD)
- Demeclocycline:
  - Antibiotic that blocks ADH receptors
  - Used in SIADH

Nocturnal Enuresis

00:24:40

- Age criterion: Treatment required if child is > 6 years old.
- First-line management: Training
  - ↓ Water intake before sleep
  - Alarm method: Alarm rings when a child passes urine to wake them up
- Second-line management: Pharmacotherapy
  - **D**esmopressin:
    → DOC
    → ↓ Urine production
    → Nasal spray used for small children
  - **O**xybutynin:
    → Anticholinergic drug
    → Relaxes the bladder
  - **I**mipramine:
    → Tricyclic Antidepressant (TCA)
    → Has Anticholinergic action → relaxes the bladder

Diabetes Insipidus (DI)

00:26:10

- Pathophysiology:
  - Defect in ADH hormone (Antidiuretic Hormone) → Water excreted in urine
- Clinical signs: Polyuria + Low osmolar urine
- Neurogenic DI
  - Cause: Brain neurons/Hypothalamus not producing ADH
  - DOC: Desmopressin
  - Other drugs: Carbamazepine, Chlorpropamide (↑ ADH secretion from brain)
- Nephrogenic DI
  - Cause: Kidney receptors do not respond to ADH.
  - Note: Desmopressin is contraindicated
  - DOC: Thiazide diuretics + NSAIDs (e.g., Indomethacin).
  - Mechanism of Thiazides in DI: Sodium loss → Kidney ↑ PCT absorption of water and sodium → ↓ Urine volume
- Lithium-induced DI: Thiazides are contraindicated (↑ risk of Lithium toxicity).
  - DOC: Amiloride

Drugs Causing SIADH (↑ ADH)	Drugs Causing Diabetes Insipidus (↓ ADH effect)
• C - Carbamazepine, Chlorpropamide • V - Vincristine • S - SSRI	• L - Lithium • A - Alcohol • P - Phenytoin • Dog-Demeclocycline (tetracycline antibiotic)

Important Information

- Antiepileptic causing hyponatraemia → Carbamazepine (causes SIADH)
- Diabetes mellitus drug causing hyponatraemia → Chlorpropamide (causes SIADH)
- Drug causing polyuria → Lithium (blocks ADH → polyuria)

ANTIHYPERTENSIVE DRUGS

00:30:00

Ras Inhibitors

- General function of RAAS: ↑ BP.
  - Inhibitor function: ↓ BP (Antihypertensive).
- RAAS Pathway
  - Angiotensinogen + Renin (from Kidney JG cells) → Angiotensin I
  - ACE (from Lung endothelial cells) converts Angiotensin I → Angiotensin II
  - Angiotensin II acts on AT-1 receptor (Gq Type of G protein-coupled receptor) → Outcome: ↑ Aldosterone + Vasoconstriction + Sodium retention + Potassium loss → ↑ BP.
- Inhibitor Classes
  - Direct Renin Inhibitor: Aliskiren.
  - ACE Inhibitors (ACEI): End in "-pril".
  - AT1 Receptor Blockers (ARBs): End in "-sartan".
- Pharmacological Effects of RAAS Inhibitors
  - Vasodilation (Arteries and Veins).
  - Sodium loss in urine (Diuretic action).
  - Potassium preservation → Side effect: Hyperkalemia

Contraindications of ACEI and ARBs

- Pregnancy: Risk of fetal renal agenesis.
- Hyperkalemia: Avoid combining with Potassium-Sparing Diuretics
  - Both cause hyperkalaemia → dangerous arrhythmias
- Bilateral Renal Artery Stenosis:
  - Already ↓ GFR.
  - Drugs further ↓ GFR → Acute renal failure/Oliguria

Side Effects of Aceis (bradykinin Related)

- ACE enzyme normally degrades Bradykinin
  - ACEIs ↑ Bradykinin levels → Allergic reactions.
- Most common SE: Dry cough.
- Serious SE: Angioedema (swollen lips/cheeks/face).
- Management:
  - Stop ACE inhibitor
  - Switch to ARBs or Aliskiren (do not ↑ Bradykinin).

Nephroprotective Drugs in CKD

- S = SGLT2 inhibitors (end with "GLIFLOZIN")
  - Examples: Canagliflozin, Dapagliflozin, Empagliflozin
  - Also used in diabetes mellitus
- A = ACE inhibitors and ARBs
  - Have nephroprotective effect
- F = Finerenone
  → Nephroprotective drug
  - Treatment Strategy:
    → First drug: Always start ACE inhibitor (Pril) or ARB (Sartan)
    → Other drugs: Add-on therapy

Special Properties ARB

- Losartan
  - ↓ Uric acid levels (good for Gout).
  - Anti-platelet effect (blocks Thromboxane A2 receptors).
- Telmisartan
  - PPAR-gamma agonist (similar to Pioglitazone).
  - ↓ Insulin resistance (good for Diabetes Mellitus).
- Side Effect: Sprue (Diarrhoea)
  - Blocking angiotensin receptors in GIT → diarrhoea
  - Maximum risk with Olmesartan

Calcium Channel Blockers (CCBs)

00:38:25

- Mechanism: Block L-type calcium channels in heart and smooth muscles.
- Classification
  - Dihydropyridines (DHP): End in "-dipine" (Amlodipine, Nifedipine)
    → Act only on blood vessels (Artery dilators) → ↓ BP.
  - Non-DHP: Verapamil, Diltiazem.
    → Act on both blood vessels and heart.
    → Inhibit SA and AV nodes.
- Clinical Applications
  - Verapamil: DOC for Supraventricular Tachycardia (SVT)
  - Diltiazem: Preferred for Angina (↓ Heart rate → ↓ Oxygen demand). Also used for SVT
  - DHP CCBs: DOC for Hypertension.
    → Amlodipine: Longest acting oral drug
    → Nicardipine: Longest acting IV drug; DOC for Hypertensive Emergency
    → Nimodipine: Crosses BBB; DOC for Subarachnoid Hemorrhage (prevents cerebral vasospasm)

Important Information

- Verapamil/Diltiazem: SE is Bradycardia
  - Never combine with Beta blockers.
- DHP CCBs: SE is Reflex tachycardia
  - Routinely combined with Beta blockers

- Side Effects (Mnemonic - Hypertensives Usually FORGeT CCB)
  - **Hypertensives** - Headache (cerebral artery dilation): M/c SE of CCBs
  - **Usually** - Urinary retention (Bladder relaxation).
  - **F** - Flushing
  - **O** - Oedema: Amlodipine specifically causes Ankle edema.
  - **Ge** - GERD (Lower esophageal sphincter relaxation).
  - **T** - Tocolytic action (Uterine relaxation).
  - **CCBs** - Constipation (Second most common SE after headache)
- Antidote for CCB toxicity: Calcium gluconate.

Vasodilators

00:43:31

- Artery dilators: Potassium channel openers
- Vein dilators: Nitrates.
- Combined (Artery + Vein): Nitroprusside.

Artery Dilator - Potassium Channel Openers

- M - Minoxidil: Used for Hypertension and Male Pattern Baldness (Alopecia)
- D - Diazoxide: ↓ Insulin secretion
  - Used for Insulinoma
  - Contraindicated in DM (causes hyperglycemia).
- H - Hydralazine: Used for HTN and Heart Failure
  - Part of SHIP drugs (Sulfonamides, Hydralazine, Isoniazid, Procainamide)
  - SE: Drug-Induced Lupus Erythematosus
- Nicorandil
  - Mechanism: Potassium channel opener + Coronary artery dilator
  - Indication: Angina.

Vein Dilator - Nitrates & Combined Dilator - Nitroprusside

- Mechanism: Nitric Oxide (NO) donors → Soluble Guanylyl Cyclase stimulation → ↑ cyclic GMP → Vasodilation
- Nitroprusside: Direct NO donor (enzyme independent)
  - Indication: Hypertensive Emergency (Fastest BP lowering drug)
- Nitrates: Enzyme dependent (MAD enzyme: Mitochondrial Aldehyde Dehydrogenase).
  - MAD enzyme only in veins → Vein dilators
  - Indication: angina and MI
- Tolerance:
  - Nitrates show tolerance due to MAD enzyme down-regulation
  - Nitroprusside does not.
- Storage: Stored in black or opaque bottles; protect from light (light destroys NO)
- S/e of Nitroprusside: Cyanide Toxicity
  - Cause: Nitroprusside metabolism in the liver produce cyanide
  - DOC for toxicity:
    → Vitamin B12 (Hydroxocobalamin): It contains cobalt and cobalt inactivates cyanide
  - Other treatments:
    → Amyl nitrite (inhalation) or Sodium nitrite (IV): Converts Hb to Methemoglobin to inactivate cyanide.
    → Sodium thiosulfate: Excretes cyanide in urine

Yourwish

Hypertension Management

00:49:42

- Essential Hypertension (BP >130/80, no comorbidities)
  - First-line drugs (CAT):
    - → CCB (DHP/Amlodipine)
    - → ACEI/ARB
    - → Thiazide diuretics
- Resistant Hypertension
  - Definition: BP not controlled by 3 drugs in combination
  - DOC: Aldosterone receptor blockers (Spironolactone or Eplerenone)
  - New Drug: Aprocitentan (Endothelin antagonist)
- Hypertension with Comorbidities
  - Kidney disease/Microalbuminuria / DM / Stroke / Retinopathy / Scleroderma: ACEI (DOC) or ARB
  - Stable Angina / HOCM / Aortic Dissection / Hyperthyroidism / Migraine: Beta blockers (DOC)
    - → Note: Beta blockers contraindicated in Asthma
    - → If Asthma present: Use Verapamil or Diltiazem
  - BPH: DOC is Prazosin (relaxes sphincter)
  - Osteoporosis: Thiazide diuretics (preserves Calcium)
  - Post-menopausal (Hot flushes): Clonidine
  - Artery Stenosis / Raynaud's / Asthma: CCB DHP Type (Amlodipine).
  - Cheese reaction: Phentolamine
  - Pheochromocytoma: Phenoxybenzamine
- Pregnancy-Induced Hypertension (Pre-eclampsia)
  - Safe drugs: Labetalol (DOC), Hydralazine, Alpha-Methyldopa, Nifedipine
  - Absolute Contraindications: ACEI and ARBs

Hypertensive Crisis

00:56:19

- BP>180/120
- Hypertensive Urgency:
  - No organ damage
- Hypertensive Emergency: End organ damage (Hemorrhage, stroke, aortic dissection)
- Drugs for Hypertensive crisis
  - Now - Nicardipine (IV) DOC for Hypertensive Emergency
  - Nobody - Nitroprusside
  - C - Clonidine (DOC for Hypertensive urgency)
  - A - ACEI (Enalaprilat, can be given IV)
  - N - Nifedipine, Clevidipine
  - H - Hydralazine
  - E - Esmolol, Labetalol
  - L - Loop diuretics
  - P - Phentolamine
- Thiazides are ineffective in crisis; use Loop diuretics.

Anti-Hypertensive Drugs - Contraindications & Side Effects

- Hyperkalemia / Renal Failure (Serum creative > 2.5mg/dL): Avoid Spironolactone
- Hyperkalemia / Renal Artery Stenosis / Pregnancy / Angioneurotic edema: Avoid ACEIs

- Gout: Avoid Thiazides
- Asthma / COPD: Avoid Beta Blockers.
- Bradycardia / AV Block: Avoid Beta Blockers and Verapamil/Diltiazem

Important Information

- Drugs causing impotence:
    - Thiazides, Beta Blockers, CCBs
- ACEIs have no Impotence risk

ANGINA

00:59:57

- Ischemic pain in heart due to blockage of coronary artery

Types of Angina

- Stable (Classical):
    - Fixed narrowing d/t atherosclerosis
    - Stable at rest; pain during exertion
- Unstable Angina:
    - Rupture of atherosclerotic plaque → platelet deposition
    - Complete blockage of coronary artery
    - Acute Coronary Syndrome: Unstable Angina + Myocardial Infarction (MI)
- Vasospastic (Prinzmetal/Variant): Sudden coronary vasospasm.

Treatment of Angina

- Note:
    - Angina treatment includes Stable angina & Vasospastic (Prinzmetal) angina
    - Unstable angina: Managed as part of Acute Coronary Syndrome (ACS), treated similar to MI
- First Line Drugs
    - Beta Blockers: DOC for long-term treatment of Chronic Stable Angina
        - → ↓ HR → ↓ O2 demand
    - CCBs: DOC for long-term treatment of Vasospastic Angina:
        - → Coronary artery dilation.
        - → Beta blockers absolutely contraindicated (cause vasoconstriction).
    - Nitrates: DOC for Acute Attack of angina
        - → Sublingual route used
        - → Venodilator → ↓ preload to heart → ↓ O2 demand

Organic Nitrates

- Drugs:
    - GTN (Nitroglycerin)
    - ISDN (Isosorbide Dinitrate)
    - ISMN (Isosorbide Mononitrate)
    - PETN (Penta erythrityl Tetra nitrate)
- Sublingual use: Only GTN and ISDN
- Chemical nature

  - Highly lipid soluble drugs
  - Also known as non-ionic drugs
  - Can be given by other routes due to high lipid solubility
- Other Routes
  - Oral Route
    - → All drugs can be given orally
    - → First-pass metabolism in liver (degraded by liver)
      - Exception: ISMN (Isosorbide Mononitrate)
      - 100% oral bioavailability, Completely absorbed
  - Transdermal Patch: GTN can be given as transdermal patch
- Pro-drug: Isosorbide Dinitrate
  - Active form = Isosorbide Mononitrate
- Nitrate tolerance
  - Continuous nitrate use → Loss of effect
  - Maximum with: Transdermal patches
  - Mechanism:
    - → MAD enzymes become down-regulated
    - → Continuous use → ↓ Enzyme activity → ↓ NO production → Loss of effect
  - Management: Nitrate-Free Interval
    - → Give 8 hours nitrate-free interval
    - → Enzymes become replenished
- Uses of nitrates
  - Angina
  - Myocardial Infarction
  - Left ventricular failure
    - → C/I in Right ventricular failure
  - Abdominal colicky pain
    - → Not effective in Renal colic

Second-line Drugs For Angina

01:05:25

- Given in resistant cases of first-line drugs
- Drugs (**Mnemonic**: No DRIFT)
  - No - NICORANDIL
    - → Potassium channel opener
    - → Coronary artery dilator
  - D - DIPYRIDAMOLE
    - → Mechanism: Coronary dilator
    - → Banned due to "Coronary Steal Syndrome" (blood diverted from ischemic to non-ischemic areas)
  - R - RANOLAZINE
    - → Blocks late sodium channel → ↓ Workload/contraction of ventricle → ↓ Oxygen demand
    - → Additional benefit: Good for diabetes mellitus (↓ HbA1C level)
  - I-IVABRADINE
    - → Causes bradycardia → Blocks funny channels on SA node
  - F-FASUDIL
    - → Coronary artery dilator
    - → Rho-kinase inhibitor

- T-TRIMETAZIDINE
  - → Metabolism shifter
  - → Inhibits P-FOX (Partial Fatty acid Oxidation) → Shifts heart from using Fatty acids (High O2 demand) to Glucose (Low O2 demand)

Angina Drug Combination Precautions

01:08:38

- Never combine:
  - Beta Blockers + Verapamil/Diltiazem (Excessive bradycardia)
  - Nitrates + Sildenafil/Tadalafil (PDE5 inhibitors):
    - → Massive vasodilation → Sudden death
    - → Required gaps: 24 hours (Sildenafil), 72 hours (Tadalafil).
- Advantage of CCB over Beta Blockers
  - Beta blockers contraindicated in Asthma patients
  - In asthmatic CCBs are preferred over Beta blockers

ACUTE CORONARY SYNDROME (MI)

01:10:07

- Initial Symptomatic treatment
  - Emergency management: MONAS
    - → Morphine: ↓ Pain and apprehension.
    - → Oxygen.
    - → Nitroglycerin: ↓ Preload.
    - → Aspirin: 325 mg (Anti-platelet).
    - → Statins: ↓ Atherosclerosis risk
  - Better morality reduction
    - → DAPT (Dual Anti-Platelet Therapy): Aspirin + Clopidogrel/Prasugrel/Ticagrelor
    - → High-Intensity Statins: Atorvastatin (80 mg) or Rosuvastatin (40 mg)
- Prevent and treat Complication: ACEI + Beta Blockers (prevent infarct expansion)
- Reperfusion Therapy (within 12 hours)
  - Thrombolytics (e.g., Streptokinase, alteplase, Tenecteplase):
    - → Only for STEMI
    - → Contraindicated in NSTEMI (low benefit, high bleeding risk).
  - PCI (Balloon Angioplasty):
    - → Safe for both STEMI and NSTEMI
    - → Preferred option

CHRONIC HEART FAILURE (CHF)

01:13:27

- Cause: Myocardial damage (post-MI) → ↓ Cardiac Output → ↓ blood supply to vital organs
- Classification of Drugs
  - Cardio-protective drug: ↓ Mortality and ↑ lifespan
  - Symptomatic relief: Diuretics (Loop > Thiazide), Nitrates, Nesiritide
  - Inotropic: Digoxin. ↑ Force of contraction; no mortality benefit.

Cardioprotective Drugs

Mnemonic: SAHIBS

- S - SACUBITRIL

- Combined with Valsartan
- First drug to be started (according to new guidelines) in CHF
  → Earlier: Aldosterone receptor blocker or ACE inhibitor were first drugs
- A - ACEI or ARBs
  - Cardioprotective drugs
- H - HYDRALAZINE
  - Cardioprotective effect
- I - IVABRADINE
  - Given in angina
  - Also given in CHF
- B - BETA BLOCKERS
  - Only 4 beta blockers have cardioprotective effect
  - Mnemonic: NBMC
    → N - Nebivolol
    → B - Bisoprolol
    → M - Metoprolol (Metoprolol Succinate salt has cardioprotective effect)
    → C - Carvedilol
- S - SGLT-2 INHIBITORS
  - Effects: Nephroprotective in CKD, Cardioprotective in CHF
  - Drugs: Canagliflozin, Dapagliflozin, Empagliflozin

Contraindications in CHF

- Calcium Channel Blockers (Verapamil, Diltiazem)
  - Absolutely contraindicated in CHF → Increase mortality
- Beta blockers:
  - Given in CHF (chronic heart failure)
  - But contraindicated in acute heart failure

Natriuretic Peptides

01:17:30

- Natriuretic Peptides cause vasodilation → ↓ Preload and Afterload → Good for CHF
- Nesiritide: Synthetic B-type Natriuretic Peptide (BNP)
- Neprilysin Enzyme (NEP): Degrades natriuretic peptides
- Sacubitril:
  - Neprilysin inhibitor
  - Always used with Valsartan (ARNI)
- Neprilysin inhibitor + ACE inhibitor (Under trial): Omapatrilat, Sampatrilat

Inotropic Drugs

01:19:53

- ↑ Force of contraction → ↑ Cardiac output
- Indications: Acute decompensated heart failure / Cardiogenic shock
- Mechanism: Beta 1 receptor stimulation → ↑ cyclic AMP → Calcium influx → Calcium binds to troponin C → Activate myosin → ↑ Force of contraction
- Drugs
  - Beta-1 Agonists:
    → Directly stimulates Beta 1 receptors

- → Drugs: Dobutamine, Norepinephrine, Dopamine
- → IV drugs
- → DOC for acute decompensated HF

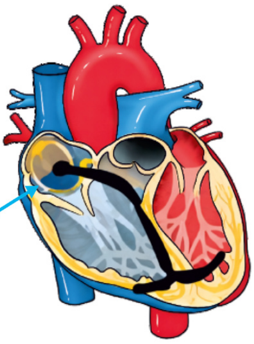
- PDE3 Inhibitors:
  - → PDE3 degrade cAMP
  - → PDE3 Inhibitors ↑ cyclic AMP.
  - → Drugs: Inamrinone, Milrinone
  - → IV drugs, given for acute decompensated HF
- Levosimendan:
  - → PDE3 inhibitor + Calcium sensitizer (Troponin C) + K+ channel opener.
- Omecamtiv Mecarbil: Myosin activator
- Digoxin:
  - → Inhibit Sodium-Potassium ATPase transporter on heart muscle
  - → Only oral inotropic drug used for Chronic heart failure.

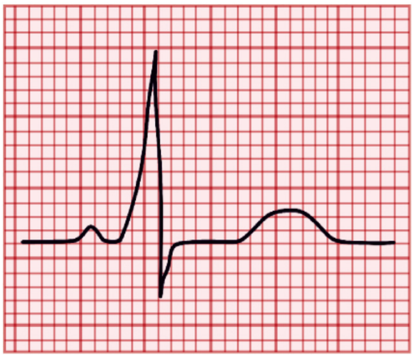
Digoxin

- Source: Digitalis plant (Foxglove)
  - Purple to pink, trumpet-shaped flowers
- Chemical nature: Cardiac glycoside
- Available: Digoxin (only)
- Other chemicals from plant (not clinically available):
  - Digitoxin
  - Oubain
- Positive Inotropic effect: ↑ Force of contraction → ↑ Cardiac output
  - Mechanism: Inhibits Na+/K+ ATPase on muscles of heart
- Negative Chronotropic effect: Inhibits SA and AV nodes (vagal effect) → ↓ Heart rate
- Uses: CHF and SVT (Atrial Flutter/Fibrillation).
- Side Effects
  - Most common: Nausea and vomiting.
  - Gynecomastia: Blocks testosterone receptors.
    - → **D**igoxin
    - → **I**soniazid
    - → **S**pironolactone
    - → **C**imetidine
    - → **K**etoconazole
    - → **O**meprazole
  - Yellow vision (Xanthopsia).
    - → Comparison: Sildenafil (Blue-green color blindness), Ethambutol (Red-green color blindness)
- Arrhythmias
  - Most common: Ventricular bigeminy (asymptomatic; no treatment)
  - Most fatal: Ventricular Fibrillation (VF)
    - → DOC for VF: Lignocaine > Phenytoin.
    - → Contraindication: DC shock/Defibrillation is absolutely contraindicated in Digoxin VF
  - Never cause atrial flutter
- Pharmacokinetics

- Narrow therapeutic range: 0.6–2.0 ng/mL
  → Requires TDM.
- High volume of distribution (Vd):
  → Deposited in organs
  → Hemodialysis ineffective in digoxin poisoning

- Antidote for digoxin poisoning: Digibind
- Digoxin is excreted in urine Via P-glycoprotein (P-gp)
  - Rifampicin: P-gp inducer → ↑ Excretion → ↓ Digoxin effect
  - Erythromycin / Clarithromycin: P-gp inhibitors → ↓ Excretion → ↑ Toxicity risk
- Absolute Contraindications
  - Renal Failure.
  - Hypokalemia (Thiazides/Loop diuretics) → ↑ Toxicity risk.
  - WPW (Wolff-Parkinson-White) Syndrome:





Wolff-Parkinson-White

    → ADH blocks normal AV node pathway; conduction shifts to abnormal accessory pathway (Bundle of Kent).
    → Results in pre-excitation; Delta waves on ECG
    → Treatment: Radiofrequency ablation.
    → Medical treatment with heart disease (e.g., MI): Procainamide.
    → Medical treatment without heart disease: Flecainide.
  - HOCM (Hypertrophic Obstructive Cardiomyopathy):
    → Digoxin ↑ contraction → ↑ Aortic obstruction
    → Treatment: Beta Blockers (DOC) or Verapamil (if asthmatic).
    → New drug: Mavacamten (reduces heart contraction).

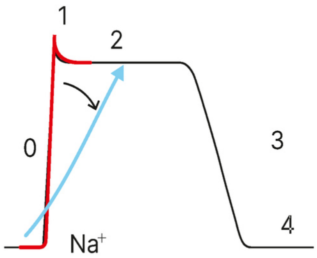
ANTI-ARRHYTHMIC DRUGS

01:32:10

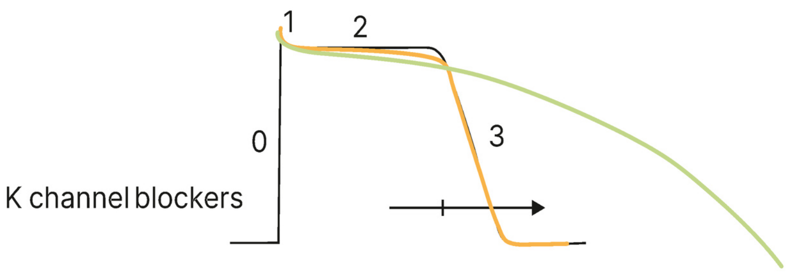
William-vaughan classification

NEET PG 2020, 2022, 2023, 2024, 2025
FMGE 2021, 2023, 2024
INICET 2022, 2024

- Class 1: Sodium (Na+) Channel Blockers
  - Subclasses: 1A, 1B, 1C
    → 1A: Blocks Potassium channels → ↑ Phase 3 duration, Increase QT prolongation → Increase Torsades de pointes risk
    → 1B: Opens Potassium channels → ↓ Phase 3/APD.
    → 1C: No effect on Potassium channels → No effect on Phase 3
  - Reduce Phase 0 slope (depolarization).
- Class 2: Beta Blockers
  - All beta blockers except Sotalol belong to Class 2.
  - Sotalol is Class 3 (Potassium channel blocker).



- Class 3: Potassium (K+) Channel Blockers



  - Increase action potential duration
  - Increase QT prolongation Risk → Increase Torsades de pointes risk
- Class 4: Calcium (Ca+) Channel Blockers
- Class 5: Miscellaneous
  - Adenosine.
  - Digoxin.
  - Atropine.
  - Magnesium Sulfate.

Class 1A Drugs

- All Class 1A drugs:
  - Sodium channel blockers → ↓ Phase 0 slope
  - Also block potassium → ↑ Phase 3 duration
- Mnemonic: **QUPD**
  - **Q** - Quinidine.
  - **P** - Procainamide:
    → SHIP drug: Causes Acetylation, S/e Drug-Induced SLE
    → Contains an Amide group: Sulfonamide derivative → Risk of Agranulocytosis/Bone marrow suppression
  - **D** - Disopyramide.

Class 1B Drugs

- MNEMONIC: **Leave PMT**
  - **Leave** - Lignocaine (also called Lidocaine)
    → Administration: IV for Ventricular Fibrillation (VF).
    → Side Effects: Peri-oral numbness (blocks nerve/nerve conduction; local anesthetic).
    → Antidote for Lignocaine/Bupivacaine toxicity: 20% Intralipid emulsion
  - **P** - Phenytoin: Used for VF.
  - **M** - Mexiletine
    → Oral prodrug of Lignocaine; used for VF and approved for Diabetic Neuropathy
    → Note: Primary DOC for Diabetic Neuropathy is Pregabalin
  - **T** - Tocainide

Class 1C Drugs

- MNEMONIC: **Famous PM**
  - **F** - Flecainide
  - **PM** - Propafenone.
- All Class 1C agents are contraindicated in MI/structural heart disease
  - Increase mortality

Class 2: Beta Blockers

01:38:54

- Drug names end with: "-lol"
  - Propranolol
  - Metoprolol
  - Atenolol
- Two IV short-acting beta blockers:
  - Esmolol
  - Landiolol (new drug): Shortest-acting beta blockers
- Indications:
  - Sympathetic Tachycardia (fever, hyperthyroidism, anxiety).
  - SVT (Atrial Flutter/Fibrillation) via AV node block; prevents VF
  - Intra-operative AF: Esmolol and Landiolol
- Side Effect: Bradycardia.
  - Antidote: Glucagon hormone (stimulates SA/AV nodes → ↑ heart rate/Tachycardia)

Class 4: Calcium Channel Blockers

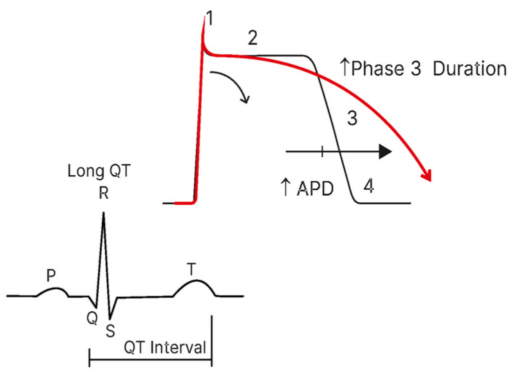
01:40:36

- Drug: Verapamil
- Mechanism: Blocks SA and AV nodes
- Indications: SVT or Atrial Fibrillation (AF)
- Contraindication: Never use in VF/Ventricular Tachycardia (VT) (increases mortality)
- Precaution: Never combine with Beta Blockers

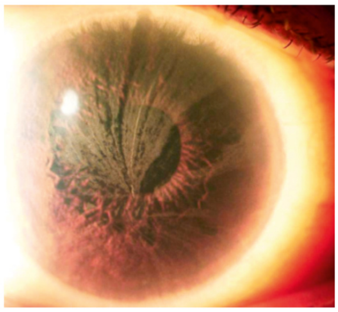
Class 3: Potassium Channel Blockers

- MNEMONIC: DIVAS
  - D - Dofetilide
  - I - Ibutilide
  - V - Vernakalant
  - A - Amiodarone
  - S - Sotalol
- Dofetilide / Ibutilide: Approved for Atrial Fibrillation (AF).
- Vernakalant, Amiodarone, Sotalol: Indicated for both AF and VF

Amiodarone



- Amiodarone is contraindicated in Long QT Syndrome and Torsades de Pointes
- Most effective anti-arrhythmic drug
- Properties: Contains 37% Iodine; interferes with thyroid function.
- Side Effects



- Blue/Purple skin (Blue / Purple man syndrome): Due to Iodine skin deposits.
- Interstitial Pulmonary Fibrosis: Most dangerous side effect.
- Thyroid problems: Causes both Hypo (more common) and Hyperthyroidism.
- Corneal Verticillata (aka Vortex Keratopathy):
  → Flower-like white hazy lines on the cornea.
  → Reversible upon discontinuation of drug.
- Hepatotoxicity.

- Dronedarone: Modified version without Iodine (no thyroid/skin side effects)

Important Information

Purple Syndromes

- Purple Man Syndrome: Amiodarone
- Purple Toe Syndrome: S/e of Warfarin (causes toe necrosis)
- Purple Glove/Hand Syndrome: Phenytoin (crystallizes and blocks blood vessels)

Purple Man Syndrome

Purple Toe Syndrome

Purple Glove Syndrome

Class 5: Miscellaneous

01:45:07

Atropine

- Only drug for bradyarrhythmias/bradycardia
- Rest all anti-arrhythmic drugs: For tachycardias

Digoxin

- Blocks AV node
- Given in **SVT** (especially in heart failure patients)
- In heart failure: Avoid beta blockers and CCBs in high doses

Adenosine

- Drug of choice for: Acute attack of PSVT (Paroxysmal Supraventricular Tachycardia)
- Mechanism: AV node blocker.
- Administration: IV only; half-life is ~10 seconds (shortest acting).
- Technique: Fast IV injection followed by a saline push/flush to ensure it reaches the heart.
- Dosage (Adult): Maximum 3 injections (6, 12, 12 mg). Total 30 mg.
- Dosage (Children): 0.1, 0.2, 0.2 mg/kg.
- Side Effect: Provokes Asthma

Magnesium Sulfate

- Drug of choice for: Torsades de Pointes
- Occurs in long QT interval on ECG

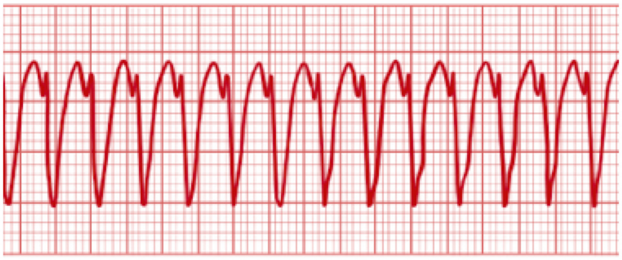
Management of Arrhythmia According To Ecg

PSVT (Paroxysmal Supraventricular Tachycardia)

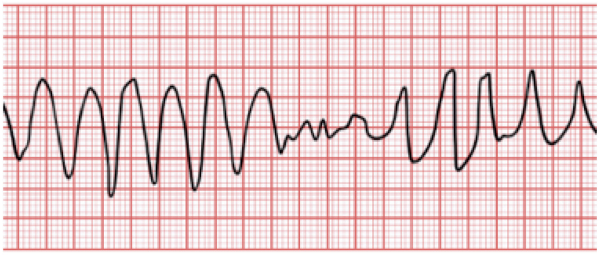
- Pathology: AV node fibers abnormally firing
- ECG:
  - Only ventricular depolarization (QRS wave) followed by T wave
  - QRS → T → QRS → T (pattern)
  - Absent P waves (no atrial depolarization)
- Treatment: AV node blockers
- Three AV node blockers
  - Adenosine: DOC for acute attack (IV).
  - Beta Blockers: For long-term maintenance.
  - Calcium Channel Blocker (Verapamil): DOC if patient has Asthma.

PSVT

Ventricular Tachycardia



VT



Torsade's de pointes

- Monomorphic VT: Identical QRS complex shapes.
  - DOC: Amiodarone.
- Polymorphic VT (Torsades de Pointes): Changing QRS shapes.
  - DOC: Magnesium Sulfate.
- Clinical Precaution: If the patient is unstable (Low BP/Hypotension), give DC Shock/Defibrillation first before drug therapy

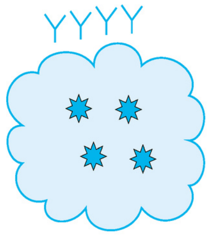
Yourwish

6. RESPIRATORY SYSTEM

ANTI-ASTHMA DRUGS

00:00:17

- Asthma is a type 1 HS reaction causing unwanted inflammation around the bronchus, causing bronchoconstriction
  - Dyspnea
  - Chest pain
  - Wheeze +



Bronchodilators	Anti-inflammatory
• Acute asthma	• Chronic/Persistent asthma
1. Beta 2 agonist 2. Anticholinergics 3. Theophylline 4. Magnesium sulphate	1. Mast cell stabilizers 2. Lipoxygenase inhibitors 3. Leukotriene receptor antagonist 4. Corticosteroids 5. Monoclonal antibodies

Management Of Asthma (gina)

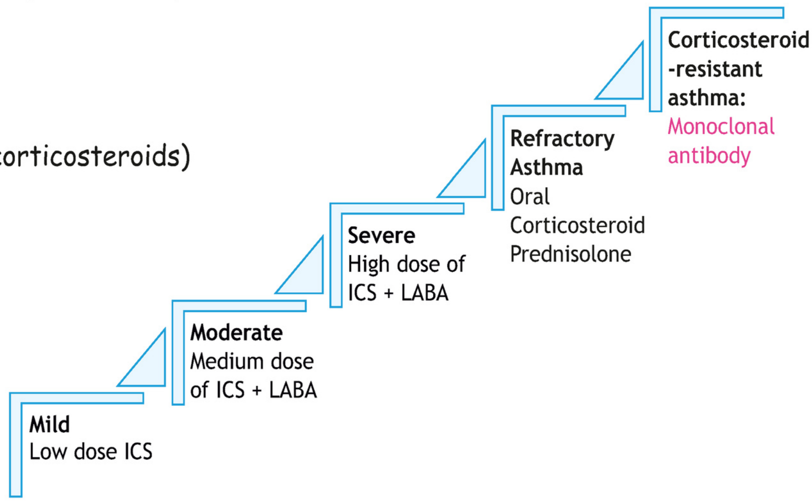
00:02:16

Acute Asthma Attack

- Beta 2 agonist, DOC: Formoterol + Budesonide (corticosteroid), both inhalational
- If not relieved, it is called acute severe asthma (AKA Status asthamaticus)
- Other bronchodilators added.
  - $MgSO_4$ inhaler/nebulizations
  - Ipratropium
  - Aminophyllin I.V 5 mg/kg
- I.V hydrocortisone to control inflammation
- MC cause of acute severe asthma is chest infection; therefore, antibiotics are started as well
- If the condition is still not GA + MV
  - GA preferred are ketamine and halothane (inhalational)
  - As they have a bronchodilatory effect

Chronic Or Persistent Asthma

- Anti-inflammatory DOC: ICS (inhalational corticosteroids)
- Mild: <1 attack of asthma per day
- Moderate: 1 attack per day



Yourwish

- Severe: bedridden and cannot do day-to-day activities
- For mild to severe, ICS is preferred with increasing dosages from low to high doses.
- LABA added for moderate to severe
- Refractory: Not controlled by the highest dose of ICS, thus started on oral corticosteroids + LABA
- Corticosteroid-resistant asthma: Not controlled by oral corticosteroids, thus starting on monoclonal antibodies

Bronchodilators In Asthma

Beta-2 Agonist

00:07:26

- MOA: Stimulates beta 2 receptors on bronchus muscles, which are Gs-coupled receptors (GPCRs), activating adenylyl cyclase inside bronchial smooth muscles, increasing cAMP, and causing bronchodilation
- cAMP is degraded by PDE4 (inhibited by Theophylline)
- SABA:
  - Salbutamol (albuterol), Terbutaline (DOC for Brittle asthma type 1)
  - Given in acute attack
- LABA:
  - Effect for 12 hrs- Twice a day
  - Salmeterol, bambuterol
  - Maintain bronchodilation in chronic asthma
- Ultra-LABA:
  - Effect for 24 hrs- Once a day
  - Indacterol, Vilanterol, Vlenbuterol (banned now due to its anabolic effect)
  - Maintain bronchodilation in chronic asthma
- Formoterol: SABA+LABA
  - Used in acute and chronic conditions
- Route of administration
  - Inhalational and oral syrups
  - Terbutaline is available as S.C injections
  - Salmeterol given as an I.V injection
- Adverse effects **(Mnemonic: 3T-2H)**
  - Tremors, due to the presence of the beta-2 receptor in skeletal muscle
  - Tachycardia, beta-2 receptor in the heart
  - Tachyphylaxis: rapid loss of effect due to desensitization of the beta-2 receptor
    → Corticosteroid doses are increased to overcome this effect
  - Hypokalemia
  - Hyperglycemia: beta-2 receptors in the liver cause glycogenolysis

Anticholinergics

00:14:43

- MOA: Block the M_3 receptor of ACh on the bronchus
- Drugs are,
  - Ipratropium:
    → SAMA, short-acting
    → Given in acute conditions
  - Tiotropium: LAMA
  - Umeclidinium: LAMA
  - Aclidinium: LAMA

- LAMA: used in treatment for COPD
- Newer drugs
  → Revefenacin
  → Glycopyrolate
- More effective in COPD: LAMA+LABA
- All are administered via the inhalational route only
- Adverse effects: Atropine-like side effects
  - Dry eyes
  - Dry mouth
  - Decrease mucous production
  - Constipation
  - Urinary retention
- Paradoxical bronchoconstriction is seen in Ipratropium
  - By blocking the M2 receptor in the vagus nerve, causing increased ACh release and bronchoconstriction
  - Tiotropium doesn't cause this, as it does not act on the M2 receptor

Theophylline 00:18:28

- Natural methylxanthines
  - Tea: Theophylline
    → More bronchodilatory effect
    → Used in asthma and COPD
    → Injections are given for apnea of the newborn
  - Coffee: Caffeine
    → Acts on the CNS
    → Used in migraine headaches
    → Injections are given for apnea of the newborn
  - Chocolate: Theobromine

Theophylline

- Aminophylline, etophylline
  - Water-soluble, thus can be given via the I.V route
- MOA:
  - PDE4 inhibitor: Increases cAMP (MAIN action)
  - Block adenosine receptor (A1)
  - Calcium blocker
  - Histone acetylation: Decreases IL-5, an anti-inflammatory effect
- Specific PDE 4 inhibitors: Approved for treating COPD
  - Roflumilast
  - Cilomilast
- Narrow therapeutic index drug: Requires monitoring
- Therapeutic range: 5-15 μg/ml
- Metabolised by CYP1A2: Drug interaction
  - CYP inducer: Rifampicin, Phenobarbital, thus decreasing the effect
  - CYP inhibitor: Ciprofloxacin and Erythromycin increase the risk of toxicity

- **TOXICITY**:
  - D/t to blocking of adenosine (A1) in the brain and kidneys
    → Seizure
    → Urination
  - D/t blocking adenosine and PDE4
    → Arrhythmia
  - D/t PDE4 inhibition
    → GIT upset (dyspepsia)
    → Headache

Magnesium Sulphate

00:24:22

- Blocks calcium channel
- Used in
  - Torsades de pointus
  - Antacid
  - Blocks Barium and calcium entry (in poisoning)
  - Laxative (diarrhea) for constipation
  - Eclampsia
  - Tocolytic effect
  - Status asthmaticus
- The earliest sign of magnesium toxicity: Loss of the knee-jerk reflex
- Magnesium monitoring
  - Blood levels
  - Respiratory rate
  - Urinary levels

Anti-inflammatory Drugs In Asthma

00:26:43

- Mast cells release inflammatory mediators and the 5-LOX enzyme, which activates leukotrienes LTC4/D4, increasing eosinophils
- Mast cell stabilizers
  - Cromoglycate
  - Nedocromil
- 5-lipoxygenase inhibitor
  - Zileuton
- Leukotriene receptor blocker
  - Montelukast, zafirlukast
  - Block LT1 receptor
  - ADR: Churg-strauss syndrome- increase in eosinophil counts
- All are used in chronic asthma
- They have a steroid sparring effect

Corticosteroids

00:29:45

- MOA: Inhibit phospholipase A_2 enzyme
- ICS drugs
  - Budesonide, Ciclesonide, Beclomethasone, Fluticasone, Mometasone
  - DOC for Chronic asthma, Aspirin-induced asthma, Seasonal asthma, and Exercise-induced asthma
- Oral steroids

- Used in refractory asthma
- Prednisone

- I.V
  - Hydrocortisone
  - Used in Status asthmaticus
- Advantages of ICS over oral steroids
  - Pregnancy: Safe, whereas oral steroids are C/I
  - No risk of Cushing syndrome
  - No risk of ACTH suppression
- Adverse effects of ICS:
  - Oral thrush: Candida in the mouth
    - → Plastic spacers could prevent this
    - → Gargles after each inhalation
    - → Antifungals:
      - Local patch: Nystatin paint
      - Widespread (pharynx, esophagus): Fluconazole

Monoclonal Antibodies

00:33:45

- Given for corticosteroid-resistant asthma
- Approved for Chronic urticaria, Churg-Strauss syndrome, and Atopic dermatitis
- Omalizumab: Blocks the IgE monoclonal antibody located on the mast cell
- Mepolizumab and reslizumab: Block IL-5
- Benralizumab: Blocks the receptor of IL-5
- Dupilumab and tezepelumab: Block IL-4 and TSL, respectively

DRUGS FOR COUGH

00:35:25

Expectorants	Anti-tussives
• Drugs that expel mucus as sputum • Used to treat productive and infectious cough • AKA mucolytic drugs **Drugs** • Ambroxol • Bromhexine • Cysteine (NAC, carbocysteine) ○ Breaks the disulfide bond that liquefies mucus	• Acts by suppressing respiratory centers, and decreasing cough • Used in non-infective cough (dry cough) • C/I in productive or infective cough **Drugs** • Dextromethorphan: Blocks the NMDA receptor • Opioids: Morphine, Codeine, Pholcodeine, Levorphanol (highly addictive) • Noscapine

DRUGS USED IN PULMONARY ARTERY HYPERTENSION

00:38:39

- Vasoconstriction in the pulmonary artery causes right heart failure
- These drugs are vasodilators of the pulmonary artery

Mnemonic: PEPSI Coca-Cola

- Prostaglandin I-2
  - Treprostinil, Epoprostinol, Iloprost
  - DOC for PAH

- **E**ndothelin antagonist
  - Bosentan, Ambrisentan, Macitentan
  - Oral drugs
  - Highly teratogenic and are C/I in pregnancy
- **P**DE-5 inhibitors
  - Sildenafil, Tadalafil
  - DOC for impotence or erectile dysfunction
- **S**oluble guanylyl cyclase activator
  - Riociguat
- **I**-2 PG receptor agonist
  - Selexipag
- **Cola-** Continuous nitric oxide inhalation
- **Cola-** CCB:
  - Amlodipine, nifedipine
  - DOC in PAH with Systemic HTN

DRUGS USED IN CYSTIC FIBROSIS

00:42:50

- Defect in CFTR cells on epithelial cells, defective production of Cl^- and HCO_3^-
- Drugs include:
  - Ivacaftor
  - Lumacaftor
  - Elexacaftor
  - Tezacaftor

1. GIT PHARMACOLOGY

Acid Peptic Disease (Apd)

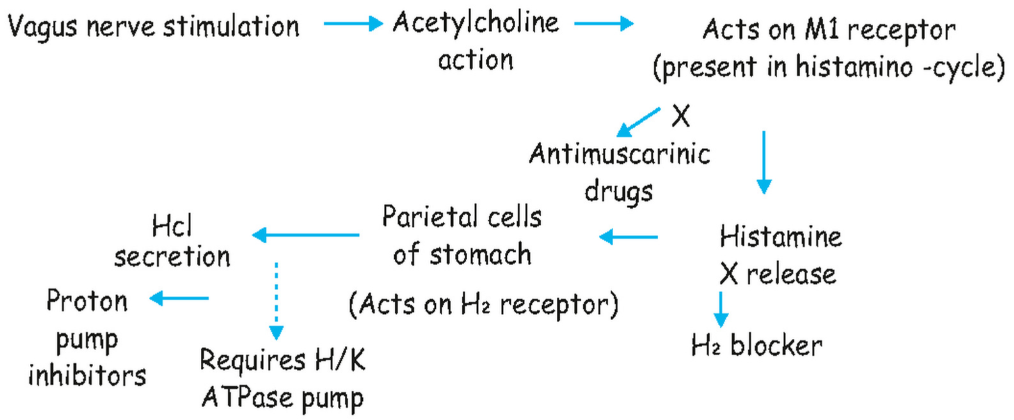
00:00:39

- Acid peptic disease = excessive HCL/acid production in stomach
- Excessive HCL → hyperacidity
- Clinical Manifestations of Hyperacidity
  - Heartburn
    - → HCL causes chest pain
    - → Pain called "heartburn"
  - Peptic Ulcer
    - → HCL damages stomach cells
    - → Leads to peptic ulcer formation
  - GERD (Gastro-Esophageal Reflux Disease)
    - → HCL goes into esophagus
    - → Causes reflux symptoms

Acid Suppressant Drugs

- Reduce HCL production
- Given for long-term basis: "Round the clock protection"

Mechanism Of Hcl Production



Types Of Acid Suppressant Drugs

Anti-muscarinic drugs	H2 receptor blockers (h2 blockers)	Proton pump inhibitors (ppis)

• Mechanism: Block M1 receptor of acetylcholine
• **Drugs**:
  ○ Pirenzepine
  ○ Telenzepine
	• Mechanism: Block H2 receptor (Histamine-2 receptor)
	• Suffix "-tidine"
	• **Drugs:**
	  ○ Cimetidine
	  ○ Ranitidine
		• Mechanism: Directly block Hydrogen-Potassium ATPase/ Proton Pump
		• Suffix "-prazole"
		• **Efficacy:**

• **Efficacy:** ○ Can reduce only 40-60% of HCL production	• **Efficacy:** ○ Can reduce 60-80% of HCL production	○ Can reduce 80-99% of HCL production ○ OR complete acid suppression • Most effective drugs • DOC for ALL acid peptic diseases

Proton Pump Inhibitors (Ppis)

- Mechanism of Action
  - Irreversible inhibitors of Hydrogen-Potassium ATPase pump on stomach
  - Irreversible inhibitor → Suicide inhibitor → Hit and run drug
- **Mnemonic: DIL RO PA DA**
  - Dexrabeprazole, Ilaproazole, Lansoprazole, Rabeprazole, Omeprazole, Pantoprazole (Most potent to least)
- All PPIs are **equally efficacious**, but differ in **potency** (dose required)
- Pro-drug - activate inside stomach
- Half-life- Very short: 2-5 hours
- Duration of action
  - Action remains for 2-5 days (even after stopping)
  - Reason: Irreversible inhibition → proton pump permanently destroyed
- All PPIs safe in pregnancy except:
  - Omeprazole = most unsafe PPI
  - Safest PPI overall: Lansoprazole (maximum data available in pregnancy)
- Acid labile → PPIs degraded in presence of acid when given orally → Cannot reach intestine → cannot enter stomach cells
  - Solution:
    → Capsule form
    → Enteric-coated tablets (acid-resistant tablets)
    → Result: PPIs become expensive drugs
- Timing of Administration
  - Must be taken: Empty stomach (30 minutes to 1 hour before food)
  - Empty stomach has maximum proton pump expression → Maximum binding occurs on empty stomach
- Metabolism & Drug Interactions
  - All PPIs metabolized by CYP 2C19 enzyme in liver
  - CYP Inhibition Property:

Drug	CYP Inhibition
Omeprazole	Maximum inhibition
Rabeprazole	Least inhibition
Pantoprazole	Least inhibition (after Rabeprazole)

- Important Drug Interaction:
  - Omeprazole + Clopidogrel = AVOID

→ Reason: Clopidogrel converted to active form by CYP 2C19

→ Omeprazole inhibits CYP 2C19 → reduces Clopidogrel activation

Uses Of Ppis

- Peptic Ulcer (Any Cause) - PPIs = DOC
- Two most common causes:
  - NSAID-induced peptic ulcer (e.g., Aspirin)
  - Helicobacter pylori-induced peptic ulcer
- GERD (Gastro-Esophageal Reflux Disease)- PPIs → DOC
  - Treatment approach:
    → Reduce acid production → give PPI
    → Close lower esophageal sphincter → give Prokinetics
    → Combination: PPI + Prokinetic
  - Prokinetic Drugs:
    → Domperidone
    → Metoclopramide
- Prevention of Aspiration Pneumonia During Surgery
  - PPI + Prokinetic combination
- Zollinger-Ellison Syndrome (Gastrinoma)
  - Tumor of gastrin-secreting cells
  - Gastrin → increases HCL production
  - Treatment:
    → PPI (to reduce HCL production)
    → + Octreotide (Somatostatin hormone) → Reduces gastrin production

New Ppis (Different Mechanism)

- Tanatoprazole → reversible PPI
- Vonoprazan, Revaprazan
  - Competitive blocker of potassium site
  - Only blocks potassium site of H-K ATPase
  - Treatment of H. pylori infection

Adverse Effects Of Ppis

- PPIs are very safe drugs
- Side effects come with continuous/long-term use
- Mechanism of Side Effects
  - Long-term PPI use →Chronic acid suppression
  - HCL required for:
    → Absorption of vitamins/minerals
    → Protection from GIT infections
  - Result: Micronutrient deficiency
    → Increased risk of infections

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Micronutrient deficiencies	↑ infection risk	Miscellaneous

• Iron Deficiency
  ○ Leads to Iron deficiency anemia
• Calcium Deficiency
  ○ Osteoporosis
• Magnesium Deficiency
• Vitamin B12 Deficiency
  ○ Leads to Megaloblastic anemia (Rarely seen in PPIs))
  ○ More common: IDA
	• Community-Acquired Pneumonia (CAP)
	  ○ Risk increased with continuous PPI use
	• Clostridium difficile Infection
	  ○ In large intestine
	  ○ Causes Pseudomembranous colitis
	• Spontaneous Bacterial Peritonitis (SBP)
		Gastrin Level Increase
		• Mechanism: → PPI decreases HCL → No negative feedback → ↑ Gastrin level
		• In Gastrinoma (Zollinger-Ellison syndrome) → Always combine PPI with Octreotide
		• Effect of increased gastrin: ↑ growth of stomach cells → Gastric polyp formation
		
		Gynecomastia & Impotence
		• PPI: Omeprazole
		  ○ Omeprazole = maximum CYP inhibitor (CYP enzyme required for testosterone production) → decreased testosterone production → Gynecomastia & Erectile dysfunction (Impotence)
		
		New Side Effects
		• Increased risk of Renal Failure
		• Increased risk of Memory Loss
		  ○ Like Alzheimer's dementia

H2 Receptor Blockers

00:14:48

- Suffix "-tidine"
- Drugs:
  - Cimetidine
    - → First drug made
    - → Maximum CYP inhibition
    - → Side effects: Similar to Omeprazole
      - – Males: ↓ testosterone production → Gynecomastia
      - – Females: ↓ estrogen production → Menstrual irregularities
      - – ↑ Prolactin level → Galactorrhea (Mechanism: Can block dopamine receptors in brain)
  - Ranitidine
  - Nizatidine (No CYP inhibition)
  - Famotidine (Non-competitive blocker of h2 receptor))
  - Lafutidine (new drugs)
    - → Increases Nitric Oxide (NO) production
      - – NO improves blood supply to stomach cells
      - – Helps in mucosal healing
    - → Increases Somatostatin level

– Somatostatin reduces gastrin production
– Further reduces HCL level

Misoprostol

- Prostaglandin E1 analogue
  - Originally used for abortion
  - Also used for peptic ulcer

Mechanism - Understanding Gastric Protection

- Normal Physiology:
- COX-1 enzyme present in stomach → Produces Prostaglandin E1 naturally → Protective for stomach
- How PG protects stomach:
  - Decreases HCL production
  - Increases protective factors:
    → Mucus production
    → Bicarbonate production

Nsaid/Aspirin-Induced Peptic Ulcer

- Mechanism:
  - Aspirin/NSAIDs → COX inhibitor → Inhibits COX enzyme → Reduces Prostaglandin E1 → Protective effect lost
- Results:
  - ↑ HCL production
  - ↓ Protective factors (mucus + bicarbonate)
  - = Peptic ulcer
- Use of Misoprostol
- Specific indication:
  - NSAID-induced peptic ulcer
  - Not for any other type of peptic ulcer
- Important note:
  - Even for NSAID-induced peptic ulcer
  - Drug of choice = PPI (not Misoprostol)
  - Misoprostol is not drug of choice

Antacids

00:19:04

- Directly neutralize HCL present in stomach → Basic drugs
- Given for **prompt pain relief** of heartburn/hyperacidity
- **Characteristic:** Very **fast-acting** drugs

Types Of Antacids

Systemic Antacids (absorbed into blood from GIT)	Non-Systemic Antacids (not absorbed into blood)
• Sodium salts ○ Sodium bicarbonate ○ Sodium citrate	• Magnesium salts: Mg hydroxide ○ Fast acting ○ GIT motility - ↑

• Calcium salts ○ Calcium carbonate/ bicarbonate	• Aluminum salts: Al hydroxide ○ Slow acting ○ GIT motility - ↓

Sodium-Containing Antacids

- Sodium Bicarbonate
  - Reacts with HCL → produces CO2 (carbon dioxide)
  - CO2 gas → stretches stomach → can perforate ulcer
  - If ulcer present → can rupture
- Sodium Citrate
  - Does not produce CO2 on reaction with HCL
- Sideeffects
  - When absorbed into blood: Can raise blood pressure
  - Absolutely contraindicated in:
    → Hypertension patients
    → Heart disease patients

Calcium-Containing Antacids

- Calcium Carbonate & Calcium Bicarbonate
- On sudden stoppage:
  - Maximum rebound acid secretion (Among all antacids)
- Milk-Alkali Syndrome
  - With continuous/regular use: Develops Milk-Alkali Syndrome
  - Triad:
    → Hypercalcemia (Calcium in blood)
    → Metabolic Alkalosis (Blood pH becomes basic)
    → Renal Stones (Calcium excreted in urine)
    → Memory aid: MILK contains calcium → Milk-Alkali Syndrome
- Special Use
  - Drug of choice in Renal Failure:
    → Reason: Renal failure patients have osteoporosis
    → Calcium antacids correct osteoporosis

Non-Systemic Antacids

- Magnesium Salts: Magnesium Hydroxide
- Aluminum Salts: Aluminum Hydroxide

Feature	Magnesium	Aluminum
Speed of Action	Very fast	Slow and sustained
GIT Motility	Increases	Decreases
GIT Effect	Diarrhea	Constipation

- Memory aid: MD = Magnesium causes Diarrhea
- Combined formulation advantages:

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- Fast & long action
- Cancel each other's GIT effects
- Minimal effect on GIT motility

- Aluminum Side Effects
  - Osteoporosis (Phosphate deficiency → Phosphate required for bone formation)
  - Encephalopathy

Ulcer Protective Drugs

- Mechanism
  - Make protective covering over the ulcer
  - Polymerize at acidic pH
  - Polymerize with help of dead proteins/dead cells over ulcer
- Drugs
  - Sucralfate (very famous drug)
  - Colloidal Bismuth Salts
    - → Bismuth subacetate
    - → Bismuth subsalicylate

Sucralfate

- SUCR = Sucrose; AL = Aluminum; FATE = Sulfate
- Must avoid with: (gap of)
  - Other drugs (Phenytoin/ Rantidine) - 120 min
  - Food - 60 min
  - Antacids - 30 min
- Side Effect: Constipation (Contains aluminum)

Colloidal Bismuth Salts

- Types: Bismuth subacetate & Bismuth subsalicylate
- Special Property
  - Can kill bacteria
  - Specific use:
    - → Peptic ulcer due to H. pylori bacteria
    - → Bismuth kills H. pylori
- Side Effects
  - Bismuth color = Black → Black tongue & feces
  - Osteoporosis - Damages bone (like aluminum)

Helicobacter Pylori Treatment

00:26:30

- Approved Antibiotics (Mnemonic: TALCM)
  - T = Tetracycline
  - A = Amoxicillin
  - L = Levofloxacin
  - C = Clarithromycin (most important)
  - M = Metronidazole
    - → Can use any drug ending with "-idazole" or "-nidazole"
    - → Examples: Ornidazole, Tinidazole

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- Treatment Guidelines
  - Not single antibiotic
    → At least 2 or more antibiotics
    → Reason: Single antibiotic → resistance
  - Add PPI
    → With antibiotics → PPI increases effectiveness of antibiotics
  - Duration
    → At least 10-14 days
    → Most common: 14 days
- Benefits of Treating H. pylori
  - Reduces risk of:
    → Peptic ulcer
    → GERD
    → MALT lymphoma (Mucosal Associated Lymphoid Tumor)
- Does not reduce risk of:
  - Barrett's Esophagus
    → Reason: Metaplasia already occurred (permanent change, cannot reverse)

Treatment Regimens

Triple regimen (3 drugs); pcm or pca:

- PCM:
  - P = Proton Pump Inhibitor (Omeprazole, Pantoprazole)
  - C = Clarithromycin
  - M = Metronidazole
- PCA:
  - P = Proton Pump Inhibitor
  - C = Clarithromycin
  - A = Amoxicillin
- Duration: 14 days

Quadruple Regimen (4 Drugs)

- Reason for use: Clarithromycin resistance in our country
- PBMT (P Bone Marrow Transplant - memory aid):
  - P = Proton Pump Inhibitor
  - B = Bismuth salts
  - M = Metronidazole
  - T = Tetracycline
- Duration: 14 days
- Indication: Clarithromycin-resistant cases

Miscellaneous Drugs

00:30:00

Alginic Acid (Antifoaming Drug)

- Mechanism:
  - Makes protective layer over HCl → Even if HCl goes to esophagus → HCl will not contact esophagus
- Specific approval:
  - GERD (Gastro-Esophageal Reflux Disease)

Simethicone (Anti-Flatulence Drug)

- Mechanism:
  - Bursts bubbles
- Effect:
  - Person will not pass gases/flatulence

Drugs For Constipation

- Laxatives
- Purgatives

Bulk Laxatives

- Mechanism
  - Come into colon/large intestine → Lead to stretching of colon → Sensory nerves stimulated → Start contraction of colon → Feces moves forward → passes out easily
- Indications (DOC)
  - Idiopathic constipation
  - IBS (Irritable Bowel Syndrome)
  - Pregnancy constipation
- Drugs
  - Psyllium (also known as Metamucil)
  - Isabgol (also known as Ispaghula) - very famous household drug
  - Bran, Husk, Methylcellulose - dietary fibers
- Absolutely contraindicated in:
  - Megacolon
    - → Constipation due to Paralytic ileus
    - → Require nerves to work
    - → In paralytic ileus → nerves not working
    - → Paralytic ileus : Even with stretching → no muscle contraction

Stimulant Laxatives

- Direct muscle stimulation (Not dependent on nerves) → Start active contraction of muscles
- Given in:
  - Resistant cases of bulk laxatives
    - → Idiopathic constipation (resistant)
    - → IBS (resistant)
- Contraindication
  - Pregnancy (Can start uterine contraction → abortion)
- Drugs
  - Bisacodyl (very famous)
  - Senna
  - Cascara
  - Prucalopride
- Note: Suffix "-pride"
  - Prucalopride
  - Mosapride
  - Stimulate Serotonin 5-HT4 receptor

- Important Contraindication: Spastic colon
  - Can themselves cause muscle spasm (Lead to spastic colon → abdominal pain)

Osmotic Laxatives

- Mechanism: Increase osmolarity in colon → Lead to water secretion → Flushing of colon
- Main Use
  - Whole bowel irrigation:
  - Clean whole bowel before:
    → Colonoscopy
    → Abdominal/GIT surgery
- Drug of Choice for Colonoscopy - PEG (Polyethylene Glycol) (most preferred drug)
- Saline Laxatives/Purgatives:
  - Sodium phosphate
  - Magnesium (has laxative effect - causes diarrhea)
- Others:
  - Mannitol
  - Urea
  - Lactulose
- **Lactulose**
  - Special property: Can reduce ammonia absorption from GIT
  - Mechanism:
    → GIT bacteria make ammonia
    → Excessive ammonia in liver disease
    → Liver cannot convert ammonia to urea
  - Specific use:
    → Drug of choice in liver disease
    → Hepatic encephalopathy (Excessive ammonia damages brain when liver not working)

Stool Softeners

- Oily/waxy substances → Soften hard stool
- Drugs
  - Docusate
  - Paraffin wax
  - Mineral oil
- Indications
  - When to avoid straining:
    → Pregnancy (mother should avoid straining)
    → After abdominal incision
    → Hernia
    → Rectal prolapse
  - Given on regular basis to soften stool

New Drugs

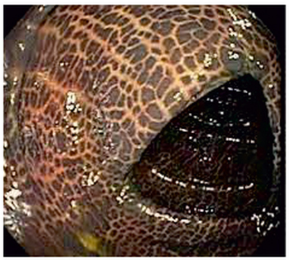
- Lubiprostone
  - Chloride Secretion Increasers

- Similar to Misoprostol
- Prostaglandin E1 analogue

- Linaclotide, Plecanatide
  - Activate Guanylyl cyclase enzyme
    → In intestine/colon
    → Leads to chloride secretion
- Tenapanor
  - Sodium Secretion Increaser
  - Mechanism:
    → Inhibits Sodium-Hydrogen antiporter
    → Leads to sodium secretion in feces
- Indication for Both Types
- Approved only for:
  - Constipation in Irritable Bowel Syndrome (IBS)

Melanosis Coli

- Colonoscopy finding:
  - Blackening of colon (Melanosis coli)
- Cause
  - Side effect of: Senna (stimulant laxative)



Melanosis coli

Laxative Of Choice

- In Pregnancy
  - Bulk laxatives (Psyllium, Ispaghula)
  - Docusate (stool softener)
- In Liver Disease/Hepatic Encephalopathy
  - Lactulose
  - Reduces ammonia absorption

Drugs For Short Bowel Syndrome

- Occurs after: Intestinal resection (part of intestine removed during surgery)
- Result:
  - Bowel becomes short
  - Food not absorbed properly
  - Patient has malabsorption'
- Treatment drugs
  - Mnemonic: GOT (Game of Thrones)
  - Growth Hormone
    → Increases growth of intestinal cells
    → Increases absorptive power
  - Teduglutide (very important drug)
    → Synthetic form of GLP-2
    → GLP-2 = Glucagon-Like Peptide 2
    → Causes growth of intestinal cells
    → Increases absorptive power

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- Octreotide
  → Reduces intestinal secretion
  → Prevents diarrhea

Drugs For Dissolving Gallstones

- Suffix - "-cholic acid"
- Ursodeoxycholic Acid (UDCA)
- Uses:
  - Dissolve gallstones
  - Primary Biliary Cholangitis

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2. ENDOCRINE SYSTEM

DIABETES MELLITUS

00:00:29

- Increase in catabolism due to defect in insulin
- Leads to hyperglycemia which causes fat breakdown → ketone production

Type 1 Diabetes Mellitus

- Autoimmune disease causing β-cell destruction
- DOC: insulin, acarbose, pramlintide

Type 2 Diabetes Mellitus

- Peripheral resistance, thus β-cell does not respond to the insulin
- DOC: metformin - + OHA
- If HbA1c > 10 → start insulin

Gestational Diabetes Mellitus

- Diabetes in pregnancy
- DOC
  - Insulin
  - Metformin
  - Glyburide

Insulin Classification

TYPE	DRUGS	DURATION
RAPID (ULTRA SHORT)	Lispro, Aspart, Glulisine	3 hrs
SHORT	Regular	6 hrs
INTERMEDIATE	NPH, Lente(amorphous + crystalline) 30:70	12-15 hrs
LONG	Detemir, Glargine, Degludec	18 / 24 / 42 hrs

- Insulin used in combination therapy (bolus + basal)
  - Bolus insulin
    - → ultra short / short
    - → before meals
    - → controls PPH
  - Basal insulin
    - → intermediate/long
    - → inhibits catabolism

- AFREZZA
  - Nasal insulin
  - Dry powder inhaled
  - Ultra short acting
  - Used before meals → PPH
  - Not used alone combine with long-acting injectable basal insulin
  - Contraindicated in
    - → Smokers
    - → COPD
    - → ↑ Risk of lung cancer

IV INSULIN	• Regular insulin
	• DOC
	  ○ DKA
	  ○ Hyperkalemia

PEAK LESS INSULIN	• Glargine • Degludec

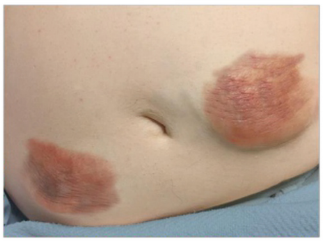
pH
- All insulin → neutral
- Glargine → acidic

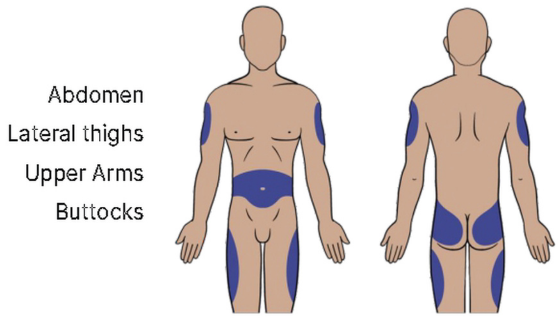
S/E
- Hypoglycemia
  - T/t: Glucose
  - Glucagon(I/M, Nasal spray)
- Weight gain
- Lipodystrophy

Iv Insulin

- Sites of S.C insulin injection
  - Abdomen
  - Upper arm
  - Lateral thigh
  - Buttocks
- Avoid
  - 2 cm around umbilicus

Lipodystrophy





OHA

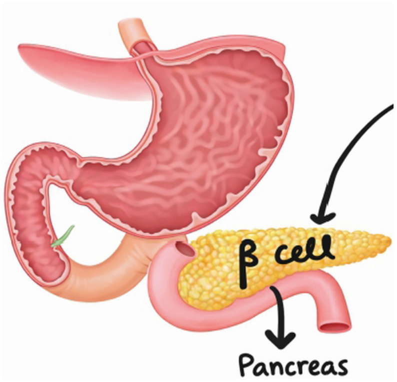
FMGE Dec 2021, Jan 2024

ACTING AT PANCREAS	ACTING AT PERIPHERAL ORGANS
• Sulfonylurea - ↑ insulin	• Biguanide ○ Metformin → liver

• Meglitinide - ↑ insulin
• Amylin analog
  ○ ↓ glucagon
  ○ ↓ appetite
	• Alpha-glucosidase inhibitor
	  ○ Acarbose → intestine
	• Thiazolidinedione
	  ○ Pioglitazone → adipose

• Incretins (GLP-1 analogue) ◦ ↑insulin ◦ ↓glucagon ◦ ↓appetite	• SGLT-2 inhibitor ◦ kidney
• DPP-4 inhibitors ◦ ↑insulin ◦ ↓glucagon ◦ ↓appetite	

Insulin Secretagogues



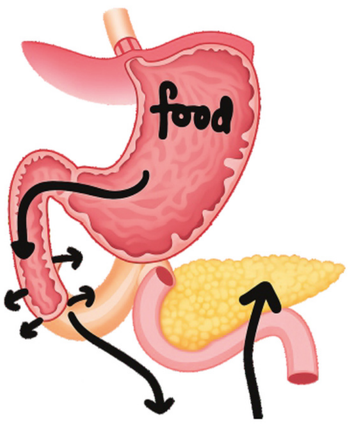
- Drug acts on pancreatic B-cell
  - Closes ATP-sensitive K+ channel
  - Depolarization causes insulin secretion

Sulfonylurea

- 1st generation
  - Chlorpropamide
  - Tolbutamide
- Sulfonylurea 2nd generation (more potent)
  - Glimepiride
  - Glipizide
  - Gliclazide
- Meglitinide
  - Repaglinide
  - Nateglinide
- S/E
  - Weight gain
  - Hypoglycemia
- Chlorpropamide
  - ↑ADH → SIADH
  - Avoid in alcoholics
    → Disulfiram-like reaction

Incretins

- Food intake causes stomach & intestine stretch leading to incretin release
- Incretins act on B-cell causing
  - ↑insulin
  - ↓glucagon
- Incretins acts on brain causing
  - ↓appetite



Glp-1 Agonists

- Given as S/C injection
  - Exenatide
  - Dulaglutide
  - Liraglutide

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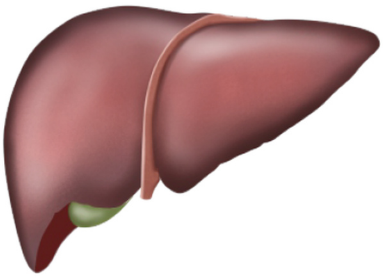
- Semaglutide
  - → Available in oral form
  - → Longest acting
- S/E
  - Weight loss
  - Pancreatitis
  - ↑ risk of pancreatic and thyroid cancer

Dpp-4 Inhibitors

- Inhibit incretin degradation
- ↑ levels of GLP - 1
  - Linagliptin
    - → Renal safe
  - Sitagliptin
  - Vildagliptin
  - Saxagliptin
    - → Inhibited by CYP3A4
- S/E
  - ↑ Inflammation
  - Arthritis
  - Nasopharyngitis

Insulin Sensitizer

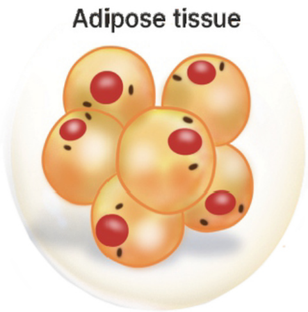
Metformin



- Insulin sensitizer
- Acts on liver → ↓ insulin resistance
- Stimulates AMPK → Inhibit hepatic gluconeogenesis
- ↓ Glucose production from lactic acid
- DOC → type 2 diabetes mellitus
- DOC → type 2 DM in PCOD
- Max dose < 2550 mg/day
- S/E
  - M/C → diarrhea
  - Megaloblastic anemia → ↓ vitamin B12 absorption
  - Most dangerous → lactic acidosis
- C/I
  - → Renal failure (GFR < 30 ml/min)

Pioglitazone

INICET Nov 2022



- Insulin sensitizer
- Acts on adipose tissue → ↓ insulin resistance
- PPAR-γ agonist
- ↑ lipogenesis (anabolic effect)
- Given as add-on with metformin
- S/E
  - Urinary bladder cancer
  - Heart failure → anti-diuretic effect → ↑ plasma volume

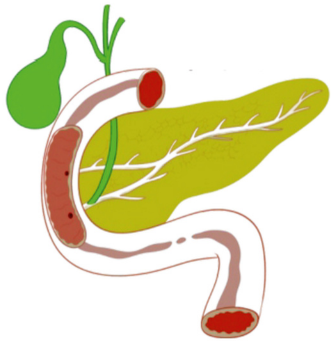
Ppar Drugs

- PPAR-α agonist
  - Fibrates
  - Use → dyslipidemia
  - ↓ triglyceride + cholesterol
- PPAR-α + γ agonist
  - Saroglitazar
  - Use → diabetic dyslipidemia

Alpha-glucosidase Inhibitors

- Drugs
  - Acarbose
  - Voglibose
- Mechanism
  - Inhibit breakdown of complex carbohydrate into monosaccharides → ↓ glucose absorption
- Taken before meals thus decreases postprandial hyperglycemia
- Weight neutral
- Sucrose will not correct hypoglycemia if the patient is on alpha glucosidase inhibitors
  - Treatment → pure glucose / fructose

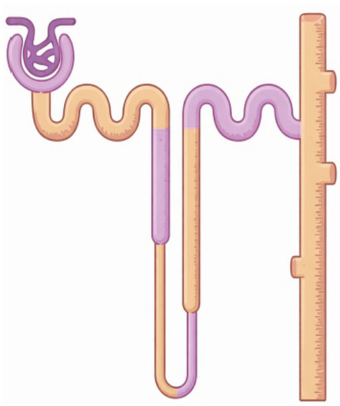
Pramlintide



- Amylin analogue secreted by b cells of pancreas
- Given subcutaneous
- Actions
  - ↓ glucagon
  - ↓ gastric emptying
  - ↑ satiety
- Causes weight loss

Sglt2 Inhibitors

- Act on PCT of nephron
- Inhibit sodium-glucose reabsorption → ↑ excretion
- Transporters
  - SGLT2 → 90% glucose reabsorption
  - SGLT1 → 10% glucose reabsorption



- Drugs
  - Canagliflozin
  - Dapagliflozin
  - Empagliflozin
  - Sotagliflozin → SGLT1 + SGLT2 inhibitor
- Effects
  - Glucosuria
  - Diuretic action
  - ↓ blood glucose

- Uses
  - Type 2 diabetes mellitus
  - Chronic heart failure
  - CKD
- Advantage
  - Cardio-protective → ↓ pressure on heart
  - Nephro-protective → ↓ pressure on kidney
- S/E (GUU)
  - F - Fournier's gangrene
  - O - Osteoporosis → fractures
  - D - Diabetic ketoacidosis
  - U - UTI (bacterial + candida)

DIABETIC GASTROPARESIS	• Erythromycin → ↑ motilin receptor → ↑ motility
DIABETIC DIARRHEA	• Clonidine → a2 receptor → ↓ intestinal secretion

DIABETIC RETINOPATHY	• Formation of abnormal blood vessels by VEGF
	• ANTI-VEGF DRUGS
	  ○ Inhibit VEGF → ↓ neovascularization
	  ○ Bevacizumab
	  ○ Ramukirumab
	  ○ Ranibizumab
	  ○ Given as intravitreal injection

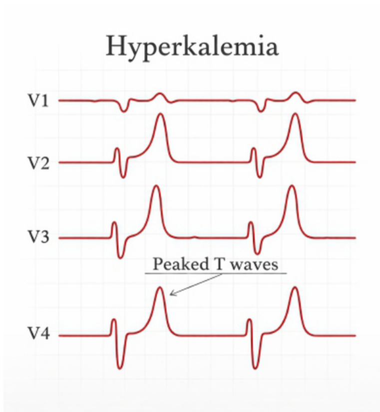
ANTI OBESITY	• Drugs
	  ○ Semaglutide
	  ○ Liraglutide
	  ○ Tirzepatide
	• Mechanism
	  ○ GLP-1 agonist
	  ○ Tirzepatide → GLP-1 + GIP agonist
	• Given subcutaneous

DIABETIC NEUROPATHY	• DOC ○ Pregabalin

RENAL SAFE	• Drugs
	  ○ Linagliptin
	  ○ Pioglitazone
	  ○ Teneligliptin
	  ○ Semaglutide
	  ○ Dulaglutide
	• No dose reduction required
	• Contraindicated
	  ○ Metformin

Additional Drugs

- Colesevelam
  - Bile acid binder
  - ↓ bile absorption
  - Use → type 2 diabetes mellitus
- Bromocriptine
  - D2 receptor agonist
  - ↓ hypothalamic-pituitary hormones
  - ↓ hyperglycemia
- Epalrestat
  - Aldose reductase inhibitor
  - Inhibits the conversion of glucose into sorbitol
  - Used in diabetic neuropathy
- Imeglimin
  - Inhibits hepatic gluconeogenesis



Hyperkalemia

- ↑ potassium → arrhythmias
- ECG change → tall T waves
- Treatment
  - Protect heart
    → Calcium gluconate → ↓ entry of potassium into heart
  - Shift potassium into cells (muscle, fat)
    → Insulin (IV regular insulin)
    → If insulin not available - Salbutamol, Epinephrine, B2 stimulation → ↑ insulin secretion
  - Remove potassium from body
    → Loop diuretic (furosemide) → ↑ urinary excretion
  - ↓ Absorption from GIT
    → Potassium binding resins - Polystyrene

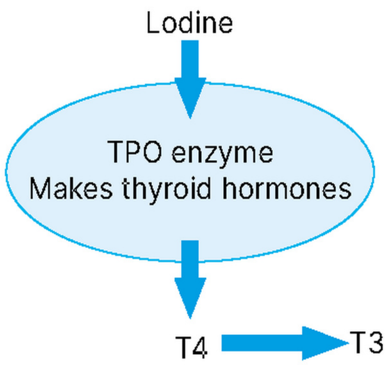
ANTITHYROID DRUGS

00:48:38

Sodium-iodide Symporter

- Sodium-iodide symporter inhibitors
  - Thiocyanate
  - Perchlorate
  - Pertechnate

Thyroid Peroxidase (tpo) Inhibitors



- Propylthiouracil (PTU)
  - Thyroid storm
- Carbimazole → prodrug
- Methimazole → active form
  - Long-term use (Graves disease)
- S/E
  - Sulfa allergy → rash
  - Agranulocytosis (bone marrow suppression) → monitor WBC

Yourwish

Release Of T3, T4 (rate Limiting Step) Inhibitors

- Sodium iodide
- Potassium iodide
- Lugol's iodine → 5% iodine + 10% potassium iodide
  - Fastest acting antithyroid drugs

Peripheral Conversion Inhibitors

- Inhibits the conversion of (T4 → T3)
- Enzyme → 5' deiodinase
- Inhibitors (PAID)
  - Propranolol
  - Propylthiouracil
  - Iodides
  - Dexamethasone

Pregnancy (hyperthyroidism)

- First trimester
  - PTU
- Second and third trimester
  - Carbimazole / Methimazole
- Contraindications
  - PTU → not in 2nd, 3rd trimester (hepatotoxic)
  - Carbimazole, Methimazole → not in 1st trimester (teratogenic)
- Teratogenic effect
  - Aplasia cutis

Radioactive Iodine

- Drug
  - Iodine-131
- Mechanism
  - Emits B-rays → destroys thyroid gland
- Half-life
  - 8 days
- Use
  - Inoperable hyperthyroidism
  - Old age (>35 years)
  - Heart disease patients
- Iodine side effect
  - Sialadenitis
  - Parotitis

Thyroid Storm

- Drugs (sequence)
  - Propranolol
  - Propylthiouracil
  - Iodides + Dexamethasone (resistant cases)

Thyroid Hormones

- T4 → Levothyroxine
  - Oral → chronic hypothyroidism
  - IV → myxedema coma
- T3 → Liothyronine
  - Faster, shorter acting
  - IV in myxedema

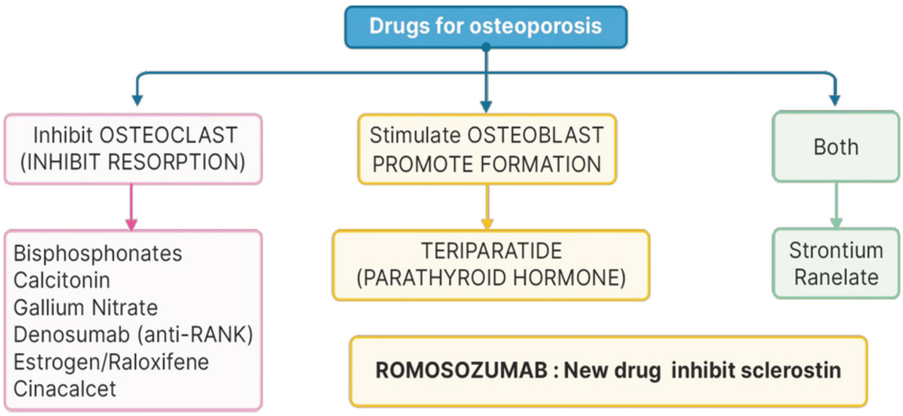
New Drugs

- Vandetanib
  - Use → medullary carcinoma thyroid
- Teprotumumab
  - Monoclonal antibody
  - Blocks IGF-1
  - Use
    - → Thyroid eye disease
    - → Proptosis

OSTEOPOROSIS

01:00:47

- ↓ Bone mineral density → ↑ fracture risk
- All drugs given with
  - Vitamin D
  - Calcium



Drug Classes

- Inhibit osteoclast (↓ bone resorption)
  - Bisphosphonates
  - Calcitonin
  - Gallium nitrate
  - Denosumab
  - Estrogen
  - Raloxifene
  - Cinacalcet
- Stimulate osteoblast (↑ bone formation)
  - Teriparatide
- Both action
  - Strontium ranelate (not available)

Bisphosphonates

- Drugs
  - Alendronate
  - Pamidronate
  - Ibandronate
  - Zoledronate
    → Longest acting
    → Once yearly IM
- Mechanism
  - Inhibit FPPS enzyme
  - ↓ ATP production in osteoclast → osteoclast death
- Uses (HOP)
  - Hypercalcemia
  - Osteoporosis
  - Paget's disease
- S/E (ROOS)
  - Renal damage
  - Osteonecrosis of mandible
  - Subtrochanteric femur fracture
  - Esophagitis

Teriparatide

- Synthetic parathyroid hormone stimulates osteoblast
- Intermittent / pulsatile PTH → stimulates osteoblast
- Continuous PTH (hyperparathyroidism) → bone destruction
- Given as intermittent injection
- Use
  - Osteoporosis
- Action
  - ↑ bone formation
- Side effect
  - Osteosarcoma
- Contraindications
  - Paget's disease of bone
  - Hypercalcemia
- Duration
  - Maximum 2 years

Calcitonin

- Fastest calcium lowering drug
- Uses
  - Hypercalcemia → IV
  - Osteoporosis → nasal spray

Denosumab
- Monoclonal antibody
- Blocks RANK ligand
- Action
  - ↓ osteoclast → ↑ bone density
- Use
  - Osteoporosis
- Advantage
  - Renal safe

Cinacalcet
- Calcimimetic drug
- Stimulates calcium sensing receptor
- Action
  - ↓ parathyroid hormone
- Use
  - Hyperparathyroidism

New Monoclonal Antibodies
- Romosozumab
  - Inhibits sclerostin
  - ↑ osteoblast
- Burosumab
  - Inhibits FGF-23
- Use
  - Osteoporosis

Hypercalcemia Treatment
- Initial
  - Normal saline + loop diuretic
- Contraindicated
  - Thiazide diuretics
- Maintenance drugs (BCD)
  - Bisphosphonates
  - Calcitonin
  - Denosumab
- Special cases
  - Corticosteroids
    → Hypercalcemia due to granulomas
  - Cinacalcet
    → Hypercalcemia due to hyperparathyroidism

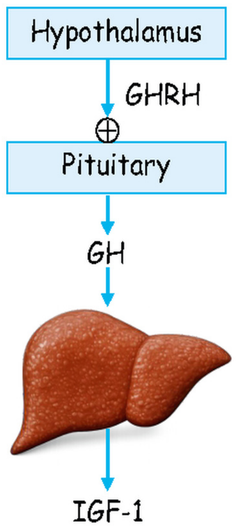
Hyperphosphatemia
- DOC
  - Sevelamer
- Others
  - Lanthanum

- Calcium
- Aluminum
- Iron
- Niacin

HPA AXIS HORMONES

01:13:44

- Hypothalamus
  - Growth hormone releasing hormone
- Pituitary
  - Growth hormone
- Liver
  - IGF-1 → growth effect



Ghrh Analogues

- Drugs
  - Somatorelin
  - Tesamorelin
- Use
  - Dwarfism

Growth Hormone

- Drug
  - Somatropin
- Given by injection
- Use
  - DOC → dwarfism
- Condition
  - Before epiphyseal closure
- S/E
  - Carpal tunnel syndrome
  - Hyperglycemia

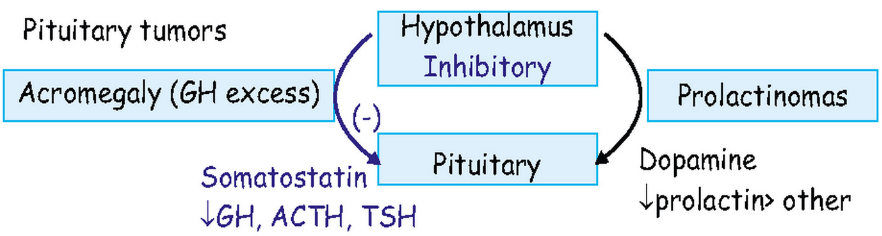
Igf-1 Analogue

- Drug
  - Mecasermin
- Use
  - Dwarfism (resistant cases)
- Action
  - Direct growth promotion
- Side effect
  - Hypoglycemia

Pituitary Tumors

Pituitary Inhibitory Hormones

- Somatostatin
  - ↓ growth hormone
  - ↓ ACTH, TSH
- Dopamine
  - ↓ prolactin (main effect)



Acromegaly (gh Excess)

- First treatment
  - Surgery → trans-sphenoidal pituitary removal
- If surgery not possible / resistant
  - DOC → somatostatin analogues
- Drugs
  - Octreotide
  - Lanreotide
  - Vapreotide
  - Pasireotide
- Resistant cases
  - Pegvisomant
  - Growth hormone receptor antagonist

Somatostatin Analogues

- Given by injection
- Longest acting
  - Lanreotide → IM depot
- Actions
  - ↓ growth hormone
  - ↓ other hormones
- Uses
  - Acromegaly
  - Insulinoma
  - Glucagonoma
  - Gastrinoma
  - PNET tumors
  - Diarrhea
    - → Carcinoid tumor
    - → VIPoma
    - → Short bowel syndrome
  - Esophageal varices (bleeding)
    - → DOC → terlipressin

Other Related Drugs

- Teduglutide
  - GLP-2 analogue
  - Short bowel syndrome → ↑ intestinal growth
- Lutetium dotatate
  - Radioactive octreotide
  - PNET tumors

Prolactinoma

- Features
  - Galactorrhea
  - Amenorrhea
  - Infertility

- First treatment
  - Drugs
- DOC
  - Cabergoline
- Pregnancy
  - Bromocriptine
- Resistant cases
  - Surgery → trans-sphenoidal

Dopamine Agonists

- Drugs
  - Bromocriptine
  - Cabergoline (most potent)
  - Pergolide
  - Quinagolide
- Actions
  - ↓ prolactin
- Uses
  - Prolactinoma
  - Suppress lactation (after neonatal death)
- Side effect
  - Ergotism → ischemic necrosis of fingers

Gnrh (gonadotropin Releasing Hormone)

- Pulsatile release
  - ↑ FSH, LH
- Continuous release
  - ↓ FSH, LH (after 7 days → receptor desensitization)

Gnrh Agonists

- Drugs
  - Histrelin
  - Buserelin
  - Triptorelin
  - Nafarelin (nasal spray)
  - Leuprolide (most common)
- Uses
  - Pulsatile
    - → Male infertility (azoospermia)
    - → Female infertility (anovulation)
    - → Delayed puberty
  - Continuous
    - → Prostate cancer
    - → Breast cancer
    - → Endometriosis
    - → Precocious puberty

Gnrh Antagonists

- Drugs
  - Cetrorelix
  - Ganirelix
  - Degarelix
  - Abarelix
  - Elagolix
- Action
  - ↓ FSH, LH (no initial surge)
- Uses
  - Prostate cancer
  - Endometriosis (elagolix)

CORTICOSTEROIDS

01:32:17

Glucocorticoids

- Uses
  - Anti-inflammatory
  - Immunosuppressant
- Most potent glucocorticoids
  - Beclomethasone dipropionate 0.5%
  - Clobetasol Propionate 0.5%

SHORT ACTING	• Hydrocortisone ○ Max mineralocorticoid activity (1:1)
INTERMEDIATE ACTING	• Prednisolone • Methylprednisolone • Triamcinolone • Deflazacort

LONG ACTING	• Dexamethasone, Betamethasone
	  ○ Most potent
	  ○ No mineralocorticoid activity

Mineralocorticoids

- Actions
  - ↑ sodium retention → ↑ BP
  - ↓ potassium → hypokalemia
- Drugs
  - DOCA
    → Pure mineralocorticoid
  - Aldosterone
    → Most powerful
  - Fludrocortisone
    → Max glucocorticoid activity

- → Oral + IV
- → DOC

- Use
  - Hypotension
- S/E
  - Hypertension

Adrenal Insufficiency

- ↓ glucocorticoid + ↓ mineralocorticoid
- DOC
  - Hydrocortisone → has both activities

Fetal Lung Maturity

- Glucocorticoids → ↑ surfactant production
- Drugs
  - Dexamethasone
  - Betamethasone
- Given
  - IM injection
  - For 2 days
  - In premature delivery

Corticosteroid S/e

- Cushing's syndrome (long-term use) causes
  - Moon facies
  - Buffalo hump
  - Central obesity
- Eye effects
  - Cataract (oral) → posterior subcapsular
  - Glaucoma (topical)

Cushing's Disease Treatment

Octreotide Pasireotide	• Somatostatin analogues ○ ↓ ACTH

Mitotane
Metyrapone
	• Steroid synthesis inhibitors
	  ○ Inhibit 11β-hydroxylase
	  ○ Medical adrenalectomy
	  ○ Use → inoperable adrenal tumors

Mifepristone	Blocks glucocorticoid receptor

Drugs Reducing Steroid Synthesis

- Ketoconazole (antifungal)
- Etomidate (general anesthetic)
- Side effect
  - Adrenal insufficiency

Progesterone Antagonists

- Drugs
  - Mifepristone (RU-486)
    → Blocks glucocorticoid receptor → Cushing's
    → Blocks progesterone receptor → medical abortion
    → Use → contraceptive, leiomyoma
  - Ulipristal
    → Blocks progesterone receptor only
    → Use → emergency contraception
    → Dose → 30 mg within 5 days

ORAL CONTRACEPTIVE PILLS

01:43:46

COMBINED OCP	PROGESTERONE-ONLY PILLS	EMERGENCY CONTRACEPTIVE PILLS

Ethinyl estradiol) + progesterone	Levonorgestrel
	Desogestrel
	Norgestrel
		• Combined OCP
		  ○ Up to 3 days
		• Levonorgestrel
		  ○ Up to 3 days
		• Ulipristal
		  ○ up to 5 days

MOA - Inhibit ovulation (↓ FSH, LH)	MOA - Thick cervical mucus	MOA - Emergency pills → inhibit embryo implantation
Efficacy (failure rate) - <0.1%	Efficacy (failure rate) - 2-5%	Efficacy (failure rate) - >5%

Ocp Effect On Cancer

- ↓ risk
  - Colorectal cancer
  - Endometrial cancer
  - Ovarian cancer
- ↑ risk
  - Cervical cancer
  - Hepatocellular carcinoma
- Least risk
  - Breast cancer

Adverse Effects Of Ocp

MILD	MODERATE	SEVERE
• Nausea, vomiting • Edema • Headache • Mastalgia • Breakthrough bleeding	• Acne • Weight gain • Melasma	• MI, stroke (old age, smokers) • Depression, migraine • Cholestatic jaundice

SERM
01:48:30

- Selective estrogen receptor modulators
- Act as an agonist or antagonist

Tamoxifen
- Prevents breast cancer
- Stimulates estrogen receptors in bone
- Increase the risk
  - Endometrial cancer
  - Cataract
  - Hepatotoxicity

Raloxifene
- Use → postmenopausal osteoporosis
- No risk of endometrial cancer associated
- S/E
  - Hot flashes
  - Thromboembolism

Other Serm

CLOMIPHENE	• Ovulation inducer • PCOD, IVF
ORMELOXIFENE (CENTCHROMAN)	• Contraceptive • Brand → Saheli, Chhaya
OSPEMIFENE	• Senile vaginitis
BAZEDOXIFENE	• Postmenopausal hot flashes

Fulvestrant
- SERD (Selective estrogen receptor downregulator)
- Estrogen receptor antagonist thus block estrogen receptor in all the organs
- Use
  - Breast cancer (tamoxifen-resistant)

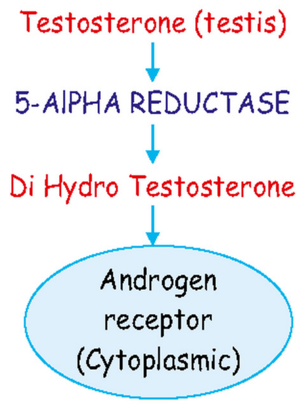
Aromatase Inhibitors
- Mechanism
  - ↓ testosterone → estrogen conversion
- Drugs
  - Anastrozole
  - Letrozole - most commonly used
  - Exemestane
  - Formestane
- Use
  - Postmenopausal breast cancer

ANTI ANDROGENS

01:54:52

- Testosterone → converted to active form by 5- alpha reductase
  - Dihydrotestosterone (DHT)

SYNTHESIS INHIBITOR	KETOCONAZOLE
5- alpha reductase inhibitors	• Finasteride • Dutasteride ○ Also used in BPH and androgenic alopecia
Androgen receptors antagonist 1. Non steroidal	• Flutamide • Bicalutamide • Enzalutamide
2. Steroidal	• Spironolactone • Cyproterone



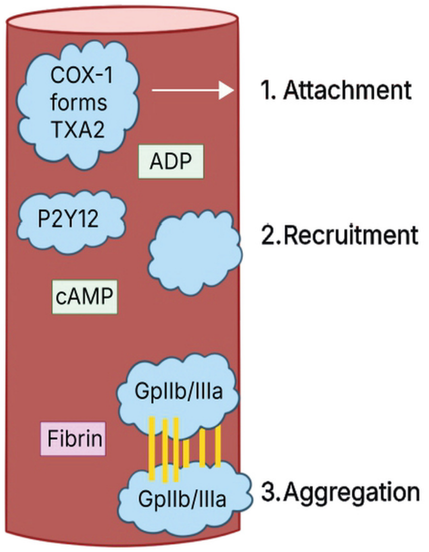
- All drugs are used for the treatment of prostate cancer in males and hirsutism in females
- Adverse effects
  - Gynecomastia
  - Impotence

Yourwish

1. BLOOD DISORDERS

ANTI-PLATELET DRUGS

00:00:35



Indications For Antiplatelet Drugs

- Antiplatelet drugs are used when there is excessive platelet deposition in blood vessels:

Location	Disease
Coronary artery	MI (Myocardial Infarction)
Brain/Cerebral artery	Ischemic stroke
Limb arteries/Leg arteries	PVD (Peripheral Vascular Disease) - Burger's disease

Physiology Of Platelet Attachment (3 Steps)

- Step 1: Platelet Attachment
  - COX-1 enzyme (Cyclooxygenase enzyme) in platelets → produces Thromboxane A2
  - Thromboxane A2 → leads to the attachment of platelets to the blood vessel
- Step 2: Platelet Recruitment
  - Attached platelet releases chemicals like ADP
  - ADP acts on other platelets via the P2Y12 receptor (purine receptor of ADP)
  - This leads to platelet recruitment (other platelets come)
  - Cyclic AMP = OPPOSITE of ADP → inhibits platelet recruitment
  - ADP causes platelet recruitment ↔ Cyclic AMP inhibits platelet recruitment
- Step 3: Platelet Aggregation (Cross-linking)
  - Recruited platelets are cross-linked with Fibrin (a cement-like substance)
  - GP 2B3A receptor (receptor of fibrin) → leads to cross-linking

Classification Of Anti-platelet Drugs

- Irreversible COX-1 Inhibitor
  - Drug: Aspirin
- ADP Receptor/P2Y12 Blockers
  - Block platelet recruitment
- Phosphodiesterase-3 Inhibitors
  - Inhibit the phosphodiesterase-3 enzyme in platelets → ↑ Cyclic AMP → inhibits platelet recruitment
- GP 2B3A Inhibitors
  - Inhibit aggregation of platelets

Drug Of Choice

- ASPIRIN = Overall drug of choice for:
  - MI
  - Stroke
  - Burger's disease
- Other antiplatelet drugs = Add-on drugs to aspirin in the treatment of these diseases

Aspirin

NEET PG 2021, 2023
FMGE 2023, 2024, 2025
INI CET 2022, 2023

- **Mechanism**
  - Irreversible inhibitor of the COX enzyme (Cyclooxygenase enzyme)
  - Also known as Suicide inhibitor or Hit and run drug
  - Inhibits COX → ↓ production of Thromboxane A2 in platelets → inhibits platelet attachment
- Indications
  - Drug of choice for MI, stroke, and Burger's disease (PVD)
- Dosing
  - Range for anti-platelet effect: 42-325 mg

Setting	Dose	Duration
Acute attack of MI/Stroke	325 mg oral	Single dose
Secondary prophylaxis (lifelong)	75 mg (can be increased up to 100 mg)	Lifelong

- Side Effects
  - ↑ Bleeding time (logical - all antiplatelet drugs)
  - Peptic ulcers (aspirin shows iron trapping in stomach cells)
    - → Treatment of Aspirin-Induced Peptic Ulcers
    - → Drug of choice: Proton pump inhibitor (Omeprazole, Pantoprazole, etc.)
    - → Alternative: Misoprostol (NOT drug of choice)
- Aspirin is stopped 7 days before major surgery
  - Reason: Aspirin blocks platelet action irreversibly
  - Platelet life in blood = 7 days
- Absolutely contraindicated in lactation/breastfeeding
  - If enters neonate through breast milk → ↑ risk of liver damage
  - Called Reye's syndrome in a neonate

Adp Receptor Blockers (P2Y12 Blockers)

- Mechanism
  - Inhibit recruitment of platelets

Classification

Type	Drugs	Notes
Irreversible blockers (Grel drugs)	- Ticlopidine - Clopidogrel - Prasugrel	Prodrugs (inactive, converted to active form in the body)
Reversible blockers (Grelor drugs)	- Ticagrelor - Cangrelor	NOT pro-drugs (themselves active)

Indications

- Given as an add-on drug to aspirin in Dual antiplatelet therapy
- Shows synergism/additive effect with aspirin → better effects
- Used in MI and stroke

Special Points

Drug	Use	Notes
Clopidogrel	MI + Stroke	-
Ticlopidine	MI + Stroke	-
Prasugrel	Only MI	Contraindicated in stroke (can cause severe bleeding risk hemorrhagic stroke)
Ticagrelor	Only MI	
Cangrelor	IV drug only	Given during stent placement (PTCA - definitive treatment of MI/stroke)

Clopidogrel

00:09:40

- Conversion to Active Form
  - Clopidogrel = pro-drug
  - Converted to active form by the CYP2C19 enzyme
- Drug Interactions with Proton Pump Inhibitors: OMEPRAZOLE
  - AVOID with Clopidogrel
  - Omeprazole = Maximum CYP inhibiting action
  - Blocks CYP enzyme → prevents conversion of clopidogrel to active form
  - Result: ↑ risk of MI/stroke with omeprazole
  - Memory aid: Next word in Clopidogrel = O → means Omeprazole avoid
- Safe PPIS to combine:
  - Rabeprazole (preferred)

- Pantoprazole (2nd choice if rabeprazole not available)
- Reason: Least CYP inhibiting action
- Memory aid: Next word in Clopidogrel = P → Pantoprazole can give

- Side Effects of ADP Receptor Blockers
  - Most common: Diarrhea (blocking ADP receptors in the intestine)
  - Dangerous: Autoimmune process
    → Antibodies against platelets when the drug attaches to platelets
    → Can lead to Thrombotic Thrombocytopenic Purpura (TTP)
  - Ticlopidine specific: Bone marrow suppression = Agranulocytosis

Phosphodiesterase-3 Inhibitors

00:12:20

- Mechanism
  - Inhibit phosphodiesterase-3 enzyme
  - ↑ Cyclic AMP
  - Cyclic AMP inhibits platelet recruitment
- Drugs - PDE-3 Memory
  - P = Pentoxifylline
  - D = Dipyridamole
  - E-3 = Cilostazol
- Indications
  - Given as an add-on drug to aspirin
  - ONLY given in stroke and Burger's disease
- Absolutely contraindicated in MI
  - Cyclic AMP and phosphodiesterase-3 enzyme are present in the heart
  - ↑ Cyclic AMP in heart → ↑ heart rate→ ↑ oxygen demand → MI aggravated
- ADP receptor blockers: Some are given in MI, but avoided in stroke
- Phosphodiesterase inhibitors: Given in stroke, avoided in MI
- Side Effects: Most common: Headache (due to vasodilation)

Drug	Special Use/Property
Cilostazol	Specifically given in Burger's disease with intermittent claudication (pain in leg arteries after walking a certain distance due to platelet blockage)
Pentoxifylline	Also known as a rheological agent (Rheo = blood flow, improves circulation in limb arteries)

GP 2B3A Inhibitors (Glycoprotein 2B3A Inhibitors)

00:14:41

- Alternative Names
  - Anti-aggregating drugs (inhibit the aggregation of platelets)
  - Anti-integrin drugs (GP2B3A receptor = part of integrin family)
- Mechanism
  - Inhibit aggregation of platelets
- Drugs - E-A-T Memory Aid
  - E = Eptifibatide
  - A = Abciximab

Yourwish

- o T = Tirofiban
- o ABCIXIMAB - Most Important
  - → Inhibits platelet attachment/aggregation
  - → Monoclonal antibody (that's why it's a "mab" drug)
- All three are IV drugs
  - o Given during stent placement: PTCA procedure (Percutaneous Transluminal Coronary Angioplasty)
- Special Properties of Abciximab
  - o Renal safe drug
    - → Rule: All monoclonal antibodies are renal safe
    - → Reason: Monoclonal antibodies = peptides and proteins
    - → Peptides and proteins are NOT excreted in urine
  - o Safe in renal failure
- Additional immunosuppressive effect
  - o Reduces the body's immunity
  - o WBCs also attach to integrin receptors and create inflammation/increased immunity

New Anti-platelet Drugs

00:16:39

Vorapaxar

- PAR-1 antagonist
- PAR = Protease Activating Receptor
- Specific receptor on platelet → causes platelet aggregation
- Inhibiting PAR → platelet won't attach
- Use:
  - o Given as an add-on drug to aspirin
  - o Approved for treatment of MI (Myocardial Infarction)

Dazoxiben

- Thromboxane A2 synthase inhibitor specific enzyme in platelets
- Memory aid: XI word coming   Thromboxin synthase inhibitor
- NOT approved currently (under trial)

ANTI-COAGULANT DRUGS

00:17:47

- Anti-coagulant drugs = Drugs that prevent fibrin deposition

Diseases With Excessive Fibrin Deposition

Deep Venous Thrombosis (DVT)

- Excessive fibrin deposition in leg veins
- Fibrin thrombus may detach/separate
- Most common complication: Pulmonary Embolism (PE)
- Reason: Immobility
- Causes of Immobility:
  - o ICU patient/unconscious patient (not moving legs)
  - o After knee and hip surgery
  - o Atrial fibrillation (incomplete/ineffective heart contraction)
  - o Mitral stenosis (speeds up fibrin deposition)

Atrial Fibrillation + Mitral Stenosis

- Gradual fibrin deposition in the heart
- Thrombus may separate brain
- Blocks small blood vessels of the brain
- Result: Ischemic stroke or Transient Ischemic Attack (TIA)
- Important:
  - TIA = Reversible neuronal damage
  - Stroke = Permanent neuronal damage
  - ONLY stroke due to atrial fibrillation → give anti-coagulant drugs
  - All other strokes → give antiplatelet drugs (aspirin)
  - Always do an ECG/Echo in stroke patients to rule out atrial fibrillation and mitral stenosis

Disseminated Intravascular Coagulation (DIC)

- Fibrin deposition in the whole body/all organs
- Foreign substance in the body activates the clotting pathway
- Causes of DIC:
  - Sepsis (most common - sepsis-induced DIC)
  - Abruptio placentae (in pregnancy)
  - Cancer cells (activate clotting pathway)
  - Mechanical/Artificial heart valves
- Treatment specifics:
  - DIC due to sepsis/abruptio placentae/cancer = EMERGENCY
    → Only drug given: IV Heparin
  - Mechanical heart valves:
    → Requires lifelong anti-coagulant
    → Only oral drug given: Oral Warfarin
- All other anti-coagulant drugs can be given in DVT/PE/AF, but the drug of choice in DIC is different

Clotting Pathways

- **Extrinsic pathway**
  - Test: **PT (Prothrombin Time)**
  - Starts from: Clotting Factor 7
- **Intrinsic pathway**
  - Test: **APTT**
  - Starts from: Clotting Factor 12
- **Common Pathway**
  - Both converge at **Factor 10** (active)
- Factor 10 = Only factor that converts **Prothrombin** → **Thrombin** (Factor 2)
- Thrombin → causes **Fibrin deposition**

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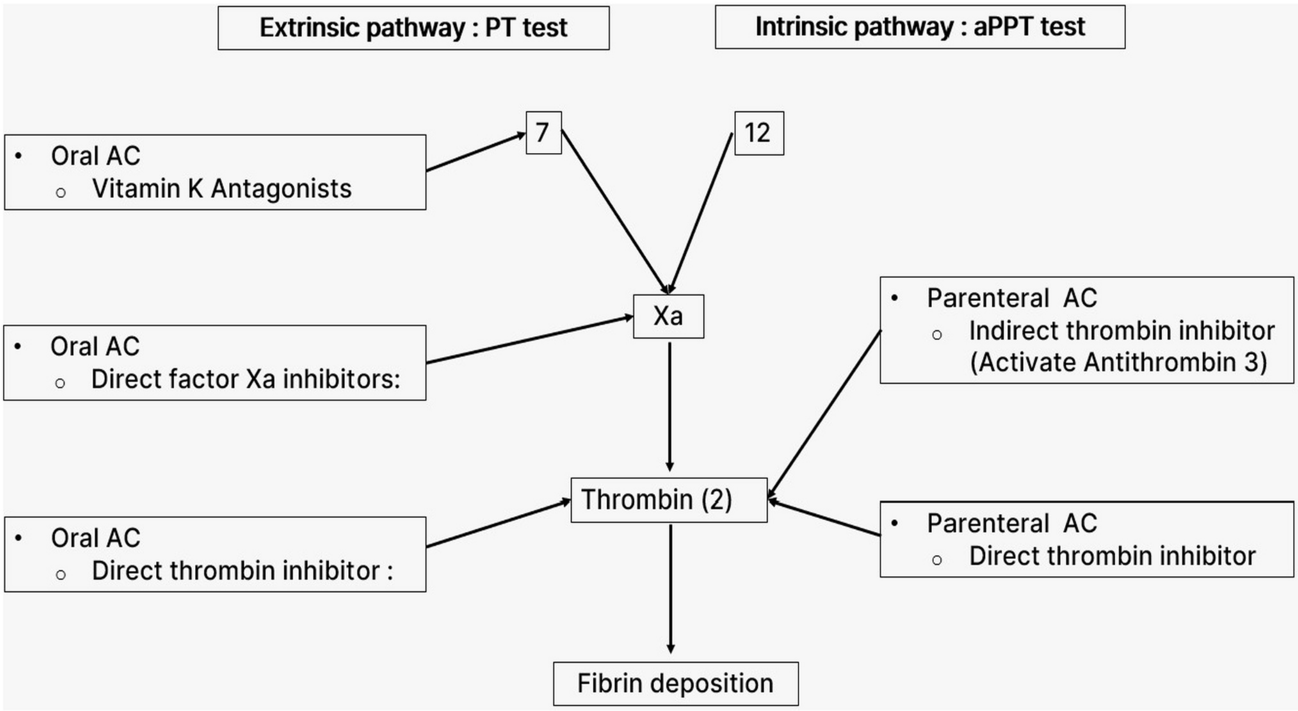

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Classification of Anti-coagulant Drugs

Oral Anti-coagulant Drugs

- Vitamin K Antagonists (Warfarin-like drugs)
    - Inhibits multiple clotting pathways
    - Main effect: Inhibition of Factor 7
    - Derived from Coumarin poison- All are coumarin derivatives
    - Warfarin (main drug - "arin" word)
    - Acenocoumarol
    - Bishydroxycoumarin
    - Dicoumarol
- Direct Factor 10A Inhibitors
    - End with the word "XABAN"
    - XA = Factor 10A inhibitor
    - Drugs:
        - → Rivaroxaban- Longest acting
        - → Apixaban
        - → Edoxaban
        - → Rivaroxaban
- Direct Thrombin Inhibitors
    - Inhibit thrombin directly
    - Drug: Dabigatran
        - → D = Direct
        - → TR = Thrombin
        - → A = Antagonist/inhibitor

COMPARISON OF ORAL ANTI-COAGULANTS

Feature	Warfarin	Rivaroxaban/Apixaban	Dabigatran
Factors reduced	2, 7, 9, 10 (4 factors)	Only Factor 10	Only Factor 2 (Thrombin)
Monitoring required	YES - PT with INR	NO	NO
Safety	Dangerous (multiple factors)	Very safe	Very safe
Antidote	Vitamin K	Andexanet alfa (synthetic form of factor XA)	Idarucizumab

NOVEL ORAL ANTI-COAGULANTS (NOACs)

- Novel drugs:
  - Factor 10A inhibitors (Rivaroxaban, Apixaban, etc.)
  - Dabigatran
- Much safer than warfarin
- Preferred in:
  - DVT and PE (Deep Venous Thrombosis and Pulmonary Embolism)
  - Atrial fibrillation (to prevent ischemic stroke and TIA)
- Despite NOACs, Warfarin remains the drug of choice in 3 situations:

Indication	Drug of Choice	Reason
1. Mechanical heart valves	Warfarin ONLY	Stronger action inhibits multiple factors. No other drug is given
2. Atrial fibrillation + Mitral stenosis	Warfarin	More risk of fibrin deposition (valves closed). If AF alone → NOACs. If AF + MS → Warfarin
3. Renal failure	Warfarin	Warfarin = renal safe. NOACs are avoided in renal failure

Warfarin

00:29:46

- WAR-F = Wisconsin Alumni Research Foundation
- -ARIN = Coumarin derivative
- Originally developed as rat poison
- Later used in humans
- Antidote of rat poison/rodenticide poisoning in humans = Vitamin K

Mechanism Of Action

- Warfarin acts on the liver
- Inhibits VKOR C1 enzyme (Vitamin K-dependent enzyme)
- VKOR = Vitamin K Epoxide Reductase enzyme

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- Competitive inhibition
- Effects
  - Reduces production of clotting factors: 2, 7, 9, 10
  - Reduces production of anti-clotting factors: Protein C and Protein S (both vitamin K-dependent)

Sequential Reduction Of Factors

Factor Reduced	Time	Special Note
1st: Factor 7	First	Main effect. Factor 7 = part of the extrinsic pathway → Monitor with PT
2nd: Protein C	After Factor 7	Anti-clotting factor
3rd: Factor 2 (Thrombin)	5 DAYS	The last factor reduced

- Complete anti-coagulant effect = After 5 DAYS

Paradoxical Effect - First 5 Days

- Warfarin PARADOXICALLY INCREASES coagulation
- Why:
  - Clotting factors are not completely reduced yet
  - But deficiency of Protein C and Protein S (anti-clotting factors)
  - Anti-clotting factor deficiency   clotting increases
- Dangerous Side Effect
  - Dermal vascular necrosis = Limb necrosis
  - Can lead to toe necrosis = Purple toe syndrome
    → Very dangerous - may require limb amputation
- Prevention
  - Combine Warfarin with Heparin injection for the initial 5 days
  - Heparin = immediate effect
  - After 5 days → stop Heparin
  - Maintain patient on oral warfarin alone

Properties Of Warfarin

- Volume of Distribution
  - Very low volume of distribution
  - Reason: 99% albumin bound
- Important:
  - Any drug highly protein-bound → NO role of hemodialysis in poisoning
  - Proteins won't allow warfarin to filter out
  - In warfarin poisoning → NO role for hemodialysis
- Enantiomers
  - Warfarin = mixture of R and S forms
  - S-warfarin = Active form
  - R-warfarin = NOT active

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- Metabolism
  - Warfarin is metabolized by the CYP 2C9 enzyme
- Genetic testing before giving warfarin:
  - Some people: high CYP enzyme
  - Some people: less CYP enzyme
  - Same for VKOR enzyme in the liver
- Warfarin requires testing of:
  - VKOR C1 enzyme
  - CYP 2C9 enzyme

Monitoring Warfarin

- Test: PT with INR
  - PT = Prothrombin Time; INR = International Normalized Ratio
- INR = Patient's PT / Normal (Control) PT
  - Normal Values
- If NOT taking any drug: PT = Normal PT
  - Normal INR = 1.0
  - Normal INR range = 0.8 to 1.1
  - Target INR on Warfarin = 2 to 3
- Means: Patient's PT should be 2-3 times normal PT
- Corresponds to PT = 12 to 15 seconds

Drug Interactions With Warfarin

00:36:50

Conditions That Increase INR (↑ Warfarin Toxicity)

Category	Examples	Mechanism
CYP Inhibitors	Ciprofloxacin, Ketoconazole	↓ Degradation of warfarin
CYP Inducers	Rifampicin	↑ Degradation of warfarin (decreases the effect)
Vitamin K deficiency	Antibiotics, Aspirin	Kill GIT bacteria (GIT bacteria produce Vitamin K)
Liver disease	-	Increases warfarin toxicity

Conditions That Decrease INR (↓ Warfarin Effect)

Factor	Mechanism
Estrogen/OCPs	↑ Production of clotting factors 2, 7, 9, 10. Estrogen itself can cause DVT/PE
Kidney disease	Albumin lost in urine → Warfarin lost with albumin (warfarin 99% albumin-bound)

Management Of Raised INR (Warfarin Overdose)

- **Scenario 1 : Raised INR WITHOUT Bleeding**

INR Level	Action
3 to 10	Simply STOP warfarin (do nothing else)
>10	Start antidote: Oral Vitamin K (2.5-5 mg)

- **Scenario 2: Raised INR WITH Bleeding**
  - Gums bleed, intracranial bleed, hematuria
  - Management:
    - → IV Vitamin K
    - → PLUS an immediate source of clotting factors from outside:

Drug	Description	Notes
4-Factor PCC (BEST)	4-Factor Prothrombin Complex Concentrate	Mixture of factors 2, 7, 9, 10. BEST treatment
FFP (if PCC unavailable)	Fresh Frozen Plasma	Instant source of clotting factors

Types Of Vitamin K

Type	Name	Notes
K1	Phytonadione / Phylloquinone	Plant product
K2	Menaquinone	-
K3	Menadione	Water-soluble form is also available

- USES OF VITAMIN K - "WEAPON" Mnemonic
  - Warfarin overdose
  - Extended antibiotic therapy (kills GIT bacteria → Vitamin K deficiency)
  - Aspirin toxicity (kills GIT bacteria → Vitamin K deficiency)
  - Phenytoin-induced osteoporosis (Vitamin K required for bone formation)
  - Obstructive jaundice (no bile flow → can't absorb fat-soluble vitamins)
  - Newborn (prophylactic - newborns deficient in Vitamin K, no GIT bacteria)

Parenteral (Injectable) Anti-coagulants

00:42:08
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Routes of Administration

- Only 2 routes:
  - Subcutaneous (SC)
  - Intravenous (IV)
- NEVER Intramuscular (IM)

- Reason: Blood collects in muscles hematoma formation
- MONITORING
  - IV anti-coagulant drugs: Dangerous
    → Require APTT monitoring

Classification

Direct Thrombin Inhibitors (Parenteral)

- DRUGS (End with "RUDIN")
  - Hirudin - Extracted from the saliva of leeches
  - Lepirudin
  - Desirudin
  - Bivalirudin
  - ARGATROBAN
- ADMINISTRATION & MONITORING
  - All given IV
  - Require APTT monitoring
- ONLY indication:
  - When CANNOT give Heparin to the patient
  - When Heparin allergy/hypersensitivity
  - Most dangerous hypersensitivity = HIT
- HIT = Heparin-Induced Thrombocytopenia
  - Drug of choice for HIT:
    → Hirudin
    → Lepirudin
    → Argatroban
- NO ANTIDOTE to stop bleeding from Hirudin/Lepirudin

Heparins

- Heparin activates the Antithrombin-3 protein in the blood
- Antithrombin-3 → inhibits thrombin
- Hence: Indirect thrombin inhibitor

Types Of Heparins

Feature	HMW Heparin (Unfractionated)	LMW Heparin (Fractionated)	ULMW Heparin (Synthetic)
Examples	Heparin	Enoxaparin Dalteparin Tinzaparin	Fondaparinux Idraparinux
Source	Ox lung / Pork intestine	Ox / Pork intestine	Synthetic
Action	Anti-Xa = Anti-IIa	Anti-Xa >> Anti-IIa	Anti-Xa only
Route	IV	SC	SC

aPTT monitoring	Required	Not required	Not required
Risk of HIT	Yes	Yes	No risk
Excretion	Reticuloendothelial (RE) cells	Urine	Urine
Renal safety	Safe	Unsafe	Unsafe
Antidote	Protamine sulfate	Protamine sulfate	No antidote

DOC By Indication

Indication	Drug of Choice	Route	Reason
DIC (Disseminated Intravascular Coagulation)	High MW Heparin	IV	Emergency, needs immediate effect
DVT prophylaxis in the ICU	Low/Ultra Low MW Heparin	SC	ICU patient can't move, can't take oral drugs. Prophylaxis = SC injection preferred

Q. Which Heparin is NOT excreted in urine?

Ans: High Molecular Weight Heparin

- Reason: Very large molecule
- Removed by RES/macrophages instead

Q. Which Heparin is safe in renal failure?

Ans: High Molecular Weight Heparin (renal safe)

Q. Which heparins are unsafe in renal failure?

- Low Molecular Weight Heparin
- Ultra Low Molecular Weight Heparin
- (Both are excreted in urine)

Anti-coagulants In Pregnancy

00:50:50

- Safest anti-coagulant in pregnancy
  - HEPARINS = Overall safest
  - Prefer: Low MW or Ultra Low MW Heparin in pregnancy
- Warfarin in pregnancy- C/I in First Trimester (0-12 weeks)
  - Maximum organ synthesis in the first 3 months
  - Warfarin → Vitamin K deficiency in fetus
  - Vitamin K required for bone and cartilage formation
  - Teratogenic effect: Fetal Warfarin Syndrome, AKA Chondrodysplasia Punctata
    → Chondro = bones and cartilage
    → Dysplasia = abnormally formed
    → Punctata = damage/punctures

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- Features:
  - → Saddle nose
  - → Limb hypoplasia
  - → Cranial defects (microcephaly)

Protocol For Pregnancy

Time Period	Drug	Notes
0-12 weeks (1st trimester)	Heparin injection ONLY	Warfarin contraindicated
After 12 weeks (2nd/3rd trimester)	Warfarin can start OR continue Heparin	Either option acceptable
After 36 weeks	Stop Warfarin, give Heparin ONLY	Preparing for delivery
1 day before delivery	STOP all anti-coagulants	Prevent postpartum hemorrhage
After delivery (postpartum)	Heparin	Heparin = drug of choice postpartum

Antidotes Summary

Drug	Antidote
Warfarin (Coumarins)	Vitamin K
Apixaban/Rivaroxaban	Andexanet alfa (Activated Factor 10A)
Dabigatran	Idarucizumab
High MW Heparin	Protamine sulfate
Low MW Heparin	Protamine sulfate
Hirudin/Lepirudin	NO antidote
Ultra Low MW Heparin (Parinux drugs)	NO antidote

- NON-SPECIFIC ANTIDOTE
  - Ciraparantag = Non-specific antidote for:
    - → Apixaban
    - → Rivaroxaban
    - → Dabigatran
    - → High MW Heparin
    - → Low MW Heparin
- SPECIAL CASE: IDRAPARINUX
  - Idraparinux = NO antidote
  - BUT: Modified version = Idrabiota-parinux
    - → Contains a Biotin molecule attached

→ Antidote: Avidin

→ Avidin neutralizes biotin → reduces effect

FIBRINOLYTIC / THROMBOLYTIC DRUGS

00:55:20

- Anti-coagulant drugs: Prevent deposition of fibrin
- Fibrinolytic/Thrombolytic drugs: Remove already deposited fibrin

Mechanism of Action

- Fibrinolytic drugs convert Plasminogen Plasmin (active form)--> Removes fibrin

Classification

Natural Enzymes

- Activate plasminogen into plasmin

Drug	Source
Streptokinase	Group C Beta-hemolytic Streptococci
Urokinase	Kidney cells of human / Cultured human kidney cells

- **Antibody Formation**
  - Streptococcal antigen → antibodies produced
  - If given again → effect reduces
  - **STREPTOKINASE GIVEN ONCE A LIFETIME**
- **Alternatives**
  - Previously used cases → give **Urokinase**
  - Nowadays, prefer: **Synthetic TPA** forms

Synthetic TPA (Tissue Plasminogen Activator)

- TPA = Tissue Plasminogen Activator (protein also produced in the body)
- Drugs (End with "TEPLASE"):

Drug	Type	Notes
Alteplase	Native/Human form of TPA	Short-acting
Reteplase	Modified TPA	Long-acting, BOLUS fibrinolytic
Tenecteplase	Mutant variety (amino acid sequence changed)	Long-acting, BOLUS fibrinolytic, BEST drug

Indications - Life-threatening Conditions Only

Indication	Timing/Notes
ST-Elevated MI (STEMI)	Contraindicated in Non-STEMI (increases mortality)

Ischemic Stroke	Must give within 4.5 hours Contraindicated in hemorrhagic stroke
Massive Pulmonary Embolism	Large/saddle embolism → right heart failure

Side Effects
- Removing fibrin suddenly → internal bleeding
- The patient may die on the table
- Highly dangerous drugs

Anti-Fibrinolytic Drugs
- To avoid bleeding from fibrinolytics

EPSILON AMINO CAPROIC ACID (EACA)	• Considered the antidote of fibrinolytics • Better drug for this purpose
TRANEXAMIC ACID	• To stop internal bleeding in various conditions: o Menorrhagia (seen in PCOD) o Dental bleeding o Other causes of bleeding

HYPOLIPIDEMIC DRUGS

01:00:13

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- Reduce blood lipid levels
- Given for the treatment of **Dyslipidemia** (abnormally raised blood lipid levels)

Two Types Of Bad Lipids
- **CHOLESTEROL**
  - o ↑ Cholesterol → Atherosclerosis
  - o Blockage of blood vessels → MI and Stroke
- **TRIGLYCERIDES**
  - o ↑ Triglycerides → Damages pancreas → Acute Pancreatitis

Drugs	LDL-C	Total TG	HDL	Drug of choice
Statins	↓ max	–	–	Hypercholesterolemia
Resins	↓	–	–	DOC in Pregnancy
Fibrates	–	↓ max	–	Hyper TG >500
Niacin	–	–	↑ max	↓ Lipoprotein (a)

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Statins

Mechanism Of Action

- In the liver, statins inhibit the HMG-CoA Reductase enzyme (competitive inhibition)
- HMG-CoA Reductase converts: HMG-CoA → Mevalonate
- Mevalonate → (through various steps) → Cholesterol
- HMG-CoA → Mevalonate = RATE-LIMITING STEP of cholesterol synthesis
- Result of blocking this step:
  - o ↓ Cholesterol synthesis in the liver
  - o Liver needs cholesterol → ↑ LDL receptors on the liver
  - o The liver takes LDL from the blood → ↓ Blood LDL level (LDL contains cholesterol) → ↓ Blood cholesterol level

Indications

- Drug of choice for Hypercholesterolemia due to:
  - o Metabolic syndrome (lifestyle, obesity, junk food) - most common
  - o Nephrotic syndrome
  - o Certain drugs (loop/thiazide diuretics, beta blockers)
  - o Alcohol use

Pleiotropic Effects

- Beyond lipid-lowering:
  - o Anti-atherosclerotic effect
  - o Anti-inflammatory effect
  - o ↓ Blood uric acid level (good for gout patients)

Drugs

Drug	Special Properties
Rosuvastatin	Most effective + Longest acting. Most commonly prescribed
Atorvastatin	Most effective + Longest acting. Most commonly prescribed
Lovastatin	Pro-drug
Simvastatin	Pro-drug
Pitavastatin	Most potent (requires the least dose)
Pravastatin	NOT metabolized by CYP (least interactions)
Fluvastatin	Metabolized by CYP2C9 (not by CYP3A4)

Metabolism

- Most statins: Metabolized by the CYP3A4 enzyme
- exceptions:
  - o Pravastatin - NOT metabolized by any CYP enzyme
  - o Rosuvastatin - NOT metabolized by any CYP enzyme

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- Fluvastatin - Metabolized by CYP2C9
- Rosuva + Prava → Least drug interactions

Side Effects

- Hepatotoxic
- Myopathy (Characteristic)
  - Muscle damage
  - Can progress to Rhabdomyolysis (muscle necrosis)
  - Features of Rhabdomyolysis:
    → ↑ CPK enzyme (Creatine Phosphokinase) in blood
    → Myoglobin comes from muscle → blood
    → Myoglobinuria → Cola-colored urine

Contraindications

- Absolutely contraindicated in:
  - Pregnancy
  - Children <12 years

Resins (Bile Acid Binders)

01:06:25

Mechanism

- Inhibit the enterohepatic reabsorption of bile back to the liver
- The liver secretes bile (which contains cholesterol)
- Normally, 95% bile returns to the liver from the intestine
- Blocking reabsorption → Liver tries to take LDL from blood → ↓Blood LDL level

Drugs (Start With "Chole")

- Cholestyramine
- Colesevelam
- Colestipol
- Drug of choice in PREGNANCY
  - Act only on GIT
  - NOT absorbed into the blood
  - Unlike statins (contraindicated in pregnancy)

Side Effects

- Malabsorption of Fat-Soluble Vitamins
  - Bile is required for the absorption of A, D, E, and K → Vitamin A, D, E, and K deficiency
- Reduced Absorption of DPT Drugs
  - **D** = Digoxin
  - **P** = Propranolol
  - **T** = Thyroxin

Fibrates

01:07:48

FMGE 2024

- AKA Lipoprotein Lipase Activators

Mechanism
- Inside the endothelial cell nucleus → Stimulate PPAR-alpha receptor → LPL enzyme (Lipoprotein Lipase)→ Removes triglycerides from blood

Indications
- Drug of choice for Hypertriglyceridemia
  - First drug started for high TG: Statins
  - If TG >500 → ADD Fibrate (stronger drug)

Drugs

Drug	Notes
Clofibrate	Banned (↑ risk of MI)
Fenofibrate	BEST drug. Also, ↓ uric acid (good for gout)
Bezafibrate	-
Gemfibrozil	CYP enzyme inhibitor → ↑ statin toxicity (myopathy). NEVER combine with statin

Side Effects
- Myopathy (like statins)
- Gallstones

Niacin (Nicotinic Acid / Vitamin B3)

01:10:00

Mechanism & Effects
- In Liver LIVER:
  - ↑ HDL level
  - ↓ Production of Lipoprotein A
- In Adipose tissue:
  - Inhibits lipolysis → Further ↓triglyceride levels

Dosing
- When used as a hypolipidemic drug, a very high dose is required
  - 2 to 6 grams (much higher than the vitamin dose)

Side Effects - Most Toxic Hypolipidemic Drug

- Facial flushing (Most Common).
  - Niacin →↑Prostaglandin D2 production
  - PGD2 on dermis → vasodilation → Flushing
  - Treatment of Niacin-Induced Flushing:
    - → Aspirin (↓ prostaglandin production)
    - → Laropiprant (specific PGD2 receptor antagonist)
- Hepatotoxic

- Hyperuricemia
- Hyperglucemia

Important Information

- A hypolipidemic drug that increases uric acid: NIACIN (bad for gout)
- A hypolipidemic drugs that reduce uric acid: Statins and fibrates (good for gout)

New Hypolipidemic Drugs

- All are used as an add-on to statins
- Purpose: Further reduce cholesterol/LDL level

Ezetimibe

- Mechanism:
  - Inhibits NPC1L1 transporter in the GIT → ↓ Cholesterol absorption from the GIT
  - This transporter is required for cholesterol absorption
- Use: Add-on to statin

Monoclonal Antibodies - PCSK9 Inhibitors

- Drugs (Contain "LOC")
  - Evolocumab
  - Alirocumab
  - Memory aid:
    → LOC = Lower Cholesterol
- Mechanism
  - PCSK9 inhibitors
  - PCSK9 enzyme degrades LDL receptors in the liver
  - Inhibiting PCSK9 → ↑ LDL receptors → Liver removes more LDL from blood → ↓ Blood LDL
- Use: Add-on to statin
- Inclisiran - Recently approved PCSK9 inhibitor
  - Also, ↓ the blood LDL level

Bempedoic Acid

- Mechanism:
  - Competitive inhibitor of the ATP Citrate Lyase enzyme
  - This enzyme is also required for cholesterol production (like statins) → ↓ LDL level
- Use: Add-on to statin

Lomitapide

- MTP (Microsomal Triglyceride Transfer Protein) inhibitor
- This protein is required for VLDL production in the liver → ↓ VLDL levels

Omega-3 Fatty Acids

- Drugs:
  - Icosapentaenoic acid
  - Docosahexaenoic acid

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- Source: Fish (rich source of omega-3 fatty acids)
- Effect:
  - o ↓ VLDL level
  - o Clinical relevance: Fish is good for heart disease, MI, and stroke patients

CETP Inhibitors

- Anacetrapib
- Torcetrapib
- CETP = Cholesteryl Ester Transfer Protein
- Effect: Inhibiting CETP → ↑ HDL level

IRON PREPARATIONS

01:15:00

- DRUG OF CHOICE: Oral Ferrous Sulfate = Most commonly used
- INDICATIONS: Given for the treatment of Iron Deficiency Anemia

Oral Iron Preparations

- 60 mg tablets available

Drug	Special Property
Ferrous sulfate	Standard
Ferrous gluconate	-
Ferrous fumarate	MAXIMUM iron content (2 F words)
Ferrous ascorbate	Contains Vitamin C → BEST absorption

Factors Affecting Oral Iron Absorption

Increase Absorption

Factor	Mechanism
Acidic environment	Favors iron absorption
Empty stomach	More acid → better absorption
Vitamin C (Ascorbic acid)	Lemon juice, amla

Decrease Absorption

Factor	Mechanism
Food, tea, coffee	↓ Acid in the stomach
Proton pump inhibitors, Antacids	↓ Acid environment
Tetracycline	Chelates with iron

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Side Effects Of Oral Iron

- Nausea and vomiting (most common)
- Blackening of stool (iron is black)
- If the patient cannot tolerate oral iron   Indication for parenteral iron

Parenteral (Injectable) Iron

- Drug: IRON DEXTRAN
  - Can be given IV and IM
  - Risk: Allergy / Anaphylaxis
  - MANDATORY: Allergen testing before use
- Technique: Given by Z-technique (discussed in General Pharma)

Earliest Response To Iron Therapy

- Not increase in hemoglobin (takes 1 week)
- Earliest response: ↑ Reticulocyte count (occurs initially)

HEMATOPOIETIC GROWTH FACTORS

01:18:15

Erythropoietin Preparations

- Natural Erythropoietin
- Produced from kidney
- In kidney failure → anemia
- **Drugs**
- Erythropoietin injections
- Darbepoetin injections (longer acting, "poetin" word)

Indications For Erythropoietin (Only 2)

Indication	Notes
Anemia due to CKD (Chronic Kidney Disease)	The kidneys don't produce erythropoietin
Anemia due to chemotherapy	Anti-cancer drugs cause anemia

Contraindications (Absolute)

- **Nutritional anemia** (iron deficiency anemia)
- **Aplastic anemia** (bone marrow cells not dividing - no use)

New Oral Drugs - Do-stat Drugs

- Drugs (End with "DO-STAT")
  - Daprodustat
  - Roxadustat
  - Vadadustat
  - Molidustat
- Mechanism: ↑ Amount of endogenous erythropoietin in the body

- Advantage: ORAL drugs (vs injectable erythropoietin)
- Indication: Specifically approved for anemia in CKD

WBC Growth Factors

Filgrastim

- Chemical name: Synthetic form of G-CSF
    - G-CSF = Granulocyte Colony-Stimulating Factor
    - "Grastim" = GRA = Granulocyte STIM = Stimulator
- Effect: ↑Neutrophil count (neutrophils = granulocytes)
- Indication: Chemotherapy-induced neutropenia

Sargramostim

- "Gramostim":
    - GRA = Granulocyte
    - MO = Monocyte
    - STIM = Stimulator
- G-M CSF = Granulocyte-Monocyte Colony-Stimulating Factor
- Effect: ↑Granulocytes AND Monocytes (monocytes = agranulocytes)
- Indication: Also given to ↑ the monocyte count in chemotherapy

Platelet Growth Factors

Drugs For Thrombocytopenia - "REO" Mnemonic

Romiplostim

- "PLO-STIM":
- PLA = Platelet
- STIM = Stimulator
- Administration & Indication
    - Given by injection
    - For treatment of ITP (Idiopathic Thrombocytopenic Purpura)

Eltrombopag

- "Trombopag":
- TROMBO = Thrombopoietin
- PAG = Thrombopoietin receptor AGonist
- Mechanism: Stimulates the thrombopoietin receptor
- Advantage: ORAL drug (why it was made)
- Indications: ITP (Idiopathic Thrombocytopenic Purpura)
- Chronic liver disease
    - Liver produces thrombopoietin
    - Liver disease → thrombopoietin deficiency thrombocytopenia

Avatrombopag

- Works similarly to Eltrombopag

- Same name pattern as Eltrombopag ("brother drug")
- Same mechanism of action
- Same indications as Eltrombopag

Oprelvekin

- Nomenclature Clue:
  - "Kin" in the name → indicates it's a type of interleukin
  - "ELV" in name → "E world" → Interleukin-11
- Drug Details:
  - Synthetic form of Interleukin-11
  - Given as an injection
- Indication: Drug of choice for chemotherapy-induced thrombocytopenia
  - Anti-cancer drugs → bone marrow suppression → ↓ platelets, WBCs, RBCs
  - Specifically for thrombocytopenia induced by anti-cancer drugs

Idiopathic Thrombocytopenic Purpura (ITP)

Pathophysiology

Autoimmune disease
↓
Antibodies produced against platelets
↓
Antibodies attach to platelets
↓
Antibody-coated platelets go to macrophages in the spleen
↓
Macrophages have FYC receptors
↓
FYC receptors recognize and bind antibody-coated platelets
↓
Macrophages kill platelets
↓
THROMBOCYTOPENIA

Treatment

- First-Line: Reduce Antibody Production
- Corticosteroids
  - Mechanism: Reduce immunity → reduce antibody production
- Rituximab (Monoclonal Antibody)
  - Used in corticosteroid-resistant cases

Block Macrophage Activity

- Fostamatinib
  - Tyrosine kinase inhibitor
  - Blocks Fyc tyrosine kinase on macrophages
  - Mechanism: Prevents macrophage activation → prevents platelet destruction

Yourwish

Increase Platelet Production From Bone Marrow

- Romiplostim
  - Directly increases platelet count from bone marrow
  - Platelet stimulator
- Eltrombopag

Refractory Cases Treatment

- Intravenous Immunoglobulin (IVIG)
  - BEST and MOST EFFECTIVE treatment for ITP
  - Mechanism: Directly neutralizes autoantibodies
- Plasmapheresis
  - Used in severe cases
  - Mechanism: Rapidly removes antibodies from circulation

Surgical Treatment

- Splenectomy
  - Removes spleen (site of platelet destruction)
  - Role: When medical management fails

CHELATORS FOR HEAVY METAL POISONING

01:26:36

NEET PG 2024

- **Definition:** Chelators neutralize metals in metal poisoning

British Anti-lewisite (BAL) / Dimercaprol

- First chelator was made during World War by the British
- Short form: BAL
- Alternative name: Dimercaprol
- Indications - Remember "BAM BAM":
  - B - Bismuth poisoning (antidote)
  - A - Arsenic metal poisoning (antidote)
  - M - Mercury poisoning (drug of choice)
    → ("Merc" in dimercaprol hints at mercury)
- Absolute Contraindications
  - C - Cadmium poisoning (NEVER give BAL)
  - I - Iron poisoning (NEVER give BAL)
  - Reason: Can form toxic complexes

Calcium Disodium Edta ($cana_2edta$)

- Indications - "MLC":
  - M - Manganese poisoning
  - L - Lead poisoning
    → Used in MLC (Medical Legal Case)
  - C - Cadmium poisoning (drug of choice)

Penicillamine

- Indication: Drug of choice for Copper poisoning
- Important Association: Wilson's Disease

Deferoxamine And Deferiprone

- Nomenclature Clue:
  - Both contain "FE" in their names → indicates iron
- Indication: Iron poisoning (drug of choice)
- Clinical Context:
  - Iron poisoning commonly occurs in thalassemia patients
  - Mechanism: Due to repetitive blood transfusions

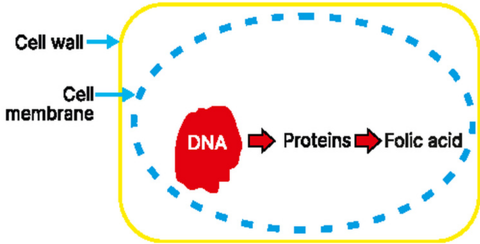
Important Information

- Metal poisoning is a **rare disease** (not common)
- Therefore, **ALL chelators are orphan drugs**
- Orphan drug = a drug for a rare disease

2. ANTIMICROBIALS PART 1

CLASSIFICATION

- Cell wall inhibitors
- Cell membrane inhibitors
- DNA/Nucleic acid inhibitors
- Protein synthesis inhibitors
- Folic acid inhibitors



CELL WALL INHIBITORS

00:01:00

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- **Beta-lactams** (Penicillin, Cephalosporin, Carbapenem, Monobactam)
  - Inhibits → Transpeptidase enzyme
- **Bacitracin** → Topical treatment of Staphylococcus Aureus
  - Not effective against MRSA
- **Cycloserine** → Used in T/t of MDR-TB
- **Vancomycin** → Inhibits Transglycosylase
- Fosfomycin → T/t of UTI (2 gram per oral single dose)

Important Information

- All are Bactericidal, except Cycloserine → Bacteriostatic
- Cell wall inhibitors are not effective against atypical bacteria like mycoplasma, chlamydia, and rickettsia, as they lack a cell wall

Penicillin G

00:03:33

- Only natural Penicillin from **Penicillium Fungus**
- **Indications:**

○ Syphillis	○ Pasteurella
○ Meningococci	○ Gas gangrene (myonecrosis)
○ Actinomycosis	○ Anthrax
○ Rat bite fever	○ Leptospirosis
○ Tetanus	○ Every Staph/Streptococcus (if sensitive)

Important Information

Meningococcal meningitis

- **T/t: Ceftriaxone** injection
- Prophylaxis (eliminate nasal carrier): Ciprofloxacin > Rifampicin

Penicillin Hypersensitivity

- All 4 types of HSR
  - Type 1: Anaphylaxis
  - Type 2: Hemolytic Anaemia (+ve Coombs test)
- Cross allergy with: Cephalosporin / Carbapenem (C/I)
  - No cross allergy with Monobactam (safe)
- DOC for Penicillin allergy → Erythromycin / Azithromycin

Drawback of Penicillin G	New synthetic Penicillin
• 1. Acid labile → Oral: Degraded by HCl	• 1. Acid stable: Oral Penicillins
• 2. Short-acting	• 2. Long-acting Penicillins
• 3. Narrow spectrum	• 3. Extended-spectrum Penicillin • → Active against Enterobacteriaceae
• 4. Acquired resistance	• a) Penicillinase resistance Penicillin • b) Beta-lactamase inhibitors

Oral Penicillins	• Not degraded by HCl in the stomach
	  ○ Penicillin V
	  ○ Oxacillin
	  ○ Dicloxacillin
	  ○ Cloxacillin
	  ○ Amoxicillin
	  ○ Ampicillin

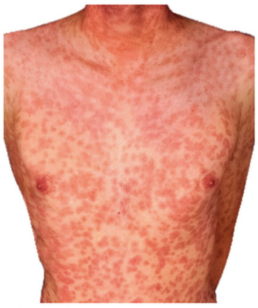
Long-Acting Penicillins	Penicillin G + Probenecid (IV)
	• Probenecid inhibits OATP in the kidney
	  ○ Inhibits the excretion of penicillin
	Depot Formulations (IM only)
	• Procaine Penicillin:
	  ○ Neurotoxic
	• Benzathine Penicillin:
	  ○ Longest-acting
	  ○ Cardiotoxic

Benzathine Penicillin	• Drug of Choice (DOC) for Rheumatic Fever / Carditis Prophylaxis ○ Benzathine penicillin 1.2 million IU administered I.M monthly
Extended-Spectrum Penicillins: For Enterobacteriaceae	• A2 → Amoxicillin, Ampicillin → Covers E. coli • CT → Carbenicillin, Ticarcillin → Covers E. coli and Pseudomonas • MAP → Mezlocillin, Azlocillin, Piperacillin → E. coli, Pseudomonas, and Klebsiella

Amoxicillin	Ampicillin (DOC)
• Primary Target: Streptococcus pneumoniae (DOC) • Common Uses: ENT infections and Community-Acquired Pneumonia	• Listeria meningitis (DOC) • Contraindication → EBV

Treatment Of Syphilis

- Early Syphilis (Primary, Secondary, Early Latent < 1 year)
  - Benzathine Penicillin → 2.4 million IU I.M, given as a single dose.
- Late Syphilis (Late Latent, Tertiary, Cardiovascular)
  - Benzathine Penicillin → 2.4 million IU IM → once weekly for 3 weeks.
- Neurosyphilis → Aqueous Penicillin (Penicillin G or Procaine Penicillin)
- Penicillin hypersensitivity in syphilis → Jarisch-Herxheimer Reaction
  - T/t- Doxycycline



Jarisch herxheimer reaction
Penicillin Hypersensitivity in syphilis

Yourwish

Resistance In Staphylococcus Aureus

00:14:52

Penicillinase-producing Staph Aureus (mssa)

- These strains produce an enzyme that degrades Penicillin G.
- To treat these, we use Penicillinase-resistant Penicillins:
  - **C**: Cloxacillin
  - **O**: Oxacillin
  - **N**: Naficillin
  - **D**: Dicloxacillin
  - **M**: Methicillin → *Side Effect:* **Interstitial Nephritis**

Methicillin-resistant Staphylococcus Aureus (mrsa)

- Resistance d/t mutation in Transpeptidase (known as PBP-2A)
- **Drugs NOT effective in MRSA:**
  - Beta-lactams → Penicillin, Cephalosporine, Carbapenem, Monobactam.
    → Except → **5th Gen Cephalosporin**
  - Macrolides → Erythromycin, Azithromycin

Treatment Of MRSA

Injections	Oral (CFTR)	Topical
Vancomycin **(DOC)** ↓Resistance (VRSA) Linezolid ↓Resistance (LRSA) Streptogramin ↓Resistance (SRSA) Daptomycin Tigecycline Ceftaroline, Ceftabiprol	C -Clindamycin, Cotrimoxazole F - Fluoroquinolones T - Tetracycline R - Rifampicin	Mupirocin 2% cream • DOC for MRSA skin infections

- **DOC for MRSA: Vancomycin**
- **DOC for VRSA: Daptomycin > Linezolid**
  - Linezolid is preferred for MRSA/VRSA **pneumonia**.
  - Other conditions, except for pneumonia → **Daptomycin**

Resistance In Gram Negative Bacteria

00:20:06

Community-acquired infection

- Meningococci
- Gonococci
- Typhoid
- H. Influenzae
- **T/t**
  - Drug of Choice (DOC): Ceftriaxone (inj), Cefixime (oral)
  - Extended-spectrum penicillins

- **ESBL (Extended Spectrum β-lactamase)**
  - Organisms develop resistance by producing ESBL.
  - To block this enzyme, β-lactams are combined with **β-lactamase inhibitors**.

Beta lactams	Beta-lactamase inhibitors
Amoxicillin / Ticarcillin	Clavulanic acid
Ampicillin / Cefoperazone	Sulbactam
Piperacillin	Tazobactam

Hospital-acquired infection (UTI, VAP)

- Klebsiella
- E. coli
- Pseudomonas
- Acinetobacter
- Burkholderia cepacia
- Serratia
- Proteus
- **T/t**
  - Drug of Choice (DOC): Carbapenems (Meropenem, Imipenem)
- **CARBAPENEMASE Resistance**
  - Some bacteria produce Carbapenemase, an enzyme that degrades Carbapenems
  - Example: The "Delhi-superbug"
  - DOC for Carbapenemase-resistant strains: Colistin

Cephalosporins

00:24:38

Gen	Spectrum	Use	Drugs
1st	Gram positive: BEST • Staphylococcus • Streptococcus (For MSSA, not for MRSA)	Surgical Prophylaxis (DOC) 30 min before incision	Oral: Cefalexin, Cefadroxil Inj: Cefazolin (Naming cue: CEFA/CEPHA)
2nd	Anaerobes	DOC for Anaerobes: Metronidazole	Oral: Cefaclor Inj: Cefuroxime
3rd	Gram-negative: BEST Community-acquired infections	• Typhoid • Meningococci • Gonococci • H. Influenzae	Oral: Cefixime, Cefpodoxime Inj: Ceftriaxone, Cefotaxime (Naming cue: -XIME, -XONE)
	Except: **Pseudomonas**		Ceftazidime, Cefoperazone, Ceftolozane
4th	Gram-negative: Hospital-acquired infections	• Pseudomonas • Klebsiella • Acinetobacter	Cefepime, Cefpirome (Naming cue: contains -PI-)
5th	MRSA only		Ceftaroline, Ceftabiprol (Naming cue: contains -ROL-)

Renal Safe Drugs

- **Cefoperazone & Ceftriaxone**
  - Primarily Excreted in Bile (Not in Urine)- Safe in Renal Failure
- Side Effect: Can cause Jaundice / Kernicterus in newborns

Cefoperazone

- Bleeding: Can reduce fibrin levels, leading to excessive Warfarin bleeding.
- Renal Safety: Safe in renal failure (as it is primarily excreted in bile).
- Alcoholics: Avoid due to Disulfiram-like Reaction.

Cephalosporins Ineffective Against

- L - Listeria (DOC: Ampicillin)
- A - Atypical Bacteria (Mycoplasma; DOC: Azithromycin)
- M - MRSA (Except 5th Gen Cephalosporins; DOC: Vancomycin)
- E - Enterococci (DOC: Vancomycin)

Carbapenems

00:31:19

- Used for Hospital Acquired Infections, as they are Resistant to the ESBL enzyme
- **Drugs (Injections):**
  - Imipenem
  - Meropenem
  - Doripenem
  - Ertapenem
- **Drug (Oral):** Faropenem
- **General Side Effects:** Neurotoxic (seizures) and Nephrotoxic.
- Most Toxic Carbapenem: **Imipenem**
  - To reduce toxicity and prevent degradation, Imipenem is combined with Cilastatin
    - → Cilastatin is a DHP-1 Inhibitor (Dehydropeptidase-1 inhibitor)
    - → Prevents the breakdown of the drug in the kidneys, thereby reducing toxicity

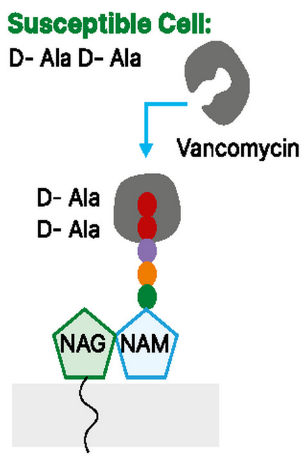
Monobactam

- **Aztreonam**- the only drug in this class
- **Advantage:** No cross-allergy with Penicillins or Cephalosporins. It can be used safely in patients with Beta-lactam hypersensitivity

Glycopeptides

00:33:50

- Vancomycin
- Teicoplanin
- **Newer Agents:** Oritavancin, Dalbavancin, Telavancin



Vancomycin

- **Mechanism of Action (MOA)** → Inhibit Transglycosylase
  - Inhibits Cell Wall Synthesis by binding to the D-Ala-D-Ala subunit
- Spectrum of Activity → Gram-positive infections only
  - Not effective against Gram-negative bacteria (e.g., Typhoid, Pseudomonas)

- **Routes and Clinical Uses:**
  - **Intravenous (I.V) Vancomycin:**
    → MRSA (Methicillin-Resistant Staph aureus)
    → Toxic Shock Syndrome
    → Enterococcal Endocarditis
  - **Oral Vancomycin**
    → Polar → not absorbed from the GIT.
    → **Indication: Clostridium difficile** (Pseudomembranous Colitis)

- **Adverse Effects of Vancomycin**
  - Ototoxic
  - Nephrotoxic
  - RED-MAN Syndrome
    → Fast i.v. infusion → Histamine release from Mast Cells
    → Prevention: Administer via slow IV infusion

Toxic Shock Syndrome

- Caused by superantigens of Staphylococcus & Streptococcus, leading to shock & scalded skin
- **Management:**
  - To kill the bacteria → Vancomycin (IV)
  - To reduce the toxin production → Clindamycin

Meningitis

Clinical Presentation

- Fever and Headache
- Stiff Neck / Nuchal Rigidity
- Vomiting
- Confusion
- Sensitivity to Light (Photophobia)
- Kernig's Sign ++

Empirical Treatment Of Meningitis

Meningococci
H. Influenzae
Streptococcus
Staphylococcus
↓
Ceftriaxone injection
(Standard Empirical Therapy)
↓
Lumbar Puncture (CSF analysis)
↓
Specific organism-based therapy

Specific Organism-based Therapy

Suspected Organism	Antibiotic
MRSA	I.V Vancomycin
Listeria	Ampicillin
Rickettsia / Chlamydia	Doxycycline
Herpes simplex	Acyclovir

Clostridium Difficile Diarrhea (pseudomembranous Colitis)

INI CET 2023

- AKA Antibiotic-associated diarrhea
- Broad-spectrum antibiotics → kill the "good bacteria" in the GIT, allowing C. difficile to overgrow and release toxins
- **High-Risk Antibiotics**
  - C - Clindamycin (Highest Risk)
  - C - Cephalosporins (3rd generation)
  - A - Ampicillin
  - F - Fluoroquinolones

MANAGEMENT

Drug / Intervention	Notes
Oral Vancomycin	Stays in the gut (not absorbed)
Fidaxomicin	**Most effective agent**
Bezlotoxumab	Monoclonal antibody targeting Toxin B
Metronidazole	Add on in serious cases
Faecal Microbiota Transplant	Replaces "good bacteria"

CELL MEMBRANE INHIBITORS

00:42:35

Daptomycin (lipopeptide Group)

- Reserve drug
- Spectrum: Targets MDR Gram Positive (+) organisms
- Effective against: VRSA, LRSA, and VRE (Vancomycin-Resistant Enterococci)
- Inactivated by pulmonary surfactant → Not effective in Pneumonia

Colistin / Polymyxin E (polypeptide Group)

- Spectrum: Targets MDR Gram Negative (-) organisms.
- Used for Carbapenem-resistant strains (e.g., E. coli, Klebsiella, Pseudomonas).
- Not effective against:
  - Burkholderia
  - Serratia
  - Proteus

DNA/NUCLEIC ACID INHIBITORS

00:44:30

Nitroimidazole

- Metronidazole
- Tinidazole
- Ornidazole
- Secnidazole (Longest acting)
- Satranidazole

Mechanism Of Action

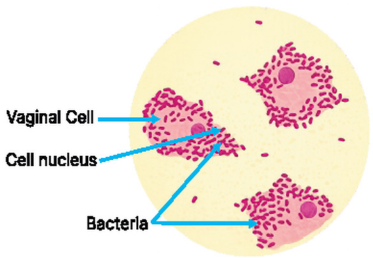
- Forms Nitric oxide → DNA Damage
- Effective against: Anaerobic organisms
- Not effective against: Aerobic organisms (O_2 prevents the formation of Nitric Oxide)

Clinical Uses

- G - Giardiasis
- U - Ulcers (*H. pylori*)
- P - Pseudomembranous Colitis
- T - Trichomonas vaginalis
- A - Amoebic Dysentery / Liver Abscess
- A - Anaerobic infections

Contraindication (c/I)

- Must be avoided in alcoholics
- Causes a disulfiram-like reaction

Guess the infection?	Guess the infection?
Grey-white, Fishy-smelling Discharge Amsel Criteria (pH > 4.5, Clue cells)  "Clue Cells", Vaginal cells with bacteria stuck to them	Yellow-green, Foul-smelling Vaginal Discharge Strawberry Cervix (Punctate haemorrhages)
Bacterial vaginosis	Trichomonas vaginalis
DOC → Metronidazole	

Fluoroquinolones

- Ciprofloxacin: A potent CYP inhibitor → ↑ Toxicity of warfarin, theophylline
- Ofloxacin / Norfloxacin
- Levofloxacin
  - Liver safe

- No CYP inhibition
- 100% oral bioavailability (BA)
- Pefloxacin, Moxifloxacin, Trovafloxacin → Hepatotoxic
  - Excreted through the bile
  - Advantage: They are safe in renal failure

Mechanism Of Action

- Inhibits DNA Gyrase/Topoisomerase IV

Side Effects

Mnemonic: Heart, ECG, P-Q-R-S-T

- Hypoglycemia (Gatifloxacin was banned due to this effect)
- Epilepsy
- Photosensitivity & QT interval prolongation
  - Max risk with Sparfloxacin and Moxifloxacin
  - Least with Ciprofloxacin
- Rashes
- Steven-Johnson Syndrome (SJS)
- Tendinitis: Risk of Achilles tendon rupture in the older age group

Urinary Tract Infection

Uncomplicated UTI (Cystitis)	Complicated UTI (Kidney involvement)
C - Ciprofloxacin C - Cotrimoxazole N - Nitrofurantoin	• Beta-lactams • Amoxicillin-Clavulanic acid • Piperacillin-Tazobactam
Avoided in Pregnancy	DOC for UTI in pregnancy → Beta-lactam group of antibiotics
Progressive Infection (Shock + Sepsis) → **Carbapenems (e.g., Meropenem)**	

PROTEIN SYNTHESIS INHIBITORS

00:53:15

Antibiotics acting on the 30s ribosome	Antibiotics acting on the 50s ribosome
• Tetracyclines, Tigecycline- Inhibits tRNA attachment on 30s ribosome • Aminoglycosides- Inhibit initiation of protein synthesis by attaching to the 30s ribosome	• Macrolides, Clindamycin, Streptogramin (Quinpristine + Dalfopristine)- Inhibits translocation (AA from the A site on 30s ribosome moves to the P site on 50s ribosome) • Chloramphenicol- Inhibits peptidyltransferase enzyme on the P site of the 50s ribosome, responsible for the peptide bond between the P site and the A site • Linezolid- Inhibits initiation of protein synthesis by attaching to the 23s subunit of the ribosome

Chloramphenicol

- **Mechanism of Action (MOA):** Inhibits the Peptidyl Transferase enzyme.
- **B** - Brain Entry Good: T/t → Meningitis.
- **B** - Bone Marrow Suppression → Aplastic Anaemia
- **B** - Baby → Neonates: Contraindicated → Grey Baby Syndrome

Tetracycline

- Inhibits tRNA binding at the A site of the ribosome.
- **Tetracycline:** Used in treatment for H. pylori.
- **Demeclocycline:** Blocks ADH in the kidney.
  - Side Effect: Can cause Nephrogenic Diabetes Insipidus (DI).
  - Therapeutic Use: Used to treat SIADH
- **Minocycline:** Used for Leprosy and Acne.
- **Doxycycline:** Renal Safe (Excreted via bile)

Adverse Effects

Mottling of teeth

- Tetracyclines chelate calcium, leading to tooth damage & discolouration
- Ingestion of Expired Tetracyclines → Fanconi Syndrome

Doxycycline

- **DOC**
  - Rickettsia
  - Cholera
  - Chlamydia (LGV, Trachoma)
  - Leptospira
  - Brucella
  - Borrelia (Lyme's disease)
- **Contraindications (C/I)**
- Pregnancy: Fetal bone & cartilage affected.
- Children < 8 years: Risk of Stunting
- Drug of Choice (DOC) → Azithromycin

Newer Tetracyclines

- Sarecycline → Severe Acne
- Omadacycline, Eravacycline, Tigecycline:
  - **M** - MRSA
  - **A** - Abdominal infections
  - **D** - Dermis / Skin infections

Tigecycline

- Renal Safe
- Resistance is uncommon (Mechanism of resistance → Efflux pumps)
- Reserve Drug for Hospital-Acquired Infections

Yourwish

Macrolides

01:02:10

- Azithromycin
- Clarithromycin
- Erythromycin
- **Uses:**
  - Chancroid
  - Corynebacterium diphtheriae
  - Community Acquired Pneumonia (CAP):
    - → **L** - Legionella
    - → **A** - Atypical (Mycoplasma)
    - → **W** - Whooping Cough (Pertussis)

Feature	Erythromycin	Clarithromycin	Azithromycin
CYP Inhibition	Max	Moderate	Least
QT Prolongation	Max	Moderate	Least
Hypertrophic Pyloric Stenosis	+	+	Not seen
Safety in Neonates	Contraindicated	Contraindicated	SAFE

Diphtheria Treatment

- **DOC:** Erythromycin/Azithromycin
  - Antitoxin is also given
- If Resistant → Rifampicin

STD

- **Gonococcal urethritis** → Ceftriaxone inj + Azithromycin (2 gm)
- **Chlamydia (LGV)** → Doxycycline + Azithromycin (1 gm)
- In case of mixed infection → Initial treatment of choice → Azithromycin (2g)

Linezolid

01:06:25

- **Mechanism of Action:** Inhibits the 23S subunit of the 50S ribosome
- 100% Oral bioavailability
- Renal safe drug
- Used for MDR Gram + infection: VRSA, VRE, MDR-TB
- **Side effects:**
  - **P** - Peripheral neuropathy
  - **O** - Optic neuritis
  - **S** - Serotonin syndrome (d/t MAO Inhibitor action)
  - **T** - Thrombocytopenia (d/t Bone marrow suppression)

Streptogramins

- **Composition:** Quinupristin (30%) + Dalfopristin (70%)
- Used for LRSA (Linezolid-resistant Staph. aureus)

Aminoglycosides

01:08:33

- Inhibits the 30S ribosome → (-) Initiation of protein synthesis

Streptomycin Amikacin Capreomycin Kanamycin	Treatment of TB
Streptomycin	DOC → Plaque, Tularemia
Gentamicin Amikacin Tobramycin	Treatment of Pseudomonas
Topical Skin Creams	Neomycin → Neosporin Framycetin → Soframycin

Oral Aminoglycosides - Neomycin

- Oral aminoglycosides are not absorbed in the GIT
- Used to kill GIT bacteria (Gut Sterilisation) → ↓ Ammonia production
- Chronic Liver Disease → Ammonia fails to convert to Urea → Hepatic Encephalopathy
- **Hepatic Encephalopathy Treatment:**
  - Lactulose
  - Neomycin
  - Rifaximin (DOC)

Side Effects

- Ototoxic: Permanent high-frequency hearing loss
- Nephrotoxic: Reversible RTA (Renal Tubular Acidosis)
- Neuromuscular blockage: Blocks Nm receptors
  - Contraindicated (C/I): Myasthenia Gravis
- **Toxicity: Antidote** → Calcium

FOLIC ACID INHIBITORS

01:12:50

- Sulfonamides
- Dapsone

Folate synthase

(-) DHFR Human

- Methotrexate

- Trimethoprim
- Pyrimethamine

Di Hydro Folate Reductase (DHFR)

PABA
↓
Folic Acid
↓
Tetra hydro folate

Mechanism Of Action

- Sulfonamides & Dapsone → Inhibits Folate synthase
- Trimethoprim & Pyrimethamine → Inhibits Dihydrofolate Reductase in Bacteria
- Methotrexate → Inhibits Di Hydro Folate Reductase (DHFR) in Humans
- Folinic acid (Leucovorin): Used as (THF) to prevent the toxicity of DHFR inhibitors
- Individual drugs are Bacteriostatic.

- **Bactericidal Combination (Synergism) → Cidal**
  - Sulfadiazine + Pyrimethamine
    → DOC for: Toxoplasma gondii
    →In Pregnancy: Use Spiramycin → (-) fetal transmission
  - Sulfamethoxazole + Trimethoprim = Cotrimoxazole
    → Combined in ratio: 5:1
    → DOC for:
    - Pneumocystis (PCP)
    - Burkholderia

Treatment Of Burns

- Silver Sulfadiazine (1% cream)
- Mafenide

Prophylaxis Of Neonatal Conjunctivitis (ophthalmia Neonatorum)

Agent	Concentration
Silver Nitrate	1% eye drops
Erythromycin	0.5% eye drops
Tetracycline	1% eye drops

Antibiotics Avoided In Neonates

- Chloramphenicol → Grey baby syndrome
- Sulfonamides (Cotrimoxazole) → Kernicterus
- Infantile hypertrophic pyloric stenosis → Erythromycin & Clarithromycin
  - Not Azithromycin

Antibiotics In Pregnancy

Safe	Avoid
• Penicillin • Cephalosporin • Macrolides (Azithromycin, Erythromycin)	• Fluoroquinolones → Bone/cartilage defect • Aminoglycosides → Ototoxic (Fetus) • Tetracyclines → Bone/cartilage defect • Sulfonamides → Kernicterus

Antibiotics Safe In Renal Failure

- Bile excreted (Not urine) → Do not require dose reduction in Renal failure
  - **Contra**: Cefoperazone
  - **Indicated**: Isoniazid
  - **R**: Rifampicin
  - **En**: Erythromycin
  - **A**: Azithromycin
  - **L**: Linezolid
  - **Failure (FQ)**: Pefloxacin, Moxifloxacin, Trovafloxacin
  - **Disease**: Doxycycline

Drugs Requiring Dose Reduction

- Aminoglycosides
- Penicillin
- These are excreted via Urine and require dose reduction in patients with Renal Failure

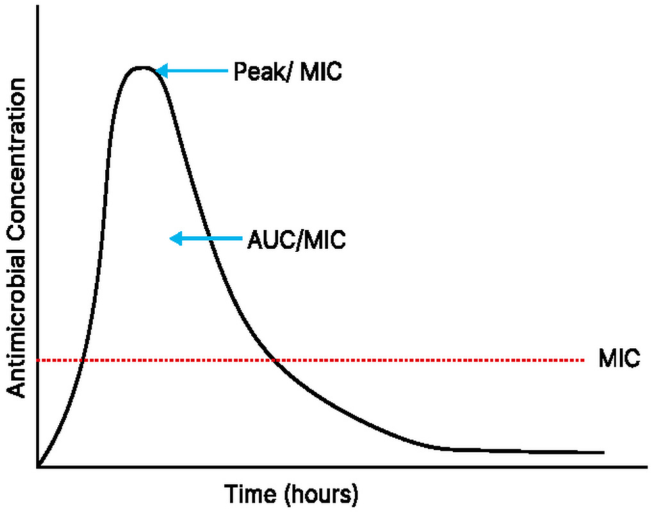
Inherent Resistance

- Inherently resistant to Aminoglycosides (e.g., Streptomycin, Amikacin):
  - **B:** Burkholderia
  - **A:** Acinetobacter
  - **T:** Typhoid
  - **A:** Anaerobes
- Inherently resistant to Colistin:
  - **B:** Burkholderia
  - **S:** Serratia
  - **P:** Proteus
- Metronidazole: Is not effective against Aerobic Bacteria.

Acquired Resistance

- **Enzymatic Degradation**
  - **A:** Aminoglycosides
  - **B:** Beta-Lactams
  - **C:** Chloramphenicol
- **Drug Efflux**
  - **A:** Antimalarials (**Chloroquine**)
  - **T:** Tetracycline
  - **T:** Tigecycline
- **Target Mutation**
  - **M (MRSA):** Mutation in PBP-2A (Penicillin Binding Protein)
  - **M (Macrolides):** Mutation in the Ribosome
  - **F (Fluoroquinolones):** Mutation in DNA gyrase

Dosing Of Antibiotics



Yourwish

- **MIC:** Minimum inhibitory concentration
- **CDK (Concentration Dependent Killing):** Effectiveness depends on reaching high peak concentrations. Usually dosed once a day
- **TDK (Time Dependent Killing):** Effectiveness depends on the duration the drug concentration remains above the MIC. Usually requires multiple doses in a day
- **PAE (Post Antibiotic Effect):** Continued suppression of bacterial growth even after the antibiotic concentration falls below the MIC

CDK + LONG PAE	CTDK + LONG PAE	TDK + LONG PAE	TDK + SHORT PAE
Metronidazole Aminoglycoside Rifampicin Streptogramin	Fluoroquinolones Vancomycin	Azithromycin Tetracycline	Clindamycin Penicillin Erythromycin Cephalosporin

Yourwish

2. ANTIMICROBIAL PART -2

MYCOBACTERIAL INFECTIONS

00:00:22

Tuberculosis (TB)

- Causative organism: Mycobacterium tuberculosis
- Treatment drugs: ATT (Anti-Tubercular Therapy)
- Treatment guidelines: NTEP (National Tuberculosis Elimination Program)
- Drug Classification
  - First-Line Drugs (for drug-susceptible TB/ New cases)
    - → H = Isoniazi
    - → R = Rifampicin
    - → Z = Pyrazinamide
    - → E = Ethambutol (Bacteriostatic)
    - → All HRZE are oral drugs

    } Bactericidal drugs
- Streptomycin:
  - Previously was the only injectable drug for TB
  - No longer a first-line drug
  - Now used only as supplemental drug when contraindications to HRZE exist
  - Treatment Regimen for Drug-Susceptible TB
- New Case of TB Rx
  - Intensive Phase:
    - → Duration: 2 months
    - → Drugs: HRZE (all four drugs orally)
  - Continuation Phase:
    - → Duration: Minimum 4 months
    - → Drugs: HRE (only three drugs)
    - → Pyrazinamide (Z) is not given in continuation phase because it is the most hepatotoxic TB drug

Drug-Resistant Tb

- Second-Line Drugs Classification
  - GROUP A (Most Effective - Mnemonic: BELL)
    - → B = Bedaquiline
    - → L = Linezolid
    - → L = Levofloxacin or Moxifloxacin
  - GROUP C (Complementary/Add-on Drugs):
    - → Clofazimine
    - → Cycloserine
  - OTHER DRUGS:
    - → Delamanid
    - → Pretomanid
  - New drugs (commonly asked): Ethionamide and Thioacetazone

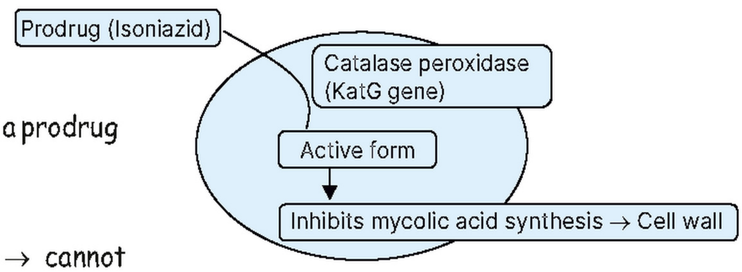
Types Of Drug-Resistant Tb

- MDR-TB (Multi-Drug Resistant TB):
  - Resistance to H + R (Isoniazid + Rifampicin)
- Pre-XDR TB (Pre-Extensively Drug Resistant TB):
  - MDR-TB + Fluoroquinolone resistance
  - Either Levofloxacin OR Moxifloxacin resistance
- XDR-TB (Extensively Drug Resistant TB):
  - MDR-TB + BELL resistance
  - Resistance to Bedaquiline, Linezolid, & Levofloxacin or Moxifloxacin

Treatment Of Drug-Resistant Tb

- MDR-TB Treatment:
  - Regimen: BPaLM for 6 months
    → B = Bedaquiline
    → Pa = Pretomanid
    → L = Linezolid
    → M = Moxifloxacin
  - BPaL treatment is also started in Rifampicin-resistant TB even if not MDR
  - Reason: Isoniazid resistance is widespread in India, so even with only Rifampicin resistance, start MDR-TB treatment
- Pre-XDR and XDR-TB Treatment:
  - Regimen: BPaL only (without M - Moxifloxacin)
  - Duration: 6 to 9 months
- Special Contraindications for Pretomanid:
  - Contraindicated in age < 14 years
  - Contraindicated in pregnancy
  - Avoided during breastfeeding
  - Replacement strategy: Replace Pretomanid with Delamanid + Clofazimine in pregnancy, breastfeeding, and young people
  - BDLfxC
    → Bedaquiline
    → Delamanid
    → Linezolid
    → Levofloxacin
    → Clofazimine

Isoniazid (H)



- Mechanism of Action
  - Isoniazid is a prodrug (inactive drug)
  - Symbol is H (different from name) because it's a prodrug
- Resistance Mechanism
  - Develops due to mutation in KatG gene
  - Mutation → no catalase-peroxidase enzyme → cannot convert isoniazid to active form
- Drug Properties

- CYP enzyme inhibitor
- Part of SHIP drugs: Sulfonamide, Hydralazine, Isoniazid, Procainamide
- Undergoes acetylation

- Acetylation Phenotypes

Fast acetylators	Slow acetylators
• Have high amounts of acetylating enzyme • Isoniazid degraded rapidly • Result: Loss of effect • Consequence: Increased risk of resistance	• Have poor quantity of acetylating enzyme • Isoniazid accumulates in body • Result: Increased risk of toxicity

- Toxicity (Mnemonic: INH)

I = Insanity: Transient memory loss Abnormal thoughts Hallucinations Person becomes "mad"	N = Neurotoxicity: Peripheral neuropathy Treatment/Prevention: Vitamin B6 (Pyridoxine) given along with isoniazid	H = Hepatotoxicity: Can damage liver	Additional Side Effect: Inhibits CYP enzyme → decreased testosterone metabolism → increased testosterone breakdown → Gynecomastia

Rifampicin (R)

- Mechanism of Action
  - Inhibits RNA polymerase enzyme in TB bacteria
  - Result: Inhibits cell division of TB bacteria
- Resistance Mechanism
  - Mutation in rpoB gene
  - rpoB gene produces RNA polymerase enzyme
  - Mutation → Rifampicin cannot inhibit RNA polymerase
- Detection test: CBNAAT test (Cartridge-Based Nucleic Acid Amplification Test)
  - CBNAAT is a type of PCR test used to detect rifampicin resistance/rpoB mutation
- Drug Properties
  - CYP enzyme inducer (opposite of Isoniazid)
  - P-glycoprotein inducer
  - Reduces effect of other drugs (enhances their degradation)
  - P-glycoprotein present in blood-brain barrier → Rifampicin cannot enter BBB
  - Must be taken empty stomach (food reduces absorption)
- Drug Interactions

With Estrogen (Oral Contraceptive Pills)	• Rifampicin induces CYP → rapid estrogen degradation • Result: Contraceptive failure
• With Digoxin	• Digoxin excreted by P-glycoprotein • Rifampicin induces P-glycoprotein → increased digoxin excretion • Result: Reduced digoxin effect
• With Warfarin	• Warfarin degraded by CYP enzyme • Rifampicin induces CYP → rapid warfarin degradation • Result: Reduced warfarin effect

Yourwish

• With Dolutegravir (HIV drug - now drug of choice)	• Degraded by CYP3A4 enzyme • Rifampicin increases degradation • Management: 2X the dose of Dolutegravir • Alternative: Stop Rifampicin, switch to Rifabutin (no CYP induction activity

- Side Effects
  - Most common: Rashes
  - Color: Orange to red → Orange-red urine (harmless, do not stop drug)
  - Hepatotoxicity and hypersensitivity → indication to STOP rifampicin

Rifamycin Group (Other Derivatives)

- Rifampicin:
  - Used in tuberculosis
  - Drug of choice for LAMBS
  - L - Leprosy
  - A - Anthrax
  - M - Meningitis prophylaxis: H. influenzae, Meningococcal meningitis
  - B - Brucella
  - S - Staph aureus (Methicillin-Resistant Staphylococcus aureus)
- Rifapentine:
  - New drug
  - Approved for prevention of TB in India (TB prophylaxis)
- Rifabutin:
  - Given in MAC infection (Mycobacterium Avium Complex)
- Rifaximin:
  - Kills GIT bacteria → Given for gut sterilization
  - Drug of choice for hepatic encephalopathy (reduces ammonia production by GIT bacteria)
  - Given to kill abnormal bacterial growth in irritable bowel syndrome
  - Drug of choice for traveler's diarrhea
- Special Color Side Effects
  - Rifampicin:
    → Orange-colored urine
  - Rifabutin:
    → Deposits in skin → Orange-colored skin
    → Causes pseudo-jaundice (looks like jaundice but isn't)
    → Can damage eyes → Anterior uveitis, Panuveitis

Pyrazinamide (Z)

- Mechanism of Action
  - Pyrazinamide is a prodrug
  - Converted into active form
  - Active form: Inhibits protein synthesis
- Toxicity
  - Most hepatotoxic TB drug
  - Hepatotoxicity ranking: Pyrazinamide > Isoniazid > Rifampicin

- Causes hyperuricemia → leads to gout → joint pain
- Maximum gout-causing TB drug: Pyrazinamide
- Other drug causing gout: Ethambutol (E)
- Not given in continuation phase because it's most toxic

Ethambutol (E)

- Mechanism of Action
  - Inhibits arabinosyl transferase enzyme
  - Reduces arabinogalactan synthesis
  - Arabinogalactan = part of cell wall of TB bacteria
  - Result: Inhibits cell wall synthesis
- Main Side Effect
  - Affects eyes (ocular side effect)
  - Red-green color blindness
  - Optic neuritis
- Drug Classification
  - Bacteriostatic drug (only bacteriostatic among HRZE)

Special Tb Drug Properties

- Sterilizing Action (Can kill dormant or slowly dividing bacteria)
- Drugs with sterilizing action:
  - Rifampicin
  - Pyrazinamide
  - Bedaquiline (drug for resistant TB)

Safety In Organ Disease

- Mnemonic: HRZES
  - First 3 drugs (HRZ): Hepatotoxic → Contraindicated in liver disease
  - Last 3 drugs (ZES): Contraindicated in renal disease

Renal safe drugs	Liver safe drugs
• Rifampicin • Isoniazid	• Streptomycin • Ethambutol

Special Clinical Situations

TB with liver disease

- Presentation: Elevated AST and ALT levels
- Management: Stop first 3 drugs (HRZ)
  - Especially STOP Pyrazinamide (most toxic)
  - Start SLE regimen: (Liver safe drugs)

    → S = Streptomycin

    → L = Levofloxacin

    → E = Ethambutol

TB with GOUT

- Problem: Pyrazinamide and Ethambutol cause arthritis
- Management:
  - Do not stop anti-tubercular drugs → Gout is not dangerous (unlike liver disease)
  - Add uric acid-lowering drugs: Allopurinol
  - Continue TB treatment with gout management

TB in PREGNANCY

- Intensive Phase (2 months):
  - Give all 4 drugs: HRZE
- Continuation Phase:
  - Give only 2 drugs: HR (not E and Z)
  - Reason: Want to give as few drugs as possible in pregnancy

Corticosteroids in Tb

- Benefits
  - Anti-inflammatory effect
  - Reduce fibrosis in TB
  - Reduce edema in TB
- Indications (MANDATORY)
  - Tubercular meningitis (prevent brain damage from fibrosis and edema)
  - Pleural TB
  - Pericardial TB
  - Any other TB variety
- Absolute Contraindication
  - Intestinal TB
  - Inhibiting fibrosis in intestine → can lead to intestinal perforation

Tb In Hiv-Positive Patients

00:22:55

- Key Principles
  - Most common opportunistic infection in HIV in India: Tuberculosis
  - If patient has both HIV and TB → First treat opportunistic infection
  - Treatment sequence:
    → Start ATT (Anti-Tubercular Therapy) FIRST
    → After gap of 2 to 8 weeks → start ART (Anti-Retroviral Therapy)
- Reason for Gap
  - If start ART initially → HIV lymphocyte count improves → immunity improves
  - Sudden immunity improvement → kills TB bacteria suddenly → inflammation
  - Results in: IRIS (Immune Reconstitution Inflammatory Syndrome)
  - NEVER start ART together with ATT

Tb Prevention (Prophylaxis)

00:24:21

- Indications
- High-risk patients:
  - Immunocompromised patients

- Mantoux positive (latent TB) with reduced immunity → risk of reactivation
- HIV-positive people
- Newborn of tubercular mother

- Prophylaxis Regimens
  - Option 1: Isoniazid only (daily)
  - Option 2: Rifampicin only (daily)
  - Option 3: Isoniazid + Rifampicin combination (daily)
  - Option 4 (NEW): Isoniazid + Rifapentine (Weekly regimen - recently approved)

Second-line tb drugs

00:25:22

Bedaquiline (from bell)

- Mnemonic
  - When sitting on BED → lying down → not spending energy
  - Bedaquiline = ATP inhibitor
- Mechanism of Action
  - Inhibits mycobacterial ATP synthase enzyme
  - Inhibits energy production in TB bacteria
- Side Effect
  - QT prolongation (Q in Bedaquiline)

Linezolid

- Side Effects (Mnemonic: POST)
  - P = Peripheral neuropathy
  - O = Optic neuritis
  - S = Serotonin syndrome (has MAO enzyme inhibiting action)
    → MAO = Monoamine oxidase enzyme (normally degrades serotonin)
    → Inhibiting MAO → increased serotonin level
  - T = Thrombocytopenia (bone marrow suppression, mainly affects platelets)

Fluoroquinolones (Levofloxacin/ Moxifloxacin)

- Part of BELL group
- Details covered in previous sections

Clofazimine (Group C)

- Important Properties
  - Shows cross-resistance with Bedaquiline
  - First-line drug for leprosy
  - Before approval: Used as brown dye in textile industry
- Side Effect
  - Brown skin hyperpigmentation → Deposits on skin

Which drug for TB and leprosy causes brown skin hyperpigmentation? Clofazimine

CYCLOSERINE (Group C)

- Mechanism of Action
  - Inhibits alanine racemase and ligase enzyme

Yourwish

- Required for cell wall synthesis in TB bacteria
- Side Effects
  - Affects CNS (brain damage)
  - Psychosis
  - Depression
  - Psychosis + Depression → increased risk of suicide

Delamanid And Pretomanid

- Mnemonic
  - Suffix "...manid"
  - MA = Mycolic Acid (cell wall of TB bacteria) → Mycolic Acid Inhibitors
- Side Effects
  - Similar to Bedaquiline
  - QT interval prolongation on ECG → Arrhythmia

Ethionamide

- Mnemonic: ETH
- E = Erectile dysfunction/impotence TH = THyroid effects
- Mechanism
  - Inhibits T3 and T4 hormone synthesis
  - Derivative of anti-thyroid drugs (Carbimazole, Methimazole)
  - Causes hypothyroid goiter

Thioacetazone

- Important Properties
  - HI word in name → HIV contraindication
  - Contraindicated in HIV-positive patients (causes allergic reactions)
  - Bacteriostatic drug (among second-line drugs)
  - First-line bacteriostatic: Ethambutol

Leprosy

00:30:14

- Basic Information
  - Causative organism: Mycobacterium leprae
  - Treatment drugs: MDT (Multi-Drug Therapy)
  - Treatment guidelines: NLEP (National Leprosy Eradication Program)
- Classification: Paucibacillary vs Multibacillary
  - Based on skin lesions (hypopigmented, anesthetic macules) & nerve thickening (palpation)

Parameter	Paucibacillary	Multibacillary
Skin lesions	1 to 5	≥6
Nerve involvement	0 or none	≥ 1
Treatment duration	6 months	12 months
Drugs	RDC	RDC

RDC: Rifampicin, Dapsone, Clofazimine

Leprosy Drug Regimens

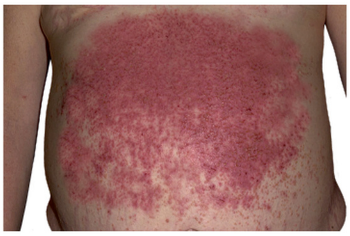
00:32:10

1st line of drugs	> 14 years old	10-14 years old	< 10 years old
Rifampicin Once a month → Supervised	600 mg	450 mg	300 mg
Dapsone Daily → Unsupervised	100 mg	50 mg	25 mg
Clofazimine Once a month → Supervised + Daily → Unsupervised	300 mg + 50 mg	150mg + 50 mg (alternate days)	100mg + 50 mg (twice a week)

Second-Line Drugs For Leprosy

- Used when first-line drugs cannot be given:
  - Ofloxacin
  - Clarithromycin
  - Minocycline
  - Ethionamide (also used in TB)
- Bactericidal drugs for leprosy:
  - Rifampicin
  - Ofloxacin
  - Rest are bacteriostatic

Dapsone



- Mechanism of Action
  - Sulfonamide
  - Inhibits folic acid synthesis in bacteria → Antifolate drug
- Additional Indications
  - Drug of choice for Dermatitis Herpetiformis
  - Dermatitis Herpetiformis = skin lesion in celiac disease/ Gluten sensitivity
- Side Effects
  - Most common: Hemolytic anemia
  - Contraindicated in G6PD deficiency (risk of hemolytic anemia)
- New Formulation
  - Acedapsone (AC Dapsone)
    → Intramuscular injection
    → Given once every 3 months
  - Dapsone = oral drug

Lepra Reactions

- Hypersensitivity developing after starting MDT

Type 1 Lepra Reaction	Type 2 Lepra Reaction
• Also called: Reversal Reaction • Type 4 hypersensitivity disease • Mnemonic: 1 + 4 = 5	• Also called: Erythema Nodosum Leprosum (ENL) • Type 3 hypersensitivity reaction • Mnemonic: 2 + 3 = 5

Treatment Of Lepra Reactions

- Primary Management:
  - Do not stop MDT (continue anti-leprosy drugs)
  - DOC: Corticosteroid (Prednisolone)
  - Prednisolone for BOTH Type 1 and Type 2
  - Anti-inflammatory effect reduces hypersensitivity
- Special Case:
  - Corticosteroid-resistant Type 2 Lepra Reaction (ENL)
  - Give Thalidomide
    - Thalidomide only for Type 2 (not Type 1)

ANTIFUNGAL DRUGS

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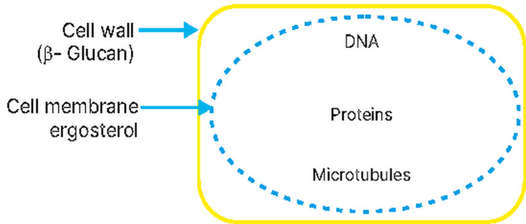


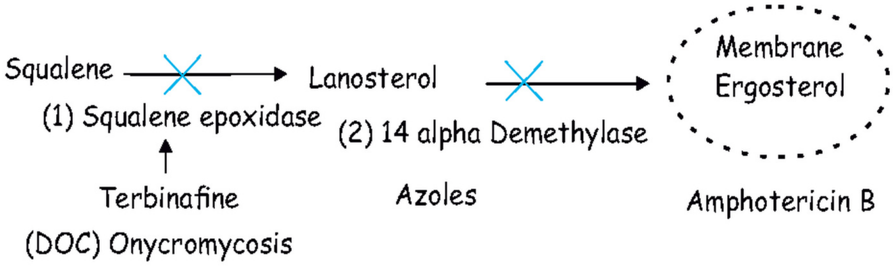
FUNGAL CELL STRUCTURE

- Cell wall made of beta-glucan
- Cell membrane made of ergosterol

Cell Wall Inhibitors

- Echinocandins (Suffix "...fungin")
- Mechanism:
  - Inhibit beta-glucan synthase enzyme
  - Inhibit cell wall synthesis
- Indications:
  - Treatment of invasive Candida and Aspergillosis
  - Not drug of choice (Amphotericin B is drug of choice for invasive infections)

Cell Membrane Inhibitors



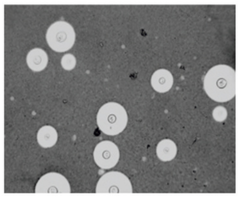
- Ergosterol Synthesis Pathway

Yourwish

- Squalene → (Squalene epoxidase enzyme) → Lanosterol → (14-alpha demethylase enzyme) → Ergosterol (cell membrane)

- Terbinafine
  - Mechanism: Inhibits squalene epoxidase enzyme
    → Blocks conversion: Squalene → Lanosterol
  - Indication:
    → Drug of choice for Onychomycosis (fungal infection of nails)
- Azoles (Ketoconazole, Fluconazole, etc.)
  - Mechanism:
    → Inhibit 14-alpha demethylase enzyme
    → Block conversion: Lanosterol → Ergosterol
    → 14-alpha demethylase = CYP enzyme in fungus

Amphotericin B



- Mechanism of Action
  - Creates pores on ergosterol cell membrane
  - Damages fungal cell membrane by creating pores
- Important properties
  - Most effective fungicidal drug
  - Intravenous drug only
  - DOC- serious fungal infection
  - Given in 5% dextrose (not normal saline or Ringer's lactate - doesn't mix)
- Major Indications
  - DOC for Mucormycosis (black fungus)
  - DOC for Cryptococcal meningitis (with 5-flucytosine combination)
  - DOC for Kala-azar
- Side Effects
  - M/c: Allergic reaction
  - Nephrotoxicity
  - Anemia
- Formulations (Evolution)

Conventional Amphotericin B:	Amphotericin B Colloid Dispersion:	Liposomal Amphotericin B (LAMB):
• Older preparation • Maximum allergy	• Older preparation • Maximum allergy	• Least toxic • Least nephrotoxic • Longest acting • Overall safest preparation

Azoles

- General properties
  - Inhibit cell membrane synthesis
  - Inhibit 14-alpha demethylase enzyme (CYP enzyme in fungus)
  - In humans: Also inhibit cytochrome P450 enzyme → Inhibiting CYP → increased toxicity of other drugs degraded by CYP
  - Most toxic Azole: Ketoconazole (maximum CYP inhibiting action)

Yourwish

- Ketoconazole toxicity
  - Due to CYP Inhibition:
    - → Increased toxicity of: Theophylline, Warfarin
    - → Avoid combining ketoconazole with other drugs
    - → CYP enzymes in liver → most hepatotoxic Azole
    - → CYP responsible for steroid hormone production
    - → Decreased testosterone production
    - → Decreased glucocorticoid and mineralocorticoid production
  - Most hepatotoxic Azole- Ketoconazole
  - Antifungal causes gynecomastia in males: Ketoconazole (reduces testosterone)
  - Azole causes adrenal insufficiency: Ketoconazole (reduces corticosteroids)
- Excretion- All Azoles excreted in bile
  - Exception: Fluconazole = only Azole excreted in urine

Individual Azoles

Clotrimazole:	• Available as pessary/ suppository (inserted in vagina) • DOC- Vulvovaginal candidiasis
Ciclopirox:	• Has anti-pruritic effect • Fungal infections cause pruritus
Ketoconazole:	• Shampoo for topical application • Given for dandruff treatment
Ketoconazole:	• Side effects: Visual defects + QT prolongation
Isavuconazole:	• Side effects: Heart failure + QT prolongation

Treatment of invasive fungal infections

Yeast-like fungi (Divide by Budding)

- Examples: Candida, Cryptococcus, Coccidiomycosis
- Treatment:
  - Induction: Amphotericin B (AMB) - first choice
  - Maintenance: Fluconazole

Dimorphic Fungi (Budding + Spore Formation)

- Examples: Histoplasma, Blastomycosis, Sporotrichosis, Paracoccidiomycosis
- Treatment:
  - Induction: Amphotericin B
  - Maintenance: Itraconazole (drug of choice)

Aspergillosis

- Treatment:
  - Overall first choice: Voriconazole
  - Voriconazole > Amphotericin B in Aspergillosis
  - Only place Amphotericin B defeated
- Exception:
  - **Voriconazole not effective in Mucormycosi**

Mucormycosis (Black Fungus)

- Treatment:
  - Induction (drug of choice): Amphotericin B
  - Maintenance (approved Azoles):
    - → Posaconazole
    - → Isavuconazole
  - Drug of choice remains Amphotericin B

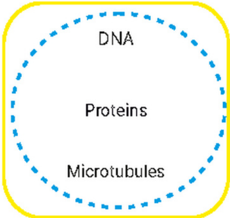
Antifungal In Pregnancy

- ONLY give Amphotericin B
- All Azoles contraindicated (teratogenic drugs

Other antifungal targets

5-flucytosine

- Mechanism:
  - Inhibits DNA synthesis via inhibiting thymidine production
  - Causes thymidine-deficient cell death
- Indication:
  - Given in Cryptococcal meningitis
  - Add-on drug to Amphotericin B



Tavaborole

- Mechanism: Inhibits protein synthesis in fungus
- Indication: New drug for Onychomycosis

Griseofulvin

- Mechanism: Inhibits microtubule in fungus
- Indication: DOC - Tinea capitis (fungal scalp infection)

Topical Antifungal Drugs

- Whitfield Ointment:
  - Contains: Benzoic acid + Salicylic acid
  - Given for Tinea pedis
- Nail Polish/Nail Lacquer:
  - For Onychomycosis (fungal nail infection)
- Ciclopirox olamine:
  - Available as nail polish/nail lacquer for Onychomycosis
  - Mnemonic: O (zero) for olamine, O for Onychomycosis
- Amorolfine:
- New drug
- Available as nail lacquer

ANTIHELMINTHIC DRUGS

00:48:19

Classification of worms

Cestodes (Tapeworms)	Trematodes (Flukes)	Nematodes
• Taenia solium (pork tapeworm) • Taenia saginata (beef tapeworm) • Hymenolepsis nana (dwarf tapeworm) • Diphyllobothrium latum (fish tapeworm)	• Paragonimus westermani (lung fluke) • Schistosoma (blood fluke)	• Ascaris (roundworm) • Necator and Ancylostoma (hookworms) • Enterobius (pinworm) • Trichuris (whipworm
DOC: Praziquantel General Rule: For ALL Cestode and Trematode infections → Praziquantel	DOC: Albendazole or Mebendazole (Broad spectrum drugs)	

Exceptions To Praziquantel

- Echinococcus (Hydatid cyst): DOC- Albendazole
- Neurocysticercosis: DOC- Albendazole
- Fasciola hepatica (Liver fluke): DOC - Triclabendazole

Special Nematodes

- Strongyloides and Onchocerca: DOC - Ivermectin
- Lymphatic Filariasis and Loa loa: DOC - DEC (Diethylcarbamazine)

Mass Deworming

- Approved drugs: Albendazole or Mebendazole
- Age restrictions:
  - Albendazole: Can be given from 1-2 years or >2 years
  - Mebendazole: Only given in children >2 years
  - NO mass deworming <1 year age
- Doses:
  - Albendazole (1-2 years): 200 mg
  - Albendazole (>2 years/adults): 400 mg
  - Mebendazole: 100 mg

Levamisole

- Primary use: Anti-helminthic for roundworm (Ascariasis)
- Special property:
  - Immunostimulant effect
  - Stimulates immunity of body

Ivermectin

- Uses:
  - Anti-helminthic drug
  - Treatment of Scabies (only oral drug for scabies)
- Scabies Treatment Drugs

- Topical drugs:
  → Permethrin 5% cream (overall DOC)
  → Crotamiton
  → Benzyl benzoate
  → Safety profile: Safe in children and pregnancy: Permethrin, Crotamiton
  → Contraindicated in children and pregnancy: Ivermectin, Benzyl benzoate

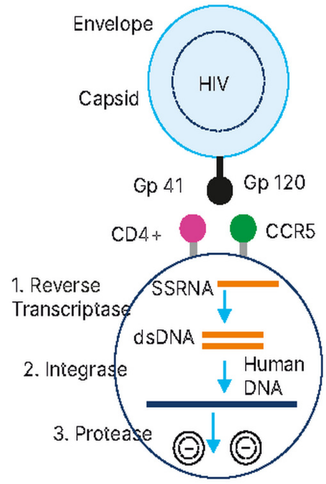
ANTIVIRAL DRUGS

00:52:40

HIV (HUMAN IMMUNODEFICIENCY VIRUS) - AR

HIV Structure

- Envelope with GP41 and GP120 proteins
- Capsid inside
- Attaches to human CD4 cells
- Needs CCR5 receptor



Entry Inhibitors (New Drugs)

GP41 Inhibitor:	• Drug: Enfuvirtide • Mnemonic: N (present on eNvelope) + inhibits fusioN
GP120 Inhibitor:	• Drug: Fostemsavir (new drug)
Capsid Inhibitor:	• Drug: Lenacapavir (high-potential question) • Mnemonic: Cap word → Capsid inhibitor
CD4 Receptor Blocker:	• Drug: Ibalizumab • Mnemonic: ...mab = monoclonal antibody • Only monoclonal antibody approved in HIV • Blocks CD4 receptor on human cell
CCR5 Receptor Blocker:	• Drug: Maraviroc • Blocks CCR5 receptor on human cell

HIV Replication Cycle

- After entry:
  - HIV single-stranded RNA → converted to double-stranded DNA by Reverse Transcriptase enzyme
  - Viral DNA integrates with human DNA by Integrase enzyme
  - HIV copies produced by Protease enzyme

Three key enzymes (RIP): • R = Reverse transcriptase • I = Integrase • P = Protease	Three drug classes: • RTI (Reverse Transcriptase Inhibitors) • Integrase Inhibitors (Suffix- "...gravir") • Protease Inhibitors (Suffix- "...navir")

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Reverse Transcriptase Inhibitors (rti)

- Converts RNA → DNA (RNA dependant DNA polymerase)
- Types:
  - NRTI: Nucleoside Reverse Transcriptase Inhibitors
  - NtRTI: Nucleotide Reverse Transcriptase Inhibitors
  - NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitors

NRTI - Nucleoside Reverse Transcriptase Inhibitors

- Mnemonic: DAZZLES
  - D = Didanosine
  - A = Abacavir
  - Z = Zidovudine (ZDV)
- Emptricitabine
- Side Effects
- Didanosine:
  - Maximum pancreatitis risk
- Zidovudine (ZDV):
  - Bone marrow suppression and anemia
  - Myopathy
  - Contraindicated if Hb <9 g/dL (causes anemia)

NTRTI: Nucleotide Reverse Transcriptase Inhibitors

- Tenofovir (Nucleotide RTI):
  - Only one NtRTI drug: Nephrotoxic
    → Damages PCT of nephron → Fanconi syndrome
    → Fanconi syndrome → phosphate loss in urine → weakens bone → Osteomalacia (adults), Rickets (children)
- HIV drug contraindicated in renal failure: Tenofovir
- HIV drug contraindicated in children: Tenofovir (Ten word → <10 years - risk of rickets)
- Note: Tenofovir has become drug of choice despite side effects

Non-Nucleoside Reverse Transcriptase Inhibitors (Nnrtis)

- Identification Pattern:
  - All NNRTI drugs have "-vir-" word in between the drug name
  - Examples:
    → Nevirapine
    → Efavirenz
    → Etravirine
    → Doravirine
    → Rilpivirine
- Common Side Effects:
  - Stevens-Johnson syndrome
  - Rashes
  - All NNRTIs can lead to Stevens-Johnson syndrome and rashes
- Comparison of First Two Drugs:
  - NEVIRAPINE - Hepatotoxic drug
- EFAVIRENZ - Neurotoxic drug

Integrase Inhibitors

- Mechanism of Action: Inhibit the integration of viral DNA to human DNA
- Identification Pattern:
  - All integrase inhibitors - suffix "-gravir"
- Examples: Bictegravir; Cabotegravir
- DOLUTEGRAVIR (important drug to remember)
  - Metabolism and Drug Interactions:
  - CYP Enzyme Interaction:
  - All integrase inhibitors are degraded by CYP3A4 enzyme
  - Rifampicin is a CYP enzyme inducer
- Important: When given with rifampicin, must double the dose of dolutegravir
- Side Effects:
  - Similar to NNRTIs
  - Can cause Stevens-Johnson syndrome/ rashes

Protease Inhibitors

- Mechanism of Action:
  - Inhibit the assembly or packing of viral protein
  - Result: Viral copies are not produced
- Identification Pattern:
  - All protease inhibitors - suffix "-navir"
- Specific Side Effects of Individual Protease Inhibitors:
- INDINAVIR
  - Side effect: Renal stones (very important)
- SAQUINAVIR
  - Side effect: QT prolongation
  - Only protease inhibitor having "QU" word in it → causes QT prolongation
- ATAZANAVIR
  - Side effect: Jaundice
  - Mechanism: Increases bilirubin level
- TIPRANAVIR
  - Side effect: Hypertension
  - Can cause intracranial hemorrhage due to hypertension
- RITONAVIR
  - Special property: Maximum CYP inhibiting property

Side effect of all protease inhibitors:

- LIPODYSTROPHY SYNDROME
  - Suffix "-navir"
  - Features (similar to not exercising and eating fatty food):
    - → Obesity
    - → Breast hypertrophy
    - → Diabetes
    - → Dyslipidemia
- Treatment of Lipodystrophy Syndrome:

- First approved drug: TESAMORELIN (Somatrolinous growth hormone releasing hormone)
- Newer drug: SEMAGLUTIDE
  - → Also an antidiabetic drug
  - → Also an anti-obesity drug
  - → Approved for treatment of lipodystrophy syndrome due to protease inhibitors if there is obesity

Boosted Protease Inhibitors

- Concept:
  - Ritonavir is a CYP enzyme inhibitor
  - It inhibits the degradation of other drugs
  - Low dose ritonavir is combined with all other protease inhibitors
- Purpose of Boosting:
  - To boost plasma levels of other protease inhibitors
  - Ritonavir inhibits degradation of other protease inhibitors like:
    - → Lopinavir
    - → Indinavir
- Cobicistat: Also a CYP inhibitor
  - Combined with other HIV drugs to boost or increase their:
    - → Plasma level
    - → Effectiveness

HIV treatment guidelines

01:03:09

National aids control program (nacp) guidelines

- Administering Organization: NACO
- Key Principles:
  - Universal Treatment
    - → Treat all HIV patients irrespective of their CD4 count
    - → All HIV patients must be treated
  - Triple Drug Therapy
    - → Give at least 3 drugs as FDC (Fixed Dose Combination)
    - → FDC = single tablet containing 3 drugs
    - → Purpose: Improves compliance in the patient

Current Treatment of Choice: Tld Regimen

- TLD Regimen Components:
  - T = Tenofovir
  - L = Lamivudine
  - D = Dolutegravir
- Adult Treatment: TLD regimen given in all adults more than 10 years of age

Treatment In Children

- Children Less Than 10 Years of Age:
  - Cannot give Tenofovir (contraindicated due to rickets risk)
  - Replace Tenofovir with:
    - → Zidovudine, OR

→ Abacavir

- Children Less Than 6 Years of Age:
  - Dolutegravir should be avoided
  - Reason: Can cause Stevens-Johnson syndrome
  - Replace Dolutegravir with:
    → Lopinavir + Ritonavir combination (Boosted protease inhibitor)

Post-Exposure Prophylaxis (Pep)

- For Healthcare Workers
  - Indications:
    → Healthcare workers (doctors, nurses) at risk of needlestick injury from HIV positive people
  - Protocol:
    → Must be started within 2 hours
    → Duration: One month (28 days)
  - Drug Regimen:
    → Same 3 drug combination = TLD combination

Pre-Exposure Prophylaxis (Prep)

- High Risk Groups (Target Population)
  - IV drug abusers
  - Commercial sex workers
  - Men having sex with men
- Purpose:
  - Given to high risk groups to prevent HIV acquisition
- Drug Regimens for PrEP:
  - Standard Oral Regimen (Drug of Choice):
    → Tenofovir + Emtricitabine combination
  - Alternative Oral Regimens:
    → Tenofovir + Lamivudine combination (daily oral)
- Injectable Options:
  - CABOTEGRAVIR (Integrase inhibitor)
    → Given as injection once in 2 months
  - LENACAPAVIR
    → Given as 6 monthly injections for pre-exposure prophylaxis

Neonatal Prophylaxis

- Background:
  - Newborn born from HIV positive mother
  - May acquire HIV from breast milk
  - Important: Breastfeeding must be continued
  - Assess whether neonate is at low risk or high risk

Low risk infants Mother HIV virus after 32 weeks < 1000 copies	Nevirapine syrup	6 weeks

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High risk infants Mother HIV virus after 32 weeks > 1000 copies	Nevirapine + Zidovudine	6 weeks (if formula feed) 12 weeks (if breast feed)

Hepatitis B Virus Treatment

01:07:45

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- First Line Drugs (DOC): Oral Reverse Transcriptase Inhibitors:
  - TENOFOVIR
  - ENTECAVIR
- Second Line Drug:
  - LAMIVUDINE
  - Reason for being second line: Resistance is now common against lamivudine

Hepatitis C Virus Treatment

01:08:30

- Current DOC: NS INHIBITORS (Non-Structural Protein Inhibitors)
- Second Line Drug:
  - RIBAVIRIN (now resistance is common)

Types of ns inhibitors in HCV:

NS3/4A INHIBITORS Suffix "-previr"	NS5A INHIBITORS Suffix "-asvir"	S5B INHIBITORS Suffix "-buvir"
• Simeprevir • Boceprevir • Grazoprevir • Paritaprevir • Voxilaprevir	• Ledipasvir • Ombitapasvir • Velpatasvir • Elbasvir • Daclatasvir	• Sofosbuvir

- Sofosbuvir + Velpatasvir (oral)
  - Important: Almost 100% cure for HCV virus
- Common Drug for Hepatitis B and C:
  - INTERFERON ALPHA - Given by injection

Important Information

- INTERFERON BETA: Given in autoimmune disease: Multiple Sclerosis
- INTERFERON ALPHA: Given as an antiviral drug

Common Antiviral Drugs Across Viruses

- Common Drugs for HIV and Hepatitis B: Tenofovir & Lamivudine
- Common Drug for Hepatitis C and Hepatitis B: Interferon Alpha
- Common Drug for Hepatitis C and Respiratory Syncytial Virus: Ribavirin

Respiratory Syncytial Virus (RSV)

01:10:55

- Bronchiolitis obliterans
  - Asthma-like disease
  - Occurs in premature neonate

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- Treatment:
  - Drug: RIBAVIRIN
  - Route of administration: Aerosols
- Prevention in High Risk Neonates:
  - Indication:
    → Premature neonates at high risk of acquiring RSV virus
  - Drug: PALIVIZUMAB
    → Monoclonal antibody against respiratory syncytial virus
    → Given for prevention of RSV virus

Influenza Virus

- Types of Influenza:
  - Swine flu: H1N1 influenza
  - Avian flu: H5N1 influenza

M2 PROTON INHIBITORS	NEURAMINIDASE INHIBITORS (DOC)
• Mechanism: Inhibit entry of virus into human cell • Identification Pattern: • Suffix "-antadine" • Amantadine & Rimantadine • Amantadine - Given in Parkinson's disease	• Mechanism: Inhibit exit or release of virus • Identification Pattern: Suffix "-mivir" • OSELTAMIVIR (Oral drug) • ZANAMIVIR (Nasal drug - Given by nasal spray) • PERAMIVIR (Parenteral drug - Given by injection)

Herpes Group of Viruses

01:13:15

- Types of Herpes Viruses:
  - HSV-1 (Herpes Simplex Virus 1)
  - HSV-2 (Herpes Simplex Virus 2)
  - VZV (Varicella Zoster Virus) →: Chickenpox and Shingles

- Drug of Choice: ACYCLOVIR
  - Not effective for: Cytomegalovirus (CMV) → DOC - Ganciclovir
- Drugs for resistant cases: FOSCARNET > CIDOFOVIR
- Cidofovir
  - Also DOC for other DNA virus
  - Also DOC for Papilloma virus
- CONGENERS OF ACYCLOVIR:
  - From acyclovir → Valacyclovir, Penciclovir, Famciclovir
  - Used in same conditions
  - Side effect: Nephrotoxic drugs
- CONGENERS OF ACYCLOVIR → Valganciclovir
  - Ganciclovir - injection/ Valganciclovir - orally
- Main Side Effect of Ganciclovir:
  - Myelotoxic (causes bone marrow suppression)

Special route for ganciclovir:

- Intravitreal injection
- Indication: CMV retinitis

- Especially in HIV positive/ Immunocompromised people
- Treatment: Ganciclovir intravitreal injection

Bell's Palsy Treatment

- Primary Aim: Protection of nerve by reducing inflammation
- DOC: PREDNISOLONE (overall drug of choice)
- After Protection: Can add Acyclovir-like drug to kill virus

ANTI-PROTOZOAL DRUGS

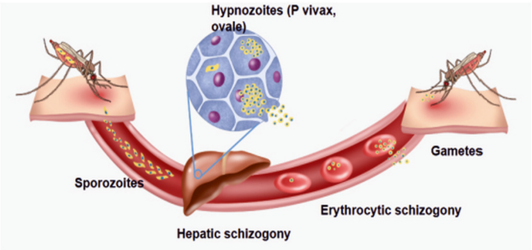
01:16:18

Malaria

- Causative Organisms: 5 Plasmodium Species:
  - P. falciparum; vivax; ovale; malariae; knowlesi
- In India:
  - More than 50% cases caused by P. falciparum
  - P. vivax and P. ovale also seen
- Transmission:
- Vector: Female Anopheles mosquito
- Guidelines: NVBDCP (National Vector Borne Disease Control Program)

Malaria Life Cycle and Stages

- Life Cycle:
  - Mosquito Bite → Human:
    → Infective stage = Sporozoite stage
  - Liver Stage:
    → Sporozoites come to liver and divide
    → Known as Hepatic Schizogony
  - Blood Stage:
    → From liver → come into blood
    → Known as Erythrocytic Schizogony
    → When RBCs get damaged → Clinical symptoms of malaria appear
  - Sexual Stage:
    → Some erythrocytic schizonts → converted into gametes
  - Mosquito Stage:
    → Infective stage to mosquito = Gametes
    → Fertilization happens in mosquito



- In P. falciparum:
  - 100% conversion into erythrocytic schizogony
  - No hypnozoite stage
- In P. vivax and P. ovale:
  - Some sporozoites become dormant → Hypnozoite stage

Types of Malaria Cure

- Causal prophylaxis: Kill hepatic schizogony
- Clinical cure: Kill erythrocytic schizogony (clinical symptoms appear when they enter RBC)

- Prevention of transmission: Kill gametes
- Radical cure: Kill hypnozoites

Antimalarial Drugs By Stage

- Drug to Kill Hepatic Schizogony (Causal Prophylaxis):PRIMAQUINE
- Drug to Kill Hypnozoites (Radical Cure):PRIMAQUINE
- Drug to Kill Gametes (Prevent Transmission):PRIMAQUINE
- Clinical Cure Drugs: All drugs except Primaquine
    - Can give: Chloroquine OR ACT therapy
- New Drug for Radical Cure: TAFENOQUINE
    - New drug similar to primaquine
    - Provides radical cure (kills hypnozoites)

Malaria Treatment Protocols

Uncomplicated Malaria - P. VIVAX AND P. OVALE

- Chloroquine → Clinical cure → Kills erythrocytic schizogony
    - Duration: 3 days
- Primaquine → Radical cure → Kills hypnozoites
    - Duration: 14 days
- Purpose of Radical Cure: Prevents relapse of malaria
    - If hypnozooids activate → can lead to relapse

Uncomplicated Malaria - P. FALCIPARUM

- Characteristic:
    - P. falciparum is chloroquine resistant in India
- Treatment:
    - A. ACT (Artemisinin-based Combination Therapy) → for clinical cure x 3 days
    - B. PRIMAQUINE
      → Only given as gametocidal drug to kill gametes
      → Given as single dose on day one
    - Important Note:
      → Do Not require radical cure in P. falciparum → no hypnozoite stage

ACT Regimens by Location:

- ALL STATES OF INDIA:
    - ASP Regimen:
      → AS = Artesunate (type of artemisinin)
      → P = Sulfadoxine + Pyrimethamine combination
    - Dosing:
      → Artesunate: 3 days
      → Sulfadoxine + Pyrimethamine: Single dose on day one
- NORTHEASTERN STATES OF INDIA:
    - AL Regimen:
    - A = Artemether

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  - L = Lumefantrine combination
- With: Primaquine as gametocidal drug (single dose on day two)

Complicated Malaria

- Patient w/ emergency symptoms (High fever, Cerebral malaria, Kidney damage)
- Treatment: DOC: IV ARTESUNATE
  - Seen in cases of P. falciparum

Malaria In Pregnancy

- Primaquine is absolutely contraindicated
- Treatment of P. vivax and P. ovale in pregnancy: Only give: Chloroquine

Treatment of P. FALCIPARUM in Pregnancy:

- First trimester: Quinine + Clindamycin combination
- Second and Third trimester: Artemisinin-based combination therapy (All states of India except Northeastern States)

Complicated malaria in pregnancy:

- Treatment: ARTESUNATE
  - Given in all trimesters of pregnancy in complicated malaria
- Artesunate should be avoided in uncomplicated malaria
- Contraindicated in first trimester of pregnancy

Traveler's Prophylaxis

Non-endemic country:

- Malaria is not very rampant (Examples: Arab countries, Gulf countries)
- Drug: Chloroquine
- Dose: 600 mg weekly (one dose per week)

Endemic country:

- Malaria is common (Examples: Southeast Asia region, India, Pakistan, Thailand)
- Endemic countries → (+) Chloroquine resistance
- Drugs:
  - Mefloquine -250 mg once a week (weekly)
  - Doxycycline - 100 mg daily
- All these drugs must be taken for another 4 weeks after coming back to home country

Gametocidal Drug

- Drug: PRIMAQUINE
  - Kills gametes of all species of plasmodia
  - Prevents transmission of malaria
- Primaquine is not effective in killing erythrocytic schizogony
  - Not given for clinical cure of malaria

Chloroquine

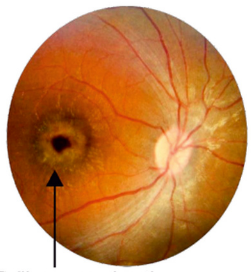
- Highest VD: More than 15,000 liters of plasma → Chloroquine gets deposited in all organs
- Side effects of chloroquine occur in all organs
- Additional Property: Immunosuppressive action → Chloroquine also given in autoimmune diseases

Uses of chloroquine - mnemonic "malarias"

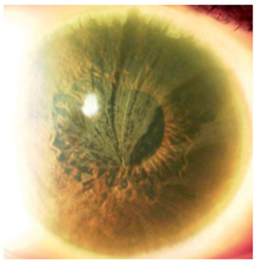
- M = Malaria
- A = Amoebic liver abscess (to control inflammation)
- L = Lepra reaction
- A = Autoimmune hemolytic anemia (very important)
- R = Rheumatoid arthritis (to reduce inflammation)
- I = Idiopathic thrombocytopenic purpura
- A= Atopic dermatitis or photodermatitis
- S = SLE (autoimmune disease)
- Rule: Any autoimmune disease → can give chloroquine

Side effects of chloroquine:

- Brain: Seizures, Psychosis
- Eye: Retina - bull's eye retinopathy:
  - Chloroquine deposits like concentric rings/targets in retina
  - Pattern looks like a target (Shooting Board/ Bull's Eye)
    → Permanent blindness
  - Cornea - Vortex keratopathy:
    → Chloroquine deposits like a flower on cornea
    → Also seen with anti-arrhythmic drug: Amiodarone
- Ear: Tinnitus & Deafness
- Heart: QT prolongation



Bull's eye maculopathy



Comparative Toxicity Of Antimalarials

- Maximum CNS Side Effects: Mefloquine (seizures and psychosis)
  - Contraindicated in cerebral malaria
- Maximum Ear Damage (Ototoxicity): Quinine (Tinnitus & Deafness)
  - Ototoxicity due to quinine is known as Cinchonism (obtained from Cinchona plant)
- Maximum QT Prolongation: Quinine & Lumefantrine
- To Avoid in G6PD Deficiency: Quinine, Primaquine
  - Can lead to hemolysis in G6PD deficient patients
- Safe in G6PD Deficiency: Mefloquine

Artemisinin Group

- Source: Plant: Artemisia annua
- Most Effective and Fastest Acting Drug for Malaria
- Important Contraindication: Never given for prophylaxis of malaria
  - In prophylaxis, can lead to development of resistance
- Examples: (prefix "ART"): Artesunate; Artemether; Arteether; Artemol
- Metabolism: Degraded by CYP3A4 enzyme
- Main Side Effect: Allergic reaction

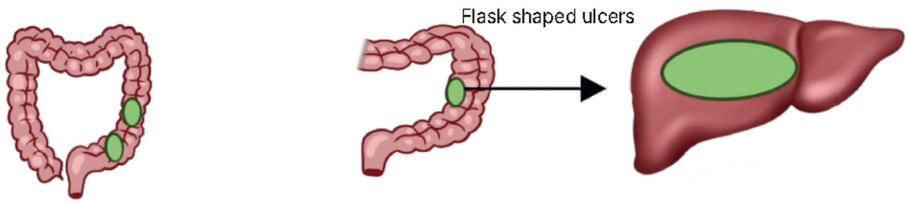
Quinine

- Source: Cinchona bark tree
- Side Effects: Cinchonism
    - Ototoxicity
    - Hypoglycemia (Given in 5% dextrose solution to prevent hypoglycemia)

AMEBIASIS

- Causative Organism: Entamoeba histolytica
- Transmission: Food poisoning/ Oro-fecal route (unhygienic food)

Life cycle and stages:



Luminal amebicides
- Paromomycin
- Diloxanide furoate
- Quinodochlor
- Iodoquinol

Amoebic dysentery
Metronidazole and Similar

Amoebic liver abscess
Metronidazole
+
Chloroquine

- LUMINAL AMEBIASIS: Cyst of Entamoeba histolytica comes to lumen of intestine → Asymptomatic stage
- AMOEBIC DYSENTERY: → Cyst converts into trophozoite → Trophozoite damages wall of intestine → Can lead to flask-shaped ulcer → Bleeding starts
- AMOEBIC LIVER ABSCESS: From intestine → reaches liver → leads to amoebic liver abscess

Treatment:

- Amoebic Dysentery and Amoebic Liver Abscess:
    - DOC: Metronidazole (Ornidazole, Tinidazole)
- Amoebic Liver Abscess Specifically: Chloroquine + Metronidazole

Luminal amebicidal drugs:

- Purpose: Kill the cyst stage
- Paromomycin (DOC)
- Diloxanide Furoate: (Commonly used)
- Rarely used: Quinidochlor / Iodoquinol
- Side effect of Quinidochlor: SMON = Subacute Myelo-Optic Neuritis

KALA AZAR (VISCERAL LEISHMANIASIS)

01:33:42

- Causative Organism:Leishmania donovani (aka Visceral Leishmaniasis)
- Diagnosis:
    - RK39 Rapid Diagnostic Kit (Developed in India)
- Epidemiology: Highly prevalent/endemic disease - North part of India
- Treatment - Memonic "LAMPAS"
    - Efficacy Order (L to S = Most to Least Effective):

→ L = LIPOSOMAL AMPHOTERICIN B (Drug of Choice - Most Effective)
→ A = Amphotericin B (older preparation)
→ M = Miltefosine
→ P = Paromomycin
→ A = Amphotericin B (older preparation)
→ S = Sodium Stibogluconate (Least Preferred - Resistance developing)

- Only Oral Drug in Kala Azar: Miltefosine
- All other drugs given by injection
- Dosing:
  - Liposomal Amphotericin B: 10 mg/kg IV single dose
  - Sodium Stibogluconate: 20 mg/kg by injection for one month
- Drug of Choice in Pregnancy and Children: Liposomal Amphotericin B
- Absolutely Contraindicated: Miltefosine
- Antimonial Drug: Sodium Stibogluconate (contains antimony metal → kills Kala Azar)

Skin manifestation of kala azar:

- PKDL = Post-Kala Azar Dermal Leishmaniasis
- Not a dangerous condition
- DOC: Oral Miltefosine

Trypanosomiasis

01:36:19

- Two Diseases Caused by Trypanosoma:
  - Sleeping sickness (African type)
  - Chagas disease (South American type)

Sleeping sickness: African type	Chagas disease:	
West African type	East African type	South American type
Trypanosoma brucei gambiense	Trypanosoma brucei rhodesiense	Trypanosoma cruzi
• Early stage (blood) -Pentamidine	Suramin	
		DOC: Benznidazole
• Late stage (CNS-coma) - Eflornithine + Nifurtimox	Melarsoprol	

- Fexinidazole - New drug that can kill both stages of West African type of trypanosomiasis

PNEUMOCYSTIS JIROVECII INFECTION

01:39:00

- Clinical Presentation:
  - Causes pneumonia
  - Opportunistic infection in HIV people → occurs when CD4 count falls less than 200
- Prophylaxis and treatment:
  - Indication for prophylaxis → patient with CD4 count less than 200
  - DOC (Both Prevention and Treatment): Cotrimoxazole
- Resistant cases:
  - Alternative Drug: PENTAMIDINE (aerosols/ IV)

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12. ANTI-CANCER DRUGS AND IMMUNOMODULATORS

CYTOTOXIC DRUGS

00:00:37

- Kill rapidly dividing cells → cancer + normal cells → highly toxic drugs
- Common toxicities (Mnemonic: Bharat Mata)
  - Bone marrow suppression
  - Mucosal ulceration (GIT)
  - Alopecia
  - Teratogenicity
  - Azoospermia/anovulation (Infertility)

Bone Marrow Suppression

- Seen with all cytotoxic drugs except (Mnemonic: VBC)
  - Vincristine
  - Bleomycin
  - Chlorambucil
- Effects of bone marrow suppression
  - ↓RBC → anemia → treat with Erythropoietin
  - ↓WBC → neutropenia → treat with Filgrastim
    → Filgrastim = G-CSF (granulocyte colony-stimulating factor)
  - ↓Platelets → thrombocytopenia → treat with oprelvekin
    → Oprelvekin = IL-11 analog
  - All given by injection

Mucosal Toxicity

- Causes severe diarrhea
- Treatment → Palifermin
- Palifermin is a Keratinocyte growth factor → regenerates the GIT mucosa

Tumor Lysis Syndrome

- Due to tumor cell destruction → intracellular contents are released
- DNA → uric acid → Gout
- ↑potassium → hyperkalemia
- ↑phosphate → hyperphosphatemia
- ↓calcium → hypocalcemia (phosphate binds calcium)
- Management of tumor lysis syndrome
  - Hyperuricemia → Allopurinol
  - Resistant → Rasburicase, Pegloticase
  - Hypocalcemia → calcium supplementation
  - Hyperkalemia + hyperphosphatemia → hemodialysis
  - Hyperkalemia → risk of arrhythmia

Classification of Cytotoxic Drugs

- Based on the cell cycle
  - Cell cycle non-specific (CCNS) → act in all phases
  - Cell cycle specific → act in specific phase

CELL CYCLE NON-SPECIFIC DRUGS	CELL CYCLE SPECIFIC DRUGS
• Types ○ Alkylating agents ○ Platinum compounds • Mechanism ○ Direct DNA damage → DNA present in all phases → CCNS • Platinum drugs ○ Cisplatin ○ Carboplatin ○ Oxaliplatin	• **M phase (mitosis)** ○ Microtubule inhibitors → Vincristine, Paclitaxel • **G2 phase** (Mnemonic: BED) ○ Bleomycin, Etoposide, Doxorubicin • **G1 phase** ○ Palbociclib ○ CDK 4/6 inhibitor → blocks G1 → S transition • **S phase** (Mnemonic: HATE) ○ Hydroxyurea ○ Antimetabolites → Methotrexate, 5-FU ○ Topoisomerase inhibitors → Topotecan, Etoposide

Alkylating Agents

00:08:50

- Cell cycle non-specific
- MOA: Donate alkyl group → Binds N7 guanine → DNA damage
- Drugs
  - Mechlorethamine
  - Dacarbazine
  - Procarbazine
  - Melphalan

Mechlorethamine & Dacarbazine

- Used in Hodgkin's lymphoma
- T/t Regimen for Hodgkin's lymphoma
  - Drug of choice → ABVD

MOPP	ABVD
• Mechlorethamine • Oncovin (vincristine) • Procarbazine • Prednisolone	• Adriamycin • Bleomycin • Vinblastine • Dacarbazine

Procarbazine

- Adverse effects
  - Azoospermia → infertility
  - Depression
  - Disulfiram-like reaction with alcohol

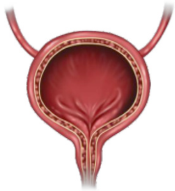
Melphalan
- Use → Multiple myeloma

Cyclophosphamide

INICET 2022

Uses	• Non-Hodgkin lymphoma → R-CHOP regimen
	  ○ Rituximab
	  ○ Cyclophosphamide
	  ○ Hydroxy Daunorubicin
	  ○ Oncovin
	  ○ Prednisolone
	• CLL → FCR regimen
	  ○ Fludarabine + Cyclophosphamide + Rituximab
	• Burkitt lymphoma
	• Breast cancer
	• Autoimmune disease → Wegener granulomatosis (DOC)

Metabolism	• Liver → 4-hydroxycyclophosphamide → Aldophosphamide & Acrolein
	  ○ Aldophosphamide → active anticancer
	  ○ Acrolein → toxic

Toxicity	• Acrolein → hemorrhagic cystitis • Feature → painful hematuria 
Drugs causing hemorrhagic cystitis	• Cyclophosphamide • Ifosfamide

T/t of hemorrhagic cystitis	• Mesna (Removes acrolein)
	  ○ Oral → prevention
	  ○ IV → treatment

Chlorambucil And Busulfan

Chlorambucil	Busulfan

• Acts on peripheral lymphocytes
• Spares bone marrow
• Uses → CLL, ALL
• Does not cause bone marrow suppression
	• Acts on bone marrow (myelocytes)
	• Spares peripheral lymphocytes
	• Uses → CML, AML
	• Maximum risk of bone marrow suppression
	• Also causes Budd-Chiari-like syndrome
	  ○ Hepatic vein fibrosis → Venous occlusive disease of the liver
	  ○ Antidote → Defibrotide

Primary Brain Tumors

- Most common → Astrocytoma
- Dangerous → Malignant glioma
- Most dangerous → Glioblastoma multiforme
- Drug of choice for Astrocytoma → Temozolomide
  - Good blood-brain barrier penetration
- Resistant cases: Add drugs ending with "-mustine"
  - Carmustine
  - Lomustine
    → Side effect → delayed neutropenia
    → Prolonged bone marrow suppression even after stopping the drug

Platinum Compounds

FMGE 2022, 2023

- Cell cycle non-specific drugs
- Drugs → Cisplatin, Carboplatin, Oxaliplatin
- Most commonly used anticancer drugs
- Uses
  - Lung cancer (most common cancer) → DOC
  - Osteosarcoma
  - GIT cancers → esophagus, stomach, colorectal, anal
  - Head and neck cancers → oral, laryngeal
  - Urogenital cancers → testicular, cervical (DOC: Cisplatin)
  - Retinoblastoma → Carboplatin (DOC)
- Combination therapy
  - Platinum + 5-fluorouracil
  - Used in GIT + head and neck cancers
  - Reason → Radiosensitizers (Increase sensitivity to radiotherapy)

Side Effects Of Platinum

- Most emetogenic drug → Cisplatin
- Most Ototoxicity → Cisplatin
- Most Nephrotoxicity → Cisplatin
- Most Neurotoxicity → Oxaliplatin
- Least toxic → carboplatin
  - Least vomiting, nephrotoxicity, ototoxicity
- Nephrotoxicity management
  - Antidote → Amifostine (Nephroprotector)
  - Mannitol + Chloride diuresis: Enhances excretion

Radiosensitizers And Radioprotectors

Radiosensitizers	Radioprotector

• Cisplatin + 5-FU → GIT + head & neck cancers
• Gemcitabine → cancer
	• Amifostine
	  ○ Also nephroprotector
	  ○ Cannot cross BBB → not neuroprotector

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S Phase Drugs

- Inhibits DNA synthesis

Hydroxyurea

- Mechanism → inhibits ribonucleotide reductase
- Uses
  - Polycythemia vera (DOC)
  - Essential thrombocytosis
  - Myelofibrosis
  - Sickle cell disease (DOC)

Sickle Cell

- Mechanism in SCD
  - ↑ fetal Hb (α2γ2)
  - Compensates for β-chain defect
- Sickle cell additional drugs
  - Voxelotor → prevents Hb polymerization
  - Crizanlizumab
    → Anti-P-selectin monoclonal antibody
    → Prevents RBC adhesion → prevents vaso-occlusion

Antimetabolites

- Metabolites are fake substrates → inhibit DNA synthesis
- Antimetaolites
  - Folate analogues
  - Purine analogues
  - Pyrimidines analogues

1. Folate Analogs

- Drugs → Methotrexate, Pemetrexed, Pralatrexate, Trimetrexate
- Mechanism
  - Inhibit DHFR (dihydrofolate reductase)
  - ↓ tetrahydrofolate →↓ DNA synthesis
- Antidote for folate analog toxicity
  - Folinic acid (leucovorin)
  - Alternative → folic acid + vitamin B12
- Uses
  - Pemetrexed → Mesothelioma
  - Pralatrexate → Cutaneous T-cell lymphoma
  - Trimetrexate → Pneumocystis infection

Methotrexate

Category	Details
Drug of choice	• Choriocarcinoma →↑ beta-hCG

Uses in autoimmune disease	• Rheumatoid arthritis (DOC) • Psoriatic arthritis (Erthrodermic)
Toxicity	• Megaloblastic anemia (folate deficiency) • Hepatotoxicity • Pneumonitis
Monitoring	• CBC • Liver function test • Chest X-ray

Antidote to methotrexate toxicity	• Folinic acid (leucovorin rescue)
	• Additional treatments
	  ○ Glucarpidase- Degrades methotrexate directly
	  ○ Forced alkaline diuresis

- Folinic acid
  - Active form → Tetrahydrofolate
  - Also called → Leucovorin, Citrovorum factor
- Uses of folinic acid
  - With methotrexate → reduces toxicity
  - With 5-FU → increases the anticancer effect

2. Pyrimidine Analogs

FMGE 2020, 2023

Category	Details

5-Fluorouracil (5-FU)	• Fake uracil → pyrimidine analog
	• **Mechanism**
	  ○ Inhibits thymidylate synthase
	  ○ ↓ thymidine → DNA synthesis stops → cell death

Capecitabine	• Oral prodrug → converted to 5-FU

Uses	• 5-FU (IV) → GIT + head & neck cancers
	• 5-FU (topical)
	  ○ Mycosis fungoides
	  ○ Basal cell carcinoma
	• Capecitabine → breast cancer

Side effect	• Hand-foot syndrome
	  ○ Drug excreted in sweat → palms & soles damage
	  ○ More with capecitabine
	

Important Regimen

- Colorectal cancer regimen → FOLFOXIRI + bevacizumab
  - FOL → folinic acid
  - F → 5-FU
  - OX → oxaliplatin
  - IRI → irinotecan
  - Bevacizumab
    → Anti-VEGF monoclonal antibody
    → Inhibits angiogenesis

Other Pyrimidine Analogs

Category	Details
Cytarabine (cytosine arabinoside)	• Drug of choice → AML • Side effect → cerebellar toxicity ○ Ataxia, nystagmus, diplopia
Gemcitabine	• Drug of choice → Pancreatic cancer • Radiosensitizer
Azacitidine, Decitabine	• Hypomethylating agents • Inhibit DNA methylation • Uses → Myelodysplastic syndrome (MDS)

3. Purine Analogs NEET PG 2020

- 6-mercaptopurine, 6-thioguanine
  - Converted to fake nucleotides by the HGPRT enzyme
  - Inhibit DNA synthesis
- Lesch-Nyhan syndrome
  - HGPRT deficiency
  - Drugs ineffective
- Uses- Resistant lymphomas

Azathioprine

Category	Details
General	• Prodrug → converted to 6-mercaptopurine • Not anticancer → immunosuppressive drug
Uses	• Autoimmune diseases ○ Drug of choice → IBD (Crohn's, ulcerative colitis)
Metabolism	• Liver → Degraded by Xanthine oxidase • Cells → Degraded by TPMT (thiopurine methyltransferase)
Drug interaction	• Allopurinol inhibits xanthine oxidase ○ ↑ toxicity of azathioprine/6-MP ○ Reduce dose by 75%

TPMT deficiency	• Causes severe bone marrow suppression • Requires genetic testing before use

Adenosine Analogs

- Fludarabine
  - Drug of choice → CLL
- Cladribine
  - Drug of choice → hairy cell leukemia
  - Also used in histiocytosis
- Pentostatin
  - Older drug → CLL, hairy cell leukemia
- Mechanism
  - Inhibit adenosine deaminase
  - ↑ adenosine → toxic to lymphocytes
- Causes severe immunodeficiency
  - Kill lymphocytes
  - Risk of pneumocystis infection
- Prophylaxis
  - Co-trimoxazole

Microtubule Inhibitors

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Category	Details
General	• Act on M-phase → inhibit mitosis
Types	• Vinca alkaloids → Vincristine, Vinblastine, Vinorelbine • Taxanes → Paclitaxel, Doxetaxel, Cabazitaxel
Mechanism	• Vinca → inhibits polymerization of microtubules • Taxanes → inhibit depolymerization

Side effect	• Common S/E: Neurotoxicity
	• Vincristine
	  ○ Most neurotoxic
	  ○ Causes
	  ○ Foot drop (peroneal nerve damage)
	  ○ SIADH (↑ ADH release)
	  ○ No bone marrow suppression
	• Vinblastine
	  ○ Causes bone marrow suppression
	• Taxanes
	  ○ Cause glove-stocking neuropathy

Other drugs	• Eribulin, Ixabepilone → breast cancer
	Estramustine → prostate cancer
	• Colchicine
	  ○ Microtubule inhibitor
	  ○ Use → acute gout
	  ○ Mechanism → inhibits WBC migration

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Topoisomerase Inhibitors

00:48:40

- Act on G2 and S phase
- Topoisomerase 1 inhibitors
  - Irinotecan
  - Topotecan
- Topoisomerase 2 inhibitors
  - Etoposide
  - Teniposide
- Irinotecan
  - Side effect → Severe diarrhea
  - Contraindications → Crigler-Najjar, Gilbert syndrome
  - Treatment of diarrhea → Loperamide

Important Information

- Topoisomerase 4 in bacteria is inhibited by Fluoroquinolones

Antitumor Antibiotics

00:50:20

- Derived from Streptomyces

Anthracyclines

Category	Details
Drugs	• Doxorubicin, Daunorubicin, Epirubicin, Idarubicin
Mechanism	• Topoisomerase II inhibition
Uses	• Breast cancer
Regimen → CAT	• C → Cyclophosphamide • A → Adriamycin (Doxorubicin) • T → Taxane
Side effect	• Cardiotoxicity → Dilated cardiomyopathy
Antidote for toxicity	• Dexrazoxane

Mitoxantrone

- MOA: Topoisomerase II inhibition
- Less cardiotoxic
- Use → Multiple sclerosis

Bleomycin

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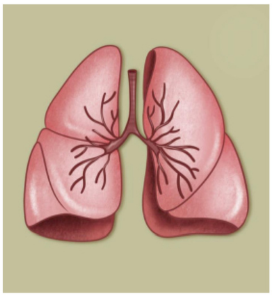
Category	Details
General	• G2 phase specific • Mechanism → Direct DNA damage
Uses	• Testicular cancer → BEP regimen • Hodgkin lymphoma → ABVD

Side effects	• Lung → Pulmonary fibrosis (Type 1 alveolar damage); increased risk with radiotherapy
	• Skin
	  ○ Flagellate pigmentation
	  ○ Hyperkeratosis (ichthyosis)
	  

Actinomycin D (Dactinomycin)

- Uses
  - Wilms tumor
  - Rhabdomyosarcoma

Mitomycin

- Use- Superficial bladder cancer → Intravesical injection
- Also used in Laryngotracheal fibrosis d/t antifibrotic property
- Side effect- HUS-TTP
- Alternative intravesical drug- BCG vaccine

Streptozotocin

- Mechanism → Destroys beta cells
- Use → Insulinoma

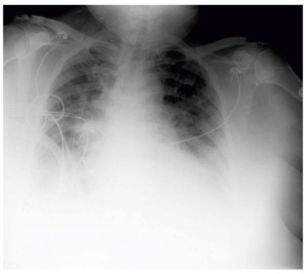
Miscellaneous anticancer drugs

00:58:55

Apml (acute promyelocytic leukemia)

Category	Details
Drug of choice	• All-trans retinoic acid (ATRA / Tretinoin)
Vitamin with anti-cancer property	• Vitamin A
ATRA-resistant cases	• Arsenic trioxide
Mechanism	• Differentiation inducer • Causes rapid maturation of tumor cells • Leads to spontaneous apoptosis

Side effects	• **ATRA**
	  ○ Leukocytic maturation syndrome
	  ○ Lung inflammation → Pleural effusion
	  ○ Prevention → Dexamethasone
	• **Arsenic trioxide**
	  ○ QT prolongation
	  ○ Mees lines (white nail lines)

Side effects	• **Arsenic trioxide** ○ QT prolongation ○ Mees lines (white nail lines)  

Enzyme Therapy

- L-asparaginase
  - Use → ALL
  - Side effect → pancreatitis

Cytotoxic Drugs Summary

Toxicity	Drugs/Antidote
SIADH	• Vincristine
Ototoxic drugs	• Cisplatin • Cyclophosphamide
Most emetogenic drugs	• Cisplatin
Hair cell damage	• Cytarabine
Pulmonary fibrosis	• Bleomycin
Cardiotoxicity	• Doxorubicin (rubicin drugs) ○ Antidote → Dexrazoxane
Veno-occlusive disease (liver)	• Busulfan ○ Antidote → Defibrotide
Nephrotoxicity	• Platinum drugs ○ Antidote →Amifostine
Hemorrhagic cystitis	• Cyclophosphamide, Ifosfamide ○ Antidote → Mesna
Hand-foot syndrome	• 5-FU, Capecitabine
Flagellate pigmentation	• Bleomycin

Important Regimens

Regimens of choice

FMGE 2020

Hodgkins lymphoma

ABVD
- Adriamycin
- Bleomycin
- Vinblastine
- Dacarbazine

MOPP
- Mechlorethamine
- Oncovin (vincristine)
- Procarbazine
- Prednisolone

Cladribine
- Histiocytosis
- Hairy cell leukemia

CLL

FCR
- Fludarabine
- Cyclophosphamide
- Rituximab

Non-Hodgkin's Lymphoma

R-CHOP
- Rituximab
- Cyclophosphamide
- Hydroxy daunorubicin
- Oncovin
- Prednisolone

AML

7C + 3D
- Cytarabine + Daunorubicin

ALL

VPAD M
- Vincristine
- Prednisolone
- Asparaginase
- Daunorubicin
- Methotrexate

Retinoblastoma

VEC
- Vincristine
- Etoposide
- Carboplatin

Breast cancer

CAT
- Cyclophosphamide
- Adriamycin
- Taxane

Colorectal cancer

FOLFOXIRI+ Bevacizumab
- Folinic acid
- 5-fu
- Oxaliplatin
- Irinotecan

APML

- ATRA
- Arsenic Trioxide

TYROSINE KINASE INHIBITORS (TKI)

01:05:32

- AKA Protein kinase inhibitors
- Mechanism- Blocks mutated receptor →↓ cancer growth
- Identification
  - Drugs end with "-nib"
  - Oral drugs
- Common side effects
  - Skin rash
  - Diarrhea

BCR-ABL TKI

Category	Details
Drugs	• Imatinib • Dasatinib • Nilotinib • Bosutinib • Ponatinib
Use	• CML → Drug of choice = Imatinib
Imatinib-resistant cases	• Nilotinib, Dasatinib
Side effect	• Pulmonary artery hypertension
Other use	• GIST (Imatinib, Sunitinib, Regorafenib)

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Other Tkis-

RENAL CELL CARCINOMA DRUGS	• Drugs
	  ○ Sorafenib
	  ○ Sunitinib
	  ○ Pazopanib
	  ○ Axitinib
	• Mechanism- VEGF inhibition → anti-angiogenesis
	• Additional uses
	  ○ Sorafenib → HCC
	  ○ Sunitinib → GIST

NON-SMALL CELL LUNG CANCER (NSCLC)	• EGFR inhibitors • Erlotinib (avoid with food) • Gefitinib (safe with food) • Osimertinib → T790M mutation, Afatinib ○ ALK inhibitors • Crizotinib, Ceritinib, Alectinib
BREAST CANCER TARGETED DRUGS	• Lapatinib (used in Trastuzumab-resistant cases) • Neratinib
MEDULLARY CARCINOMA OF THE THYROID	• Vandetanib

MALIGNANT MELANOMA	• BRAF inhibitors
	  ○ Vemurafenib, Dabrafenib
	• MEK inhibitors: Tremetinib, Cobemetenib
	  ○ Added in resistant cases

BTK INHIBITORS	• Drugs
	  ○ Ibrutinib
	  ○ Acalabrutinib
	  ○ Zanubrutinib
	• Uses
	  ○ CLL, SLL
	  ○ Mantle cell lymphoma
	  ○ Marginal cell lymphoma
	  ○ Waldenström macroglobulinemia

CDK (CYCLIN-DEPENDENT KINASE) INHIBITORS	• Drugs- Palbociclib, Riociclib, Abemaciclib • Mechanism- G1 phase arrest • Use- ER-positive breast cancer
PARP INHIBITORS	• Drugs- Olaparib, Rucaparib, Iniparib, Talazoparib • Use- BRCA positive breast/ovarian cancer • Mechanism- DNA repair inhibition

Epigenetic Drugs

- Histone deacetylase inhibitors
  - Remove acetyl group → inhibit DNA activation
  - Drugs end with "-stat"
  - Vorinostat → Cutaneous T-cell lymphoma
  - Belinostat → Peripheral T-cell lymphoma
  - Panobinostat → Multiple myeloma
- Histone methyltransferase inhibitors
  - Inhibit DNA methylation
  - Drug → Tazemetostat
  - Use → Epithelioid sarcoma

Proteasome Inhibitors

Category	Details
Mechanism	• Inhibit proteasome → DNA death
Identification	• Drugs end with "-zomib"
Drugs	• Bortezomib • Carfilzomib • Ixazomib
Use	• Drug of choice → Multiple myeloma
Side effect	• Herpes zoster infection
Multiple myeloma regimen	• Bortezomib + Thalidomide/Lenalidomide/Pomalidomide + Dexamethasone

Sonic Hedgehog Pathway Inhibitors

Category	Details
Mechanism	• Inhibit embryonic development pathway
Drugs	• Vismodegib • Sonidegib • Glasdegib
Use	• Basal cell carcinoma
Contraindication	• Pregnancy (teratogenic)

Nuclear Export Inhibitor

- Drug- Selinexor
- Use
  - Multiple myeloma
  - Diffuse large B-cell lymphoma

BCL-2 INHIBITORS

- Mechanism- Inhibit anti-apoptotic protein →↑ apoptosis

- Drugs
  - Venetoclax
  - Obinutoclax
- Use- CLL (with 17p deletion)

HIF INHIBITOR

Category	Details
Drug	• Belzutifan
Mechanism	• Inhibits hypoxia-inducible factor
Use	• Von Hippel-Lindau syndrome cancers ○ Increased risk of Renal cell carcinoma ○ Pheochromocytoma ○ Hemangioblastoma ○ Pancreatic lesions ○ Eye dysfunction ○ Liver, renal, and pancreatic cysts
Side effect	• Anemia (↓ erythropoietin)

CAR-T CELL THERAPY

- Mechanism: Modified T-cells with chimeric antigen receptor (Cd19)
- Use- CD19-positive lymphomas
- Drugs
  - Axicabtagene ciloleucel → DLBCL
  - Tisagenlecleucel → ALL
  - Brexucabtagene autoleucel → Lymphoma

Therapeutic Cancer Vaccine

Category	Details
Mechanism	• Modified immune cells directly kill cancer
Drug	• Sipuleucel-T ○ Target- Prostate acid phosphatase ○ Use- Advanced prostate cancer • Lifileucel- Used in Melanoma

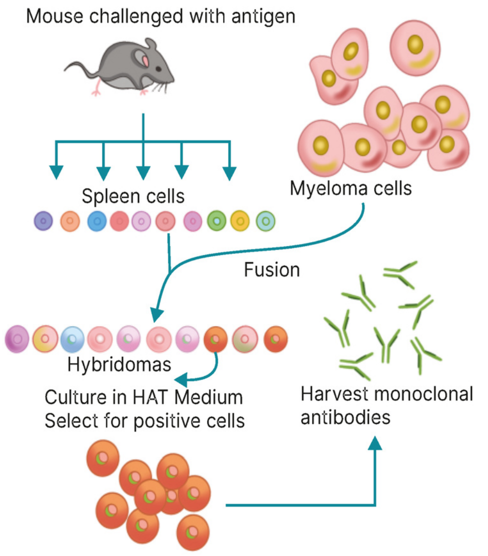
MONOCLONAL ANTIBODIES

01:22:00

FMGE 2021

- Production- Hybridoma technique
- Identification
  - Drugs end with "- mab"
- Types
  - -momab → Fully mouse

- -ximab → Chimeric
- -zumab → Humanized
- -umab → Hully human



Anti-Tumor Monoclonal Antibodies

INICET 2022, 2023, 2024

Drugs	Target	Primary Uses
Trastuzumab (cardiotoxic), Pertuzumab (cardiosafe & add-on drug)	HER2/neu	HER2+ breast cancer
Lapatinib	HER2/neu	Trastuzumab-resistant HER2+ breast cancer
Cetuximab, Panitumumab, Necitumumab	EGFR (HER1)	Colorectal cancer, NSCLC, head & neck cancer
Rituximab, Obinutuzumab	CD20 (B cells)	Re- Rheumatoid arthritis L- Lupus erythematosus I- ITP A- AIHA N- Non-Hodgkin lymphoma Ce- CLL
Alemtuzumab	CD52	CLL (resistant cases)
Daratumumab, Isatuximab	CD38	Multiple myeloma
Mogamulizumab	CCR4	Mycosis fungoides (Sezary syndrome)
Eculizumab, Ravulizumab	Complement C5	Paroxysmal nocturnal hemoglobinuria

Immune Checkpoint Inhibitors

INICET 2022

- Mechanism
  - Cancer cells produce PD-L1 → binds PD-1 on T-cell
  - Suppresses lymphocyte activity
  - CTLA-4 receptor also inhibits T-cell activity
  - Blocking these receptors → ↑ immunity → cancer cell death
- Side effect
  - Cytokine storm
  - Inflammation due to excessive immunity

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CTLA-4 inhibitors	Ipilimumab Tremelimumab	Melanoma Lung cancer Hodgkin lymphoma
PD-L1 inhibitors	Atezolizumab Avelumab Durvalumab	urothelial cancer Anaplastic thyroid cancer Non-small cell lung cancer Endometrial cancer
PD-1 receptor inhibitors	Nivolumab	Malignant melanoma Non-small cell lung cancer Hodgkin's lymphoma
	Pembrolizumab	Lung cancer (Keynote trial) Endometrial cancer Melanoma Breast cancer Renal cell carcinoma Esophageal and gastric cancer

Monoclonal Antibodies (Non-Cancer Uses)

Condition	Details

Psoriasis	• IL-17 inhibitors- Secukinumab, Ixekizumab
	  ○ Uses- Plaque psoriasis
	• IL-23 inhibitor- Tildrakizumab
	  ○ Uses- Plaque psoriasis
	• IL-12/23 inhibitor- Ustekinumab
	  ○ Uses- Plaque psoriasis, IBD

SLE	• Belimumab → Blocks BAFF • Anifrolumab → Blocks interferon
Hemophilia A	• Emicizumab ○ Mechanism → Acts on the factor VIII pathway
Type 1 diabetes	• Teplizumab ○ Blocks CD3 →↓ autoimmunity

Anti-Microbial Monoclonal Antibodies

01:35:00

- Viral
  - Palivizumab → RSV
- Toxin
  - Bezlotoxumab → Clostridium difficile toxin B
- Bacterial
  - Raxibacumab → Anthrax

Angiogenesis Inhibitors

- Mechanism
  - Inhibit VEGF → ↓ blood vessel formation

DRUGS

- Bevacizumab- Used in Cancer (colorectal, breast)
- Ramucirumab & Ranibizumab- Uses
  - Cancer (colorectal, breast)
  - Diabetic retinopathy
  - Age-related macular degeneration
  - Route (eye diseases)- Intravitreal injection
- Aptamer
  - Pegaptanib, Alfibercept
  - Blocks VEGF (not a monoclonal antibody)

Armed Monoclonal Antibodies

Category	Details
Definition	• Monoclonal antibody + toxin
Uses	• Advanced/refractory cancers
Drugs	• Brentuximab vedotin → Hodgkin lymphoma, Large B cell lymphoma • Gemtuzumab ozogamicin → Relapsed AML • Moxetumomab pasudotox → Hairy cell leukemia

IMMUNOSUPPRESSIVE DRUGS

01:39:23

- Uses
  - Autoimmune diseases
- Organ transplantation
- Mechanism pathway
  - Calcineurin → IL-2 → CD25 → mTOR → T-cell proliferation

Calcineurin Inhibitors

Category	Details
Drugs	• Cyclosporine • Tacrolimus
Mechanism	• ↓ IL-2 → ↓ T-cell activation
Binding proteins	• Cyclosporine → Cyclophilin • Tacrolimus → FK 506-binding protein
Uses	• Drug of choice → Organ transplantation
Side effects	• Nephrotoxicity • Hyperkalemia
Advantage	• No bone marrow suppression

Category	Details
CD25 (IL-2 RECEPTOR) BLOCKERS	• **Drugs** ○ Basiliximab ○ Daclizumab • **Mechanism** ○ Block IL-2 receptor → ↓ T-cell proliferation
mTOR INHIBITORS	• **Drugs** ○ Sirolimus ○ Everolimus • **Mechanism** ○ Inhibit T-cell proliferation
ANTIPROLIFERATIVE DRUG	• **Drug** ○ Mycophenolate mofetil • **Mechanism** ○ Inhibits IMP dehydrogenase ○ ↓ guanine synthesis → ↓ DNA synthesis
CD3 BLOCKER	• **Drug** ○ Muromonab • **Mechanism** ○ Blocks T-cell receptor →↓ immunity

Cyclosporine

INICET 2022

- Cosmetic side effects
  - Hypertrichosis (facial hair growth in females)
  - Gingival hyperplasia
- Hepatic effect
  - Cholestatic jaundice
  - Mechanism → inhibition of P-glycoprotein (MRP transporter)

Important Information

- Drugs causing Gingival hyperplasia (Mnemonic: PCC)
  - Phenytoin
  - Cyclosporine
  - Calcium channel blockers (Amlodipine)

Tacrolimus

- Structure
  - Macrolide antibiotic (similar to erythromycin)

Thalidomide

INICET 2023, 2025

Category	Details
Mechanism	• Inhibits cereblon protein ○ ↓ Interleukins (IL-2, IL-4, IL-6) ○ ↓ TNF-alpha ○ ↓ NK cell activity ○ Inhibits angiogenesis
Uses (Mnemonic: TOM)	• Type 2 lepra reaction (ENL) • Oral ulcers (Behcet disease) • Myelodysplastic syndrome • Multiple myeloma
Related drugs	• Lenalidomide • Pomalidomide
Side effects	• Neurotoxicity (permanent) • Constipation
Teratogenicity	• Category X drug • Causes phocomelia (short limbs) 
Enantiomers	• Form → sedative • S form → teratogenic ○ Enantiomeric conversion (R ⇄ S) ○ Both forms are contraindicated in pregnancy

IMMUNOSTIMULANTS

01:48:35

- Aldesleukin- Synthetic form of IL-2
- ↑ Immunity
- Uses
- Renal cell carcinoma
- Melanoma
- Levamisole
  - Anti-helminthic (Ascariasis)
  - Also immunostimulant
  - Use → Steroid-resistant nephrotic syndrome
- Imiquimod
  - Mechanism- Stimulates Toll-like receptors (TLR) → ↑ Interleukin production → ↑ NK cells
  - Uses- Condyloma (genital warts – HPV), Basal cell carcinoma
  - Route- Topical only

Immunostimulants In Pregnancy

- Contraindicated
  - ↑ Immunity can harm the fetus
- Condyloma in pregnancy
  - Treatment → Cryotherapy
  - Do NOT give imiquimod