PHARMACOLOGY & THERAPEUTICS SUPPLEMENTS

NISHTAR MEDICAL UNIVERSITY MULTAN

A L I R A Z A C H A U D A R Y (N 6 7)

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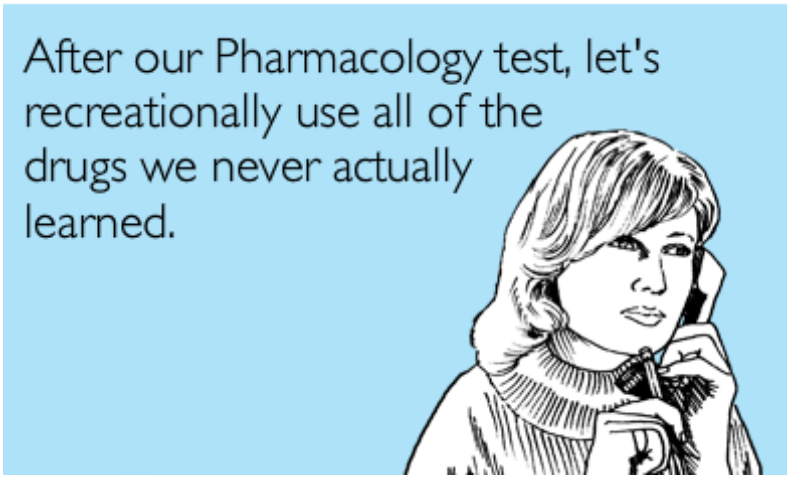

After our Pharmacology test, let's recreationally use all of the drugs we never actually learned.

REFERENCES

PHARMACOLOGY AND THERAPEUTICS

1. Katzung & Trevor's Pharmacology, Examination & Board Review, 12th Ed. (MINI KAZUNG)
2. Lippincott Illustrated Reviews: Pharmacolog, 6th Ed.
3. Basic and Clinical Pharmacology by Katzung, 14th Ed., Mc Graw-Hill (BIG KATZUNG)
4. Kaplan USMLE Step 1 Video & Lecture Notes 2020: Pharmacology

CONTENTS

1

GENERAL PHARMACOLOGY

1 SEQ + 5 MCQs = 12 Marks

PHARMACOKINETICS

(The actions of the body on the drug) OR (It is study of ADME)

Four pharmacokinetic properties determine the onset, intensity, and the duration of drug action:

1. **A**bsorption: Absorption from the site of administration permits entry of the drug (either directly or indirectly) into plasma.
2. **D**istribution: Drug may then reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids.
3. **M**etabolism/Biotransformation: Drug may be biotransformed by metabolism by the liver or other tissues.
4. **E**limination: Drug and its metabolites are eliminated from the body in urine, bile, tears, breast milk, saliva, sweat, or feces

ABSORPTION

(Absorption is the transfer of a drug from the site of administration to the site of action/bloodstream.)

MECHANISMS FOR PERMEATION OF DRUGS

FEATURE	PASSIVE TRANSPORT	FACILITATED TRANSPORT	ACTIVE TRANSPORT	ENDOCYTOSIS	EXOCYTOSIS
Definition	Movement of drug from region of higher to lower concentration	Movement of drug from region of higher to lower concentration by the help of carrier or channel protein	Energy requiring movement of substances across a plasma membrane.	Type of vesicle transport that moves substances into a cell.	Type of vesicle transport that moves substances out of a cell.
Incidence	Very Common	Less Common	Least Common	Least Common	Least Common
Process	Slow & Passive	Fast & Passive	Very Fast & Active	Very Fast & Active	Very Fast & Active
Relation with gradient	Along the gradient	Along the gradient	Against the gradient	Against the gradient	Against the gradient
Fick's Law	Applicable	Not applicable	Not applicable	Not applicable	Not applicable
Carrier	Not required	Required	Required	Required	Required
Energy	Not required	Not required	Required	Required	Required
Selectivity	No	Yes	Yes	Yes	Yes
Saturablity	No	Yes	Yes	Yes	Yes
Direction	Bidirectional	Bidirectional	Unidirectional	Unidirectional	Unidirectional
Metabolic Inhibition	No	Yes	Yes	Yes	Yes
Examples	Aqueous or lipid diffusion in capillaries	Ions, Neurotransmitters, Metabolites and Xenobiotics' transporters	Na/K ATPase pump	Vitamin B_{12}, Iron, Proteins	Neurotransmitters

FACTORS AFFECTING ABSORPTION OF DRUGS

LOCAL FACTORS (RELATED TO BODY)

Fick's Law

$$\text{Rate} = C_1 - C_2 \times \frac{\text{Permeability coefficient}}{\text{Thickness}} \times \text{Area}$$

1. **Area of Absorptive Surface (directly proportional)** e.g. intestine > stomach
2. **Contact time at the Absorption Site**
   - ↑GIT Motility → ↓Absorption
   - ↓GIT Motility → Delayed absorption
3. **Food/Other drugs** (Dilutes the drug and slows gastric emptying i.e delayed absorption)
4. **Blood Flow to Absorption Site (directly proportional)** (Intramuscular, Subcutaneous & GIT sites)
5. **Expression of P-glycoprotein (inversely proportional)** ("pumps" drugs out of the cells & provide multidrug resistance)
6. **Route of administration** (affects rate and efficacy of the absorption)
7. **Local pH**

PHARMACOLOGICAL FACTORS (RELATED TO DRUG)

1. **Solubility**

$$\text{Absorption} \propto \frac{1}{\text{Aqueous Solubility}} \propto \frac{1}{\text{ElectrostaticCharge (ionization \& } polarity)}$$

$$\text{Absorption} \propto \text{Lipid Solubility} \propto \frac{1}{\text{Charge}}$$

2. **Degree of Ionization (inversely proportional)** By Henderson-Hasselbalch Equation

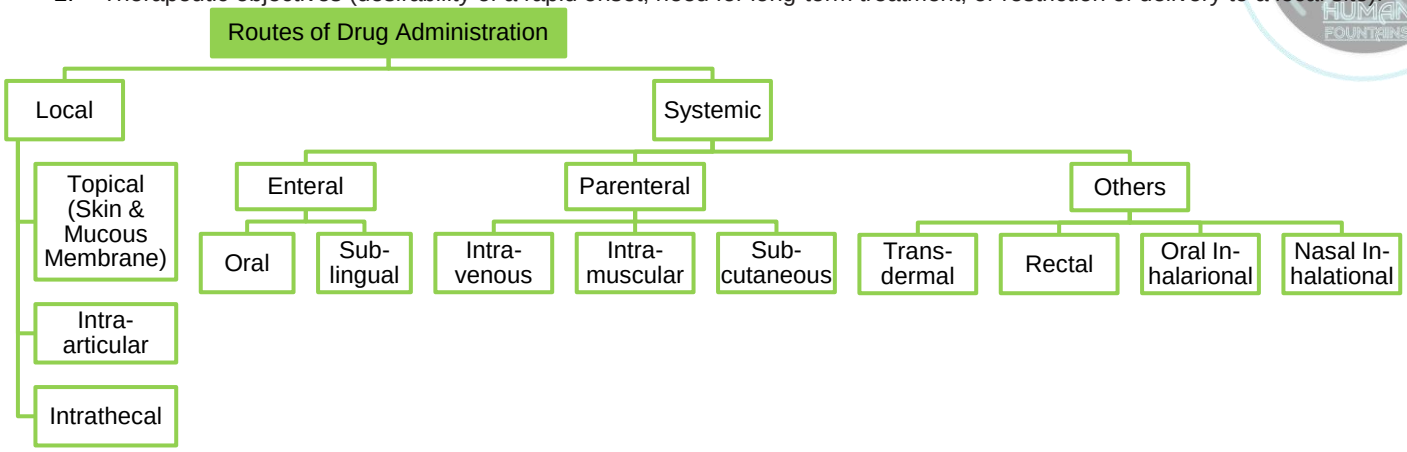
$$\log\left(\frac{\text{Pronated form}}{\text{Unpronated form}}\right) = pK_a - pH$$

3. **Nature of drug & pH of the medium** **(WHEN MEDIUM IS SAME, DRUGS CAN CROSS THE MEMBRANE)**
   - Acidic pH (e.g. Stomach):
     Weak acidic drugs become more unionized → More lipid soluble → More absorbable e.g. aspirin
     Weak basic drugs become more ionized → More aqueous soluble → Less absorbable e.g. amphetamine
   - Alkaline pH (e.g. Intestine):
     Weak basic drugs become more unionized → More lipid soluble → More absorbable
     Weak acidic drugs become more ionized → More aqueous soluble → Less absorbable
4. **Size (inversely proportional)** e.g. powder form is more absorbable
5. **Concentration at the site of administration** i.e. by Fick's Law

ROUTES OF ADMINISTRATION OF DRUGS

It is determined by

1. Properties of drug (solubility, ionization)
2. Therapeutic objectives (desirability of a rapid onset, need for long-term treatment, or restriction of delivery to a local site).



ROUTE	PATTERN	ADVANTAGES	DISADVANTAGES
LOCAL EFFECTS			
Topical	• Applied on skin or mucous membranes of eye, throat, ear, nose, airway or vagina • E.g. clotrimazole applied to skin for fungal infections.	• Low systemic effects • Steady level of drugs to the system	• Not well absorbed in deeper layers of skin
Intraarticular	• Introduce drugs in to inflamed joint cavity directly • E.g. hydrocortisone	• Low systemic effects • Rapid delivery to the local tissue	• Difficult to hit joint surfaces • Difficult to calculate dose for joints • Irritate joints and cause infections • Painful procedure, expert is needed
Intrathecal/ ventricular	• Introduce drugs directly into the cerebrospinal fluid. For • E.g. amphotericin B is used in cryptococcal meningitis	• Low systemic effects • Bypasses BBB and BCB	• Painful procedure, expert is needed
SYSTEMIC EFFECTS			
ENTERAL ROUTE (through the mouth)			
Oral (by mouth)	• Variable; many factors **PREPARATIONS:** • Enteric-coated e.g. aspirin for protecting the stomach • Extended-release (ER/XR) e.g. morphine to prolong duration of action for drugs with small half lives	• Safest, most common, convenient, and economical route • Self administered • Toxicities overcome by antitodes e.g. activated charcoal	• Drugs may be metabolized before systemic absorption (first pass effect) • Limited absorption due to low GIT pH • Food may affect absorption • Patient compliance is necessary
Sublingual (under tongue) **OR Buccal** (between cheek and gum)	Depends on the drug: • Few drugs (for example, nitroglycerin) have rapid, direct systemic absorption • Most drugs erratically or incompletely absorbed	• Bypasses first-pass effect , • Absorb directly to systemic venous circulation • Bypasses destruction by GIT acid • Drug stability maintained because the pH of saliva relatively neutral • May cause immediate pharmacological effects	• Limited to certain types of drugs • Limited to drugs that can be taken in small doses • May lose part of the drug dose if swallowed
PARENTERAL ROUTE (other the mouth) **Usage:** • Drugs poorly absorbed from the GI tract (e.g. heparin) • Drugs unstable in GIT (e.g. insulin) • Unable to take oral medications (unconscious patients) • Require a rapid onset of action **Advantage:** highest bioavailability (not subject to first-pass metabolism or the harsh GI environment) **Disadvantage:** Irreversible and may cause pain, fear, local tissue damage, and infections			
Intravenous (25° angle)	• Absorption not required • 100% Bioavailability	• Can have immediate effects • Ideal if dosed in large volumes • Suitable for irritating substances and complex mixtures • Valuable in emergency situations • Dosage titration permissible • Ideal for high molecular weight proteins and peptide drugs	• Unsuitable for oily substances • Bolus injection may result in adverse effects like hemolysis and thrmobosis • Most substances must be slowly injected • No antitodes like activated charcoal • Strict aseptic techniques needed

Subcutaneous (45° angle)	Depends on drug diluents. **PREPARATIONS:** • Aqueous solution: prompt • Depot preparations: slow and sustained **EXAMPLES:** • Insulin • Heparin	• Suitable for slow-release drugs • Ideal for some poorly soluble suspensions • Less adverse effects like hemolysis and thrombosis as in IV bolus.	• Pain or necrosis if drug is irritating • Unsuitable for drugs administered in large volumes
Intramuscular (90° angle)	Depends on drug diluents. **PREPARATIONS:** • Aqueous solution: prompt • Depot preparations: slow and sustained (non-aqueous vehicle like polyethylene glycol) e.g. haloperidol & depot medroxyprogesterone	• Suitable if drug volume is moderate • Suitable for oily vehicles and certain irritating substances • Preferable to intravenous if patient must self-administer	• Affects certain lab tests (creatine kinase) • Can be painful • Can cause intramuscular hemorrhage (precluded during anticoagulation therapy)
OTHERS			
Transdermal (patch)	• Slow and sustained depending upon thickness of skin and lipid solubility at site of administration **EXAMPLES:** • Nitroglycerin • Scopolamine • Nicotine	• Bypasses the first-pass effect • Convenient and painless • Ideal for drugs that are lipophilic and have poor oral bioavailability • Ideal for drugs that are quickly eliminated from the body	• Some patients are allergic to patches, which can cause irritation • Drug must be highly lipophilic • May cause delayed delivery of drug to pharmacological site of action • Limited to drugs that can be taken in small daily doses
Rectal/ Suppository	• Erratic (unpredicatable) and variable	• Partially bypasses first-pass effect • Bypasses destruction by GIT acid • Ideal if drug causes vomiting • Ideal in patients who are vomiting, or comatose	• Drugs may irritate the rectal mucosa • Not a well-accepted route
Inhalation (Oral or Nasal)	• Systemic absorption may occur; this is not always desirable **EXAMPLES:** **Oral Inhalational** • Anesthesia • Albuterol • Fluticasone **Nasal Inhalational** • Oxymetazoline, • Mometasone • Desmopressin for diabetes insipidus.	• Absorption is rapid; can have immediate effects • Ideal for gases e.g. anesthesia • Effective for patients with respiratory problems • Dose can be titrated • Localized effect to target lungs: lower doses used compared to that with oral or parenteral e.g. bronchodilators & corticosteroids • Fewer systemic side effects	• Most addictive route (drug can enter the brain quickly) • Patient may have difficulty regulating dose • Some patients may have difficulty using inhalers

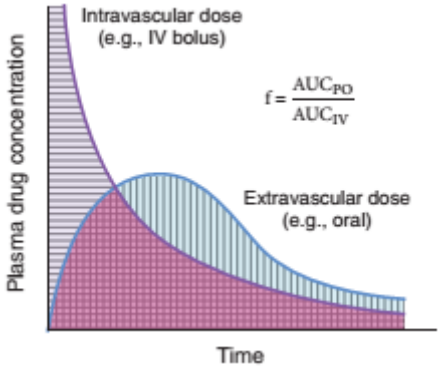
BIOAVAILABILITY (F)

(rate and extent to which an administered drug reaches the systemic circulation)

DETERMINATION

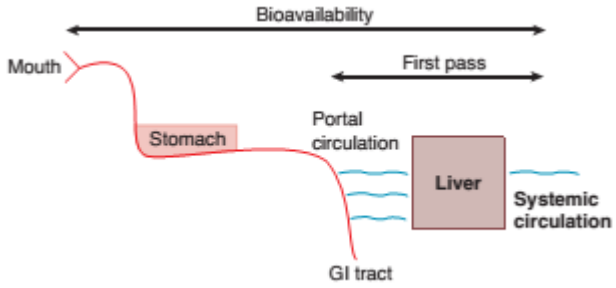
- Unity (100%) for IV administration.
- Important for calculating drug dosages for non-IV routes of administration.
- Determined by comparing;

$$\text{Bioavailability (F)} = \frac{\text{AUC}_{\text{Route}}}{\text{AUC}_{\text{IV}}} \times 100$$



FACTORS AFFECTING

1. **First-pass hepatic metabolism:**
   - When a drug is absorbed from GIT, it enters initially in portal circulation and rapidly metabolized in liver or gut wall and amount of unchanged drug entering the systemic circulation is decreased. Eg. nitroglycerin is primarily administered via sublingual or transdermal.
   - Results in lower systemic bioavailability of parent compound, diminished therapeutic response.
   - Drugs with high first-pass metabolism should be given in doses sufficient to ensure that enough active drug reaches desired site of action.



ORAL DOSE

- > Sublingual / Parenteral
- Marked individual variation
- ↑Oral F Liver disease or when in competition with other drug
- Short plasma $t_{1/2}$.

SITE

- Liver (major site)
- Gut wall & lumen

2. **Solubility of the drug:**
   - Hydrophilic → poorly absorbed in lipid bilayer membranes
   - Lipophilic → poorly absorbed in aqueous body fluids
   - For a drug to be readily absorbed, it must be largely lipophilic, yet have some solubility in aqueous solutions.
3. **Chemical instability:**
   - Penicillin G, unstable in pH of gastric contents.
   - Insulin, destroyed in GIT by degradative enzymes.
4. **Nature of the drug formulation:**
   - Particle size
   - Salt form
   - Crystal polymorphism
   - Enteric coatings
   - Presence of excipients (such as binders and dispersing agents)

EQUIVALENCE

FEATURE	BIOEQUIVALENCE	THERAPEUTIC EQUIVALENCE
Definition	Two drug formulations are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations.	Two drug formulations are therapeutically equivalent if they are pharmaceutically equivalent (that is, they have same dosage form, contain same active ingredient, and use same route of administration) with similar clinical and safety profiles.
Rate	Same	-
Bioavailability	Same	-
Clinical Effect	-	Same
Safety Profile	-	Same
Pharmaceutical Equal	✓	✓
Pharmaceutical Alternative	✓	×

DISTRIBUTION

(Process by which a drug reversibly leaves bloodstream and enters interstitium and tissues.)

For drugs administered IV, absorption is not a factor, and initial phase (from immediately after administration through rapid fall in concentration) represents distribution phase, during which drug rapidly leaves the circulation and enters the tissues.

C_{max} = maximal drug level obtained with the dose.

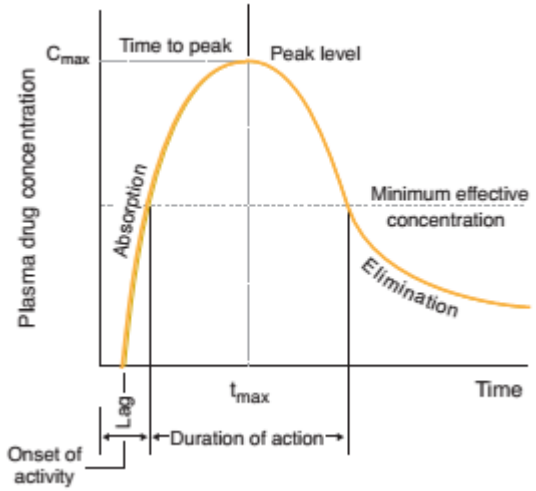
t_{max} = time at which C_{max} occurs.

Lag time = time from administration to appearance in blood.

Onset of activity = time from administration to blood level reaching minimal effective concentration (MEC).

Duration of action = time plasma concentration remains greater than MEC.

Time to peak = time from administration to C_{max}.



FACTORS AFFECTING DISTRIBUTION OF DRUGS

1. **Blood flow to capillaries** (Does not affect the amount of drug in the tissue at equilibrium)
   - Well-Perfused Tissues: Brain, Heart, Kidney, Splanchnic organs >>> Skeletal Muscles
   - Poorly-Perfused Tissues: Fat, Bone and other viscera
   - **Example:** IV bolus of propofol → High blood flow & high lipophilicity → Rapid distribution into CNS → Anesthesia → Hypnosis →Subsequent slower distribution to skeletal muscle & adipose tissue → Plasma conc. lowered → Diffuses out of CNS down gradient → Consciousness regained
2. **Capillary permeability** (determined by capillary structure i.e. fraction of basement membrane exposed by slit junctions between endothelial cells, and by chemical nature of drug)
   - Liver & Spleen: Discontinuous capillaries + Slit junctions
   - Brain: Continuous capillaries + Tight junctions (Lipid-soluble drugs readily penetrate CNS but ionized or polar drugs e.g. levodopa, fail to enter CNS as tight junction formed by endothelial cells of BBB and is actively transport mostly)
3. **Binding of drug** (directly proportional to drug distribution)
   - Binding to plasma proteins: Reversible binding and sequesters drugs in a non-diffusible form that slows their transfer out of the vascular compartment. **Example:** Warfarin is bound to Albumin.
     - ⇒ Acts as a drug reservoir
     - ⇒ Maintains free drug concentration in plasma.
   - Binding to tissue proteins: Accumulate drug in tissues by binding to lipids, proteins and nucleic acids, leading to higher concentrations in tissues than in extracellular fluid and blood. **Example:** acrolein accumulates in bladder cause hemorrhagic cystitis
     - ⇒ Acts as a drug reservoir
     - ⇒ Prolong its actions or cause local drug toxicity.
4. **Lipophilicity**
   - Lipophilic → rapidly absorbed in lipid bilayer membranes
   - Hydrophilic → poorly absorbed in lipid bilayer membranes and have to pass through slit junctions
5. **Size of organ** (influence concentration gradient between blood and organ)
   - Skeletal muscle > Blood: Take large amount of drug and have high blood-tissue gradient
   - Brain < Blood: Take small amount of drug and have low blood-tissue gradient smaller
6. **Pattern of drug distribution** (2 forms)
   - Bound form: Inactive, Non-diffusible, Cannot be metabolized or excreted by kidneys
   - Free form: Active, Diffusible, Can be metabolized or excreted by kidneys
7. **Apparent volume of distribution (V_d)**

EFFECTIVE DRUG CONCENTRATION

(Concentration of drug at the receptor site)

- Readily measured in blood
- Except for topical agents, it follows;

$$\text{Effective Drug Concentration} \propto \text{Concentration at receptor site} \propto \text{Concentration in Plasma/Blood at equilibrium}$$

FACTORS AFFECTING C_p or C_b

- Rate of input of drug by absorption
- Rate of distribution by V_d
- Rate of elimination by CL

APPARENT VOLUME OF DISTRIBUTION (V_d)

(Fluid volume that is required to contain entire drug in body at same conc. measured in plasma)

- Apparent V_d has no physical equivalence that's why it is called apparent.
- It relates the amount of drug in the body to the plasma (C_p) or blood (C_b) concentration at time zero as follow;

$$V_d = \frac{\text{Amount of drug in the body}}{\text{Plasma drug concentration}} = \frac{\text{Amount of drug in the body}}{C_p}$$

UNITS OF V_d

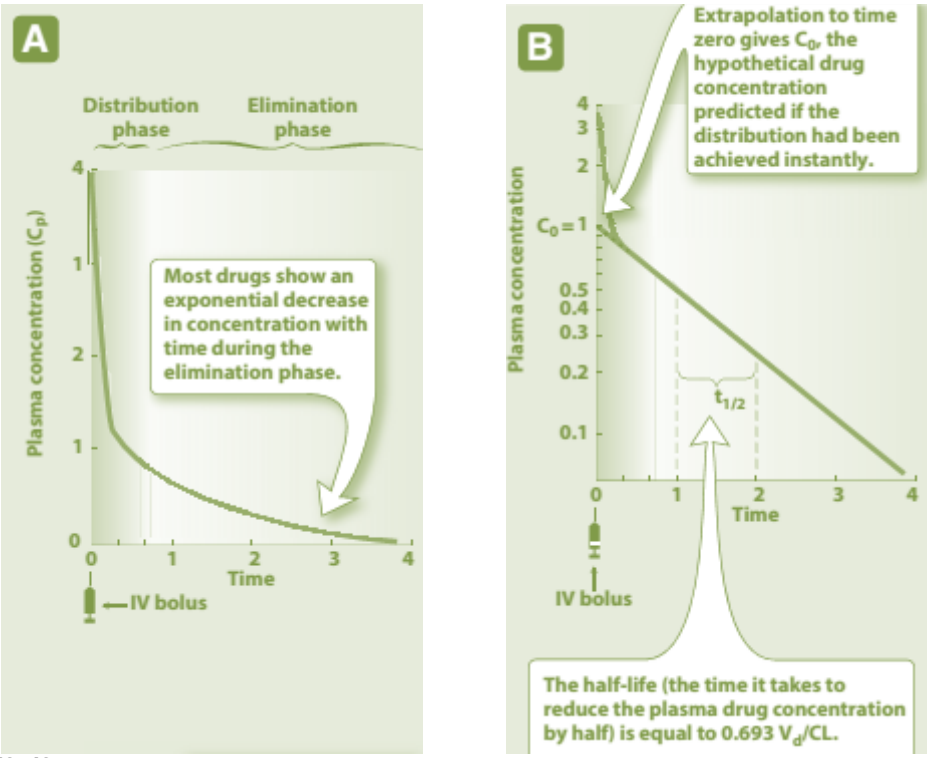
- Volume
- Volume/kg of body weight (if vary with body size)

ASPECTS

1. **Distribution into water compartments in body:** Once a drug enters the body, it distributes into any one of these or sequestered in a cellular site.

	PLASMA COMPARTMENT	EXTRACELLULAR FLUID	TOTAL BODY WATER
Model	One compartment	Two compartment	Multicompartment
Drug Features	HMW drug Extensively protein bound drug	LMW drug Hydrophilic	LMW drug Lypophilic
Crossing	Cannot cross slit junctions	Cross slit junctions but not lipid bilayers	Cross slit junctions and lipid bilayers
V_d Calculation	V_d = Plasma Volume = 4 L (4% of weight)	V_d = Plasma Volume + Interstitial fluid volume = ECF Volume = 14 L (20% of weight)	V_d = Total body water = 42 L (60% of weight)
V_d	Low	Moderate	High
Example	Heparin	Aminoglycoside	Ethanol

2. Determination:



3. Effect on Half Life:

Half life $\propto V_d \propto$ Duration of Action of Drug

METABOLISM/BIOTRANSFORMATION

(Chemical alteration of drug in body that converts non-polar or lipid soluble compounds to polar or lipid insoluble compounds)

Biotransformation
Biotransformation is required for protection of body from toxic metabolites.

SITES

- Primary Site: Liver
- Other Sites: Kidney, Intestine, Plasma, Lungs

EFFECTS

- Prodrug to Active Drug
  - ↑Stability, ↑Bioavailability, ↓Toxicity
  - Levodopa to Dopamine, Methldopa to MethylNE
- Active Drug to Inactive Drug
  - Propranolol, Morphine, Paracetamol
- Active Drug to Active Metabolite (Toxic Metabolism)
  - Phenacetin to Paracetamol, Digitoxin to Digoxin

ADVANTAGES

Terminate drug action
- ↓ Toxicity
- ↓ Lipophilicity
- ↑ Renal excretion
- ↑ Biliary excretion
- ↓ Renal reabsorption

TYPES OF BIOTRANSFORMATION

FEATURE	ENZYMATIC: MICROSOMAL	ENZYMATIC: NON-MICROSOMAL	NON-ENZYMATIC (Hoffman's Elimination)
Definition	Microsomal cytochrome P450, monooxygenase family of enzymes, which oxidize drugs.	Other than microsomal enzymes	Some drugs are metabolized through molecular rearrangement without involvement of enzymes from quaternary to tertiary structures.
Location	SER of Liver, Kidney, Intestinal and Lungs	Cytoplasm, mitochondria of Liver	Plasma
Examples	Catalyze 1. Oxidation, reduction, hydrolysis (phase I reactions) 2. Glucuronide conjugation (phase II reactions)	Monoamine oxidases (MAO), Esterases, Amidases, Transferases, Conjugates (All are phase 2 reactions)	Skeletal muscle relaxants (Atracurium and Cisatracurium)
Genetic polymorphs	Yes	May show	No
Inducers & Inhibitors	Yes	No	No

CYTOCHROME P450 SYSTEM/ MIXED FUNCTION OXIDASES

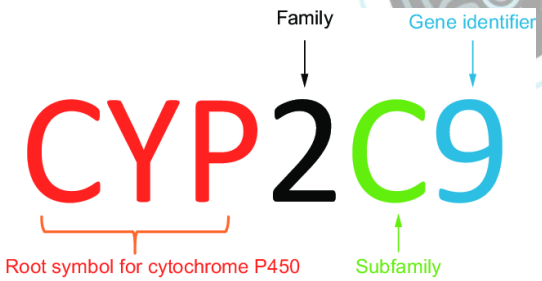
(Microsomal enzyme ranking first among Phase I enzymes with respect to catalytic versatility)

Heme-containing proteins [Complex formed between Fe^{2+} and CO absorbs light maximally at 450 nm (447-452 nm)]

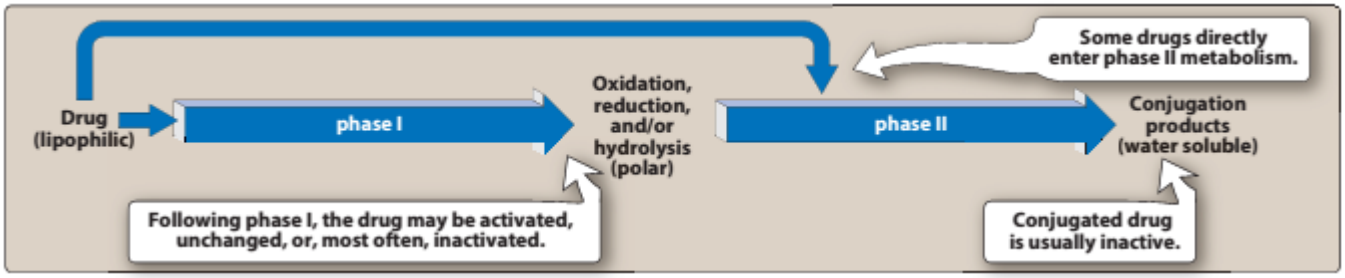
- **Substrate:** Drug that is metabolized by the enzyme system
- **Inducer:** Drug that increase synthesis and activity of enzyme system
- **Inhibitor:** Drug that decrease the metabolism of a substrate
- At least 15 P450 enzymes identified in human liver microsomes.

% of Drugs Metabolized by Enzyme System

- **3A4 & 5** **50%**
- **2D6** **25%**
- 1A2 15%
- 2C9 Small but significant interactions
- 2C19 Small but significant interactions
- 2E1 ?



TYPES OF METABOLIC REACTIONS



FEATURE	PHASE I REACTIONS	PHASE II REACTIONS
Definition	Reactions that convert the parent drug to a more polar (water-soluble) or more reactive product by unmasking or inserting a polar functional group such as -OH, -SH, or -NH_2	Reactions that increase water solubility by conjugation of the drug molecule with a polar moiety such as glucuronate, acetate, sulfate, glutathione, glycine, or methyl.
Other names	**Non synthetic / Functionalization** (A functional group is inserted)	**Synthetic / Conjugation** (An endogenous radical is conjugated)
Metabolite	Polar + Active, Inactive or Unchanged	Polar + Usually Inactive
Half life	Short	Long
Consequence	May result in metabolic activation	Facilitate Excretion (urine/ bile/ faeces)
Selectivity	Not much selective	Not much selective
Enzymes	Cytochrome P450 Enzymes mainly	Transferases mainly
True Detoxification reactions	No	Yes
Energy	Not required	Required
Examples	**1. Microsomal Oxidation (9 types)** • N-oxidation: **Chlorpheniramine** • S-oxidation: **Chloramphenicol** • O-Dealkylaton: **Phenacetin to Paracetamol** • N-Dealkylaton: **Theophylline** • S-Dealkylaton (Sulphur): **6-Methyl thiopurine** • Deamination: **Amphetamine** • Desulfuration: **Parathion to Paraoxon** • Aliphatic Hydroxylation: **Ibuprofen** • Aromatic Hydroxylation: **Propranolol** **2. Non-microsomal Oxidation** • Mitochondrial enzymes – (MAO **Adrenaline, 5-HT, Tyramine** • Cytoplasmic enzymes – (Dehydrogenases) **Alcohol to Acetaldehyde & Acetic Acid** • Plasma oxidative enzymes – (Histaminase) (Xanthine oxidase) **Allopurinol** **3. Microsomal Reduction** • N-reduction: **Chloramphenicol** • Keto-reduction: **Cortisone** **4. Microsomal Hydrolysis: Pethidine** **5. Non-Microsomal Hydrolysis** • Esters: **Aspirin** • Amides: **Indomethacin** **6. Cyclization: Proguanil** **7. Decyclization: Phenytoin, Barbiturates**	**1. Glucuronidation** (UDP glucuronyl transferase) • **Aspirin, Acetaminophen, Digoxin** **2. Acetylation** (N-Acetyl transferase) • **Isoniazid, Sulfonamids** **3. Glutathionation** (Glutathione S- Transferase) • **Ethacrynic Acid** **4. Acylation** (N-Acyl trasferase) • **Niacin, Salicylic Acid** **5. Sulfation** (Sulfotransferases) • **Acetaminophen** **6. Methylation** (Methyl transferase) • **Dopamine, Histamine** **7. Ribonucleotide or Ribonucleoside Synthesis** • **6 Mercaptopurine**

DETERMINANTS OF BIOTRANSFORMATION

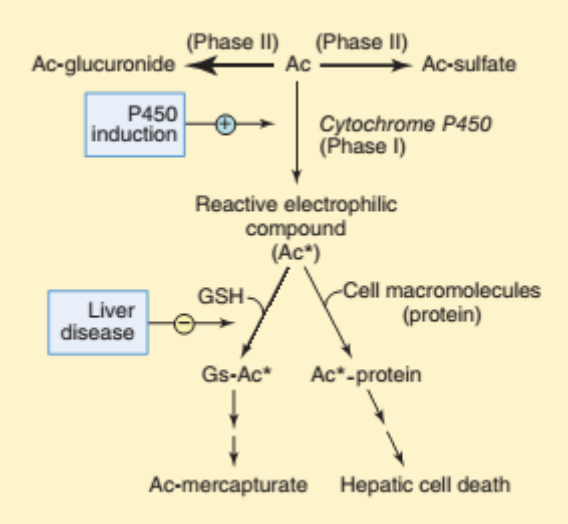
1. **Chemical Factors**
   - **Enzyme Induction** (increased synthesis and expression of SER containing CYP450 enzymes by drugs or other xenobiotic factors)
     Examples: Bull Shit SCRAP PG
     Barbiturates
     St. John's Wort
     Sulfonylureas
     Carbamazepine (auto-inducer)
     Rifampin (with contraceptives → ↓therapeutic effect of contraceptives→pregnancy)
     Alcohol (chornic)
     Phenobarbital
     Phenytoin
     Griseofulvin
   - **Enzyme Inhibition**
     Examples: SICKFACES.COM + AQ G
     Sodium Valporoate
     Isoniazid
     Cimetidine (Dcreases the metabolism of propanolol leading to enhanced bradycardia)
     Ketoconazole
     Fluconazole
     Alcohol
     Chloramphenicol
     Erythromycin
     Sulfonamides (Decrease the metabolism of phenytoin so that its blood levels become toxic)
     Ciprofloxacin
     Omeprazole
     Metronidazole
     Amidadrone
     Quinine
     Grape fruit juice
   - **Intestinal P-Glycoprotein (P-gp or MDR-1) Inhibitors** [An ATP-dependent transport molecule found in many epithelial (intestine, BBB) and cancer cells, that expels drug molecules from mucosa to lumen or from cytoplasm into extracellular space and contributes of first pass effect. Drugs include: Digoxin, Cyclosporine, Saquinavir]
     Examples: Verapamil (Calcium Channel Blocker) Furanocoumarin (Grape fruit juice component)
2. **Biological Factors**
   - **Age**
     Infants CYP450 system not fully developed → ↓Metabolism
     ⇒ Chloramphenicol: Grey baby syndrome
     ⇒ Diazepam: Floppy baby syndrome
     Elder patients' organs shrunken→↓Blood flow → ↓Metabolism
   - **Gender**
     Males BMR > Women BMR → ↑ Metabolism (Salicylates, Ethanol, Propanolol, Benzodiazepines)
     Womens on oral contraceptive → ↓ Metabolism
   - **Race (**Antimalarials & Isoniazid**)**
   - **Diet (**Deficiency of proteins, vitamins & Minerals → ↓Metabolism**)**
   - **Genetic Polymorphs (**Study of genetic factors affecting drug responses is called pharmacogenetics**)**

Type	Functional Element Defects or SNPs	Drugs Affected
Phase I Enzymes	CYP-3A4, 3A5	Cyclosporine toxicity ↑
	CYP-2D6	Codeine function & toxicity↑
	CYP-2C9	Warfarin toxicity ↑
	CYP-2C19	Clopidogrel metabolite ↑↓
	Dihydropyrimidine Dehydrogenase	5-Flurouracil toxicity↑
Phase II Enzymes	UDP GT	Irinotecan toxicity ↑
	Thiopurine MT	Thiopurine toxicity ↑
	G6DP	Hemolysis ↑
Transporter	Organic Anion Transporter (OATP)	Simvastatin myopathy ↑
Receptor	β1 receptor	Metoprolol efficacy ↑

3. **Altered Physiological Factors**
   - **Pregnancy Metabolism (**↑Phenytoin, ↓Phenobarbitone, ↓Pethidine**)**
   - **Hormonal Imbalance (**Hypothyroidism & Hyperthyroidism**)**
   - **Disease states (**CVS, Respiratory and Liver diseases impair metabolism & Renal diseases impair conjugation**)**
4. **Temporal Factors**
   - ↑Cortisterone Levels in afternoon → ↓Metabolism & vice versa for early morning
5. **Route of Drug Administration**
   - Lignocaine is given topically not orally to avoid first pass metabolism
6. **Environmental Factors**
   - Smoking, Chronic alcoholism & Pesticides or Organophosphate insecticides → Enzyme inducers.
   - Hot and humid climate →↓ Metabolism
   - High altitude →↓Oxygen →↓ Metabolism

TOXIC METABOLISM

(Active drug is converted to active metabolite i.e. toxic molecule)
Examples: Methyl alcohol, Ethylene glycol & large doses of acetaminophen



Metabolism of acetaminophen (Ac) to harmless conjugates or to toxic metabolites. Acetaminophen glucuronide, acetaminophen sulfate, and the mercapturate conjugate of acetaminophen all are nontoxic phase II conjugates. Ac* is the toxic, reactive phase I metabolite, N-acetyl-p-benzoquinoneimine. Transformation to the reactive metabolite occurs when hepatic stores of sulfate, glucuronide, and glutathione (GSH, Gs) are depleted or overwhelmed or when phase I enzymes have been induced.

ADVERSE DRUG EFFECTS

ADVERSE DRUG EFFECTS

Unpredictable Effects		Predictable Effects					
Allergy	Idiosyncrasy	Cummulation / Toxicity	Teratogenicity	Mutagenicity	Carcinogenicity	Tolerance	Dependence
Drug taken as antigen and immune response occurs	Trait that is peculiar to a group or individual mainly because of genetic problem	Drug induced poisoning	Drug induced inutero fetal defects	Drug induced gene mutations	Drug induced cancer	Decreased drug response due to many reasons	Habituation/ Addiction
Penicillin cause Anaphylactic Shock	Aspirin causes hemolysis in people with G6DP deficiency	Large one or small many doses	Ethanol, Warfarin	Aflatoxins, Anticancer drugs	Coal tar, Vinyl Chloride	Morphine, Nitrates	Tobacco, Morphine

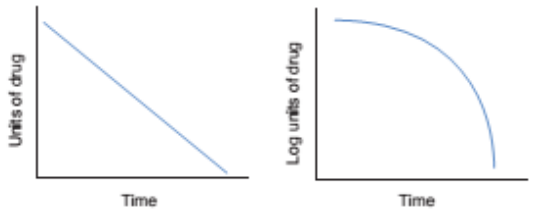
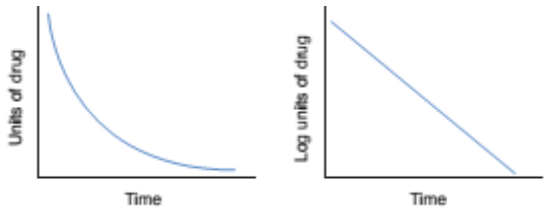
ELIMINATION

(It is drug inactivation or removal from the body by metabolism or excretion)
ELIMINATION = METABOLISM + EXCRETION

Different from excretion in terms, (drug may be eliminated by metabolism long before modified molecules are excreted from body.)

1. Most drugs and their metabolites: hepatic metabolism, biliary elimination, or urinary elimination
2. Volatile anesthetic gases: excreted by lungs.
3. Drugs with active metabolites (eg, diazepam), elimination of parent molecule by metabolism is not synonymous with termination of action.
4. Drugs that are not metabolized: Excretion is the mode of elimination.
5. Small number of drugs combine irreversibly with their receptors: So that disappearance from bloodstream is not equivalent to cessation of drug action: These drugs may have a very prolonged action. E.g. phenoxybenzamine, an irreversible inhibitor of α adrenoceptors.

DIFFERENCE BETWEEN FIRST ORDER AND ZERO ORDER ELIMINATION

FEATURE	ZERO ORDER ELIMINATION	FIRST ORDER ELIMINATION
Definition	A process that is independent of drug concentration involved in the process and is constant with passage of time	A process that is directly proportional to drug concentration involved in process
Process	Constant Rate Process	Linear Kinetic Process
Type	Capacity limited elimination	Flow dependent elimination
Rate	Independent of drug concentration	Directly proportional to drug concentration
General Expression	$\frac{dc}{dt} = -K_0C^0 = -K_0$	$\frac{dc}{dt} = -KC^1 = -KC$
Rate Constant (K	K_o	K
Units of K	mg/min	min^{-1}, hr^{-1}
General Equation	$C = C_0 - K_0t$	$C = C_0\, e^{-Kt}$ OR $\log C = \log C_0 - \frac{Kt}{2.3030}$
Graph		
Clearance (CL)	Not constant	Constant (Rapid at first & slows as conc. decreases)
Half life (like CL)	Not constant	Constant (In first order kinetics, A drug infused at a constant rate takes 4–5 half-lives to reach steady state. It takes 3.3 half-lives to reach 90% of the steady-state level.)
Half life expression	$t_{\frac{1}{2}} = 0.5\frac{C_0}{K_0}$	$t_{\frac{1}{2}} = 0.693\frac{1}{K}$
Dependence (t½)	Dependent on initial drug concentration	Independent on initial drug concentration
End	At some time, comes to end	Never comes to an end
Examples:	At high/toxic doses: Ethanol Aspirin Phenytoin	Mostly drugs follows this

CLEARANCE (CL)

(Volume of blood or plasma that can be freed of a drug in a specific time)

- It relates the rate of elimination of drug to the plasma concentration at specific time as follow;

$$CL_{Organ} = \frac{(\text{Rate of Elimination of Drug})_{Organ}}{\text{Plasma drug concentration}} = \frac{(\text{Rate of Elimination of Drug})_{Organ}}{C_p}$$

UNITS OF CL

- Volume/time i.e. mL/min or L/h
- CL/kg of body weight

FACTORS AFFECTING CL

- Drug
- Blood flow
- Conditions of the organs of elimination i.e. kidney, liver, intestines etc

$$\text{Clearance by an individual organ} = \text{Extraction capability for that drug} \times \text{Rate of delivery of drug to organ.}$$

- Clearance of a drug that is very effectively extracted by an organ is often flow-limited.

PLASMA HALF LIFE (t½)

(Time required for the amount of drug in the body or blood to fall by 50%)

- Determines the rate at which blood concentration rises during a constant infusion and falls after administration is stopped
- It relates as follow;

$$t_{\frac{1}{2}} = 0.693\,\frac{V_d}{CL}$$

UNITS OF t½

- Time

FACTORS AFFECTING t½

$$\text{Half life} \propto \frac{V_d}{CL} \propto \text{Duration of Action of Drug}$$

- V_d
- CL

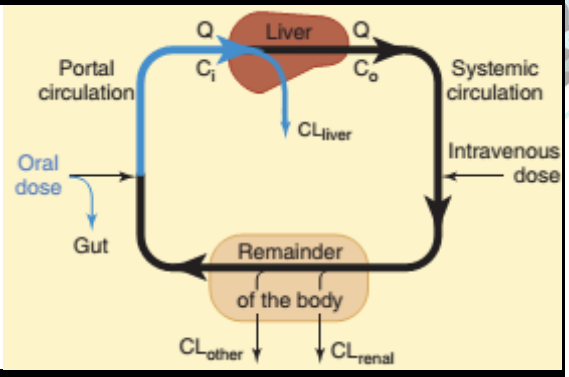
EXTRACTION RATIO

(fraction or percentage of the drug removed from perfusing blood during its passage through the organ

- After steady-state concentration in plasma has been achieved, extraction ratio is one measure of elimination of drug by that organ.
- Drugs that have a high hepatic extraction ratio have a large first-pass effect and bioavailability of these drugs after oral administration is low.
- It is determined as follow;

$$\text{Extraction by organ} = \text{Blood flow} \times (\text{Input} - \text{Output})$$

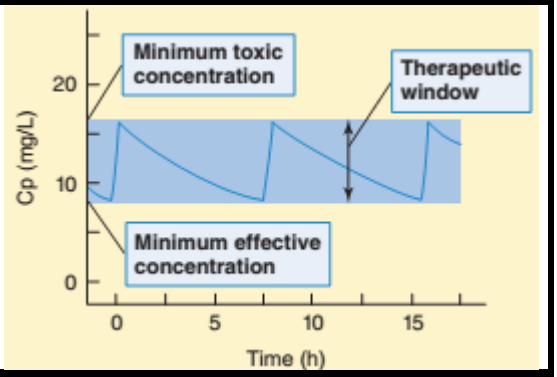
$$\text{Extraction by organ} = Q \times (C_i - C_o)$$



THERAPEUTIC WINDOW

(Safe range between the minimum therapeutic concentration and the minimum toxic concentration of a drug)

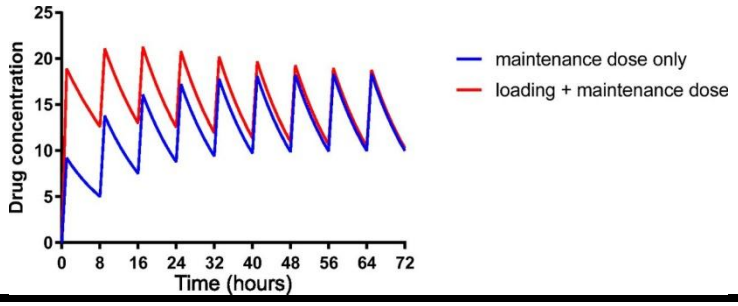
- Determine the acceptable range of plasma levels when designing a dosing regimen
  1. Minimum **effective** concentration = **trough** levels of a drug given intermittently
  2. Minimum **toxic** concentration = permissible **peak** plasma concentration
- For some drugs, therapeutic and toxic concentrations vary so greatly among patients that it is impossible to predict therapeutic window in a given patient. Such drugs must be titrated individually in each patient.



DOSAGE REGIMENS

(Plan for drug administration over a period of time)

- An optimal dosage regimen results in the achievement of therapeutic levels of drug in blood without exceeding the minimum toxic concentration and depends on;
  1. Minimum Therapeutic & Toxic Concentration
  2. V_d & CL

FEATURE	MAINTENANCE DOSE	LOADING DOSE
Definition	The dose required for regular administration to maintain a target plasma level i.e. to maintain a desired steady state (SS).	The dose required to achieve a specific plasma drug concentration level (Cp) with a single administration.
Factors	CL and t½	V_d
Expression	At Steady state: $(\text{Rate of Dosing})_{SS} = (\text{Rate of Elimination})_{SS}$ $(\text{Rate of Dosing})_{SS} = CL \times \text{Desired } C_p$ $\text{Maintenance Dose} = \frac{(\text{Rate of Dosing})_{SS}}{F} \times \text{Dosing Interval}$	$\text{Loading Dose} = \frac{V_d \times \text{Desired } C_p}{F}$
Units	$(\text{Rate of Dosing})_{SS} = \text{Dose per unit time if CL is in mL/min}$ **But** As for chronic therapy we give these doses once or a few times per day, we convert it as follow; $(\text{dose per minute} \times 60\ \text{min/h} \times 24\ \text{h/d})$ $\text{Maintenance Dose} = \text{milligrams}$	$\text{Loading Dose} = \text{milligrams}$
Dosing	Smaller and more frequent maintenance doses, **if** difference between therapeutic and toxic conc. is small. Larger and less frequent maintenance doses, **if** difference between therapeutic and toxic conc. is large.	Loading dose is large (V_d >Blood volume) then dose is given slowly Loading dose is small (V_d <Blood volume) then dose is given rapidly
Graph		

DOSAGE ADJUSTMENTS WHEN ELIMINATION IS ALTERED BY DISEASE

RENAL IMPAIRMENT:

- GFR disturbed
- Creatinine Clearance (CL_{Cr}) disturbed

1. For drugs to be removed by renal route only

$$\text{Corrected Dosage} = \text{Avergae Dose} \times \frac{\text{Patient's } CL_{Cr}}{100\text{mL/min}}$$

2. For drugs to be removed 50% by renal route and 50% by liver

$$\text{Corrected Dosage} = \frac{1}{2}\text{Average Dose(Liver)} + \frac{1}{2}\text{ Average Dose } \times \frac{\text{Patient's } CL_{Cr}}{100\text{mL/min}} \text{ (Kidney)}$$

3. Shortcut for measuring CL_{Cr} directly by Cockcroft Gault Equation

$$CL_{Cr}(\text{mL/min}) = \frac{(140 - \text{Age}) \times \text{Body weight in kg}}{72 \times \text{Serum}_{Cr}} (\times 0.85 \text{ if female})$$

4. Shortcut for measuring GFR directly by MDRD Equation

$$\text{GFR } ((\text{ml/min})/1.73\text{m}^2\text{body surface area}) = \frac{175\ (\times 0.742 \text{ if female})(\times 1.212 \text{ if African American})}{S_{Cr}^{1.154} \times \text{Age}^{0.203}}$$

PHARMACODYNAMICS

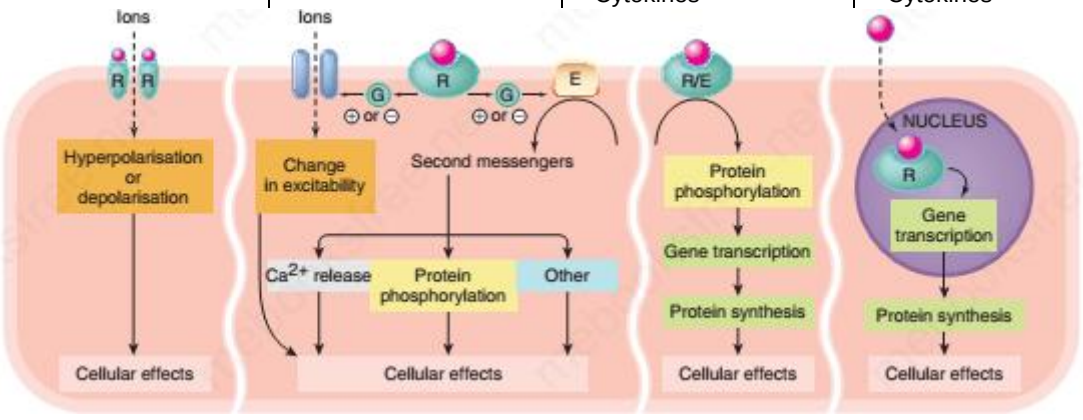
(The actions of the drug on the body)

RECEPTORS (A molecule to which a drug binds to bring about a change in function of the biologic system)

- Selective in their ligand binding characteristics
- Modifiable
- Mostly Proteins, but also Enzymes or Nucleic Acids in nature

$$[\text{Response}] \propto \text{Drug} - \text{Receptor Combinations} \propto \text{Concentration of } R_a \text{ State}$$

FEATURE	TYPE-I	TYPE-II	TYPE-III	TYPE-IV
Name	Ligand Gated Ion Channels	G-Protein Coupled Receptors	Receptor Kinases	Nuclear Receptors
Location	Membrane	Membrane	Membrane	Intacellular
Ligand Nature	Hydrophilic	Hydrophilic	Hydrophilic	Hydrophobic
Effector	Ion Channel	Channel or Enzyme	Protein Kinases	Gene Transcription
Structure	Oligomeric assembly of subunits surrounding central pore	Monomeric or oligomeric assembly of subunits comprising 7 trans-membrane helices with intracellular G protein–coupling domain	Single transmembrane helix linking extracellular receptor domain to intracellular kinase domain	Monomeric structure with receptor- and DNA-binding domains
Mode of Action	Changes in membrane potential or ionic concentration within cell	Protein phosphorylation • G_i: ↓cAMP • G_s: ↑cAMP • G_q: ↑IP_3, ↑DAG	Protein and receptor phosphorylation by formation of dimers or multisubunit complexes	Protein phosphorylation and altered gene expression
Domains	Receptor Binding + Channel Lining	Receptor Binding + G-protein Coupling	Receptor Binding + Catalytic	Receptor Binding + DNA Binding
Duration of Action	Milliseconds	Seconds	Minutes to Hours	Hours to Days
Examples	• Nicotinic Ach • Serotonin 5-HT_3 • $GABA_A$	• Muscuranic Ach • Adrenoceptors	• Insulin • Growth Factors • ANP • Cytokines	• Steroid • Vitamin D • NO • Cytokines



DIFFERENCE BETWEEN INERT BINDING SITE & RECEPTOR SITE

Feature	INERT BINDING SITE	RECEPTOR SITE
Definition	A molecule to which a drug may bind without changing any function	Specific region of the receptor molecule to which the drug binds
Function	Play an important role in buffering concentration of a drug because bound drug does not contribute directly to the concentration gradient that drives diffusion.	Drug- receptor interaction initiates the drug action
Example	Albumin & orosomucoid (α1-acid glycoprotein)	Primary receptor affinity is a basis of drug classification e.g. H1 for histamine receptors

RECEPTOR REGULATIONS

SIGNAL AMPLIFICATION

G-protein and Kinase-Linked Receptors amplify signal duration and intensity that give rise to spare receptors.

Eg.

- Insulin receptors: 99% are spare
- Heart β-receptors: 5-10% are spare

PROTECTION AGAINST EXCESSIVE STIMULATION

Tachyphylaxis/Down-regulation: When a receptor is exposed to repeated administration of an agonist, it becomes desensitized resulting in diminished effect.

- Blockage of access to G-proteins (β-arrestin)
- Internalization/Sequestration of receptors (β or morphine receptors) – during recovery unresponsive receptors are called refractory.
- Depletion of essential substrate (thiol cofactors for nitroglycerin)

Up-regulation: Repeated exposure of a receptor to an antagonist may result in up-regulation of receptors, in which receptor reserves are inserted into the membrane, increasing the total number of receptors available.

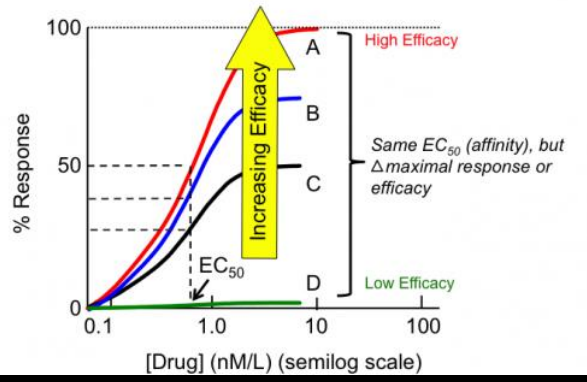
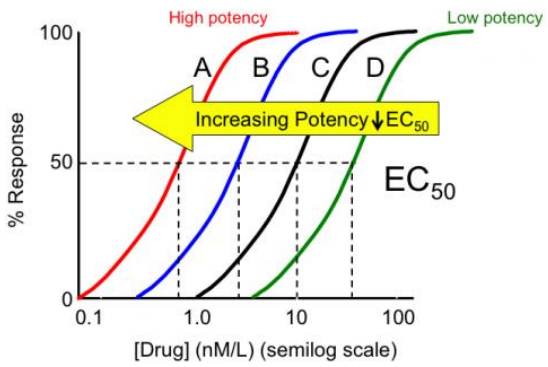
- Make the cells more sensitive to agonists
- More resistant to the effect of the antagonist

EFFECTORS

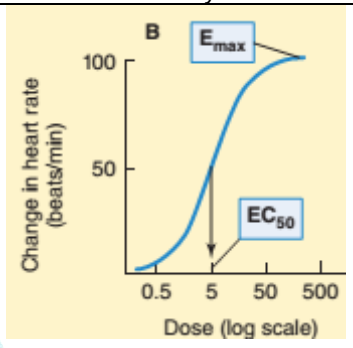
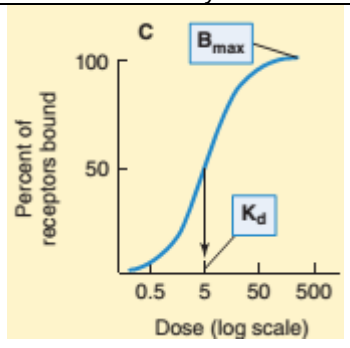
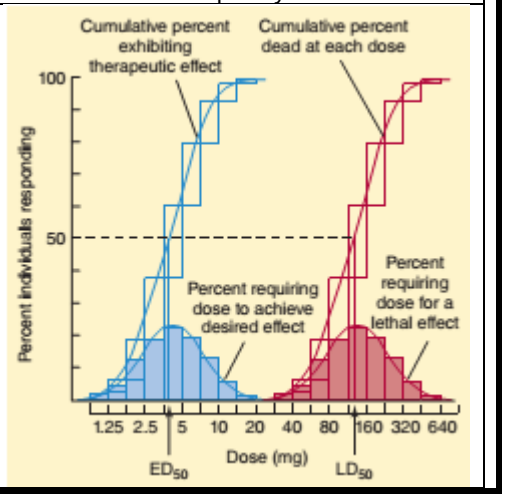
(Component of a system that accomplishes the biologic effect after receptor is activated by an agonist)

1. **Channel:** Na/K channel for N_N receptor
2. **Transporter:** M receptors
3. **Enzyme:** Adenylyl cyclase
4. **May be part of the receptor molecule:** Tyrosine kinase effector enzyme part of insulin receptor

DIFFERENCE BETWEEN EFFICACY & POTENCY

Feature	EFFICACY (E_{max})	POTENCY
Definition	The largest effect that can be achieved with a particular drug, regardless of dose	The amount or concentration of drug required to produce a specified effect
Factors Affecting	• Nature of Drug • Nature of Receptor • Nature of Effector	• Receptor Affinity • Number of Receptors available
Graded Dose Response Curve	Can be measured by it	Median Doses EC_{50}; ED_{50}; TD_{50} (Concentration or dose that causes 50% of maximal effect or toxicity)
Quantal Dose Response Curve	Cannot be measured by it	Median Doses ED_{50}; TD_{50}; LD_{50} (Concentration or dose that causes a specified response in 50% of the population under study)
Graph Represents	Y-value (E_{max}) • ↑ Y-value = ↑ E_{max} = ↑ Efficacy.	X-value (Median Doses) Left shifting = ↓ED_{50} = ↑Potency = ↓Drug needed
Mathematical Form	$E_{max} \propto$ Efficacy	$EC_{50} \propto \frac{1}{\text{Potency}}$
Graph		

DIFFERENCE BETWEEN DOSE CURVE GRAPHS

FEATURE	GRADED-DOSE RESPONSE	GRADED-DOSE BINDING RESPONSE	QUANTAL-DOSE RESPONSE
Definition	Graph between increase of response with increase of dose of drug	Graph between receptors bound by drug with increase of dose of drug	Graph between fraction of population showing that response with increase of dose of drug
Data Derived	$E_{max} \propto$ Efficacy $EC_{50} \propto \frac{1}{\text{Potency}}$	$B_{max} \propto$ DR Binding $K_d \propto \frac{1}{\text{Affinity}}$ (K_d = concentration of drug that binds 50% of receptors in system)	Potency Variables • Median effective dose (ED_{50}) • Median toxic dose (TD_{50}) • Median lethal dose (LD_{50})
Relation	Dose to intensity of effect	Dose to intensity of effect	Dose to frequency of effect
Graph			

SPARE RECEPTORS (Receptor that does not bind drug when drug concentration is sufficient to produce E_{max})

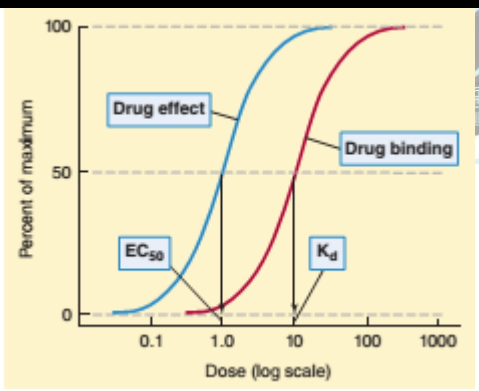
- **Reason**

$$E_{max} < B_{max}$$

OR

$$EC_{50} < K_d$$

- **Mechanisms**
  1. Duration of effector activation > DR interaction
  2. Receptors > Effectors
- Increases sensitivity to the agonist because the likelihood of a drug-receptor interaction increases in proportion to the number of receptors available



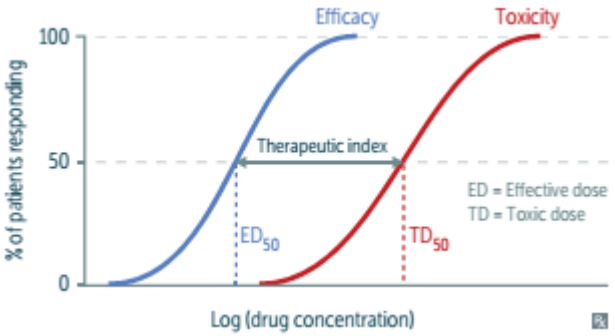
THERAPEUTIC INDEX (TI)

(Ratio of median toxic dose (or median lethal dose) to median effective dose, determined from quantal dose-response curves.)

- **Formula**

$$TI = \frac{TD_{50}}{ED_{50}} \text{ or } \frac{LD_{50}}{ED_{50}}$$

- It estimates the safety of the drug.
- Safer drugs have higher TI values.
- Drugs with lower TI values frequently require monitoring (eg, Warfarin, Theophylline, Digoxin, Lithium)



PHARMACOLOGICAL DRUG INTERACTIONS

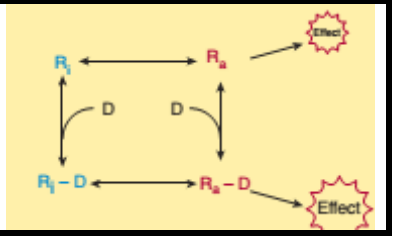
CHEMICAL INTERACTIONS

- **Mechanims**
  - Pharmacokinetic
    - Absorption
    - Distribution
    - Metabolism
    - Elimination
  - Pharmacodynamic
    - Receptor
    - Non-receptor
- **Classification**
  - Additive
  - Synergestic
  - Potentiation
  - Tachyphylactic
  - Antagonism
    - Pharma-cological
    - Physiological
    - Chemical

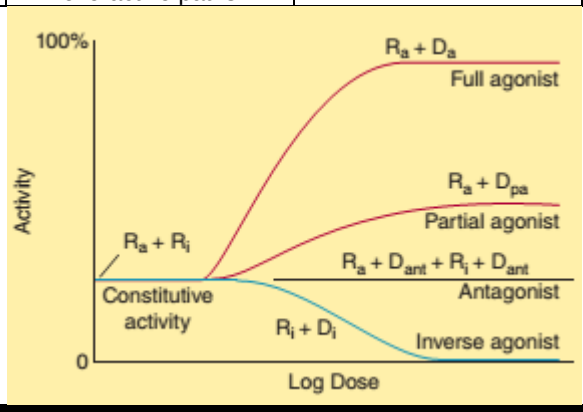
TYPE	DEFINITION	EXAMPLE
Additive	Effect of substance A and B together is equal to the sum of their individual effects i.e. A = 1, B = 1, A + B = 2	Aspirin and acetaminophen
Synergistic	Effect of substance A and B together is greater than the sum of their individual effects i.e. A = 1, B = 1, A + B > 2	Clopidogrel with aspirin
Potentiation	Presence of substance A is required for full effects of substance B A = 0, B = 1, A + B > 1	Cortisol on catecholamine responsiveness
Tachyphylactic	Acute decrease in response to a drug after initial/repeated administration	Nitrates, niacin, phenylephrine
Antagonism	**See below**	

AGONIST (A drug that activates its receptor upon binding)

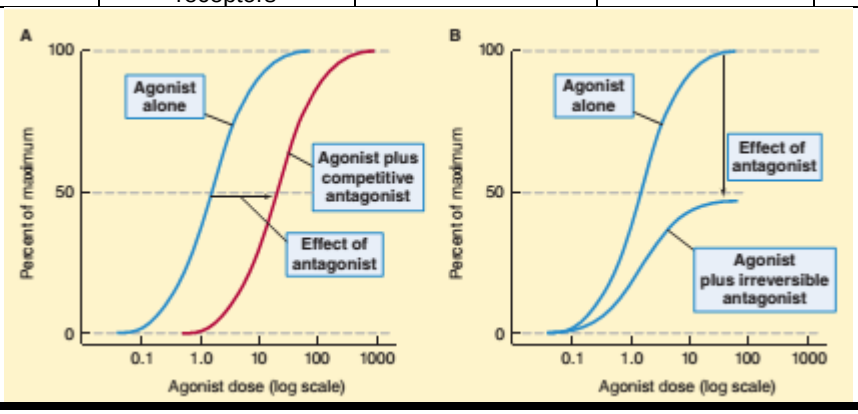
- Equilibrium is formed between $R_{inactive}$ (R_i) and R_{active} (R_a) state in absence of ligand.
- The activity in the absence of agonist ligand is called constitutive activity.
- R_i state is favoured in absence of ligand.



TYPES OF AGONISTS

FEATURE	FULL AGONIST	PARTIAL AGONIST	NEUTRAL ANTAGONIST	INVERSE AGONIST
Definition	A drug capable of fully activating the effector system when it binds to the receptor	A drug that binds to its receptor but produces a smaller effect (E_{max}) at full dosage than a full agonist	A drug binds with equal affinity to R_i & R_a states, preventing binding by agonist and preventing any deviation from level of constitutive activity.	A drug that binds to non-active state of receptor molecules and decreases constitutive activity.
Affinity for state	$R_a >>> R_i$	$R_a > R_i$ (in presence of full agonist it acts as inhibitor)	$R_a = R_i$	$R_i > R_a$
Intrinsic Activity (I)	I = 1	I >0 but <1	I = 0	I < 0
Example	Phenylephrine at α-receptors	Apripirazole at D-receptors with activate underactive paths and inactive the overactive paths	Naloxone is a competitive antagonists at all opioid receptors	H_1 and H_2 antihistaminics
Graph				

TYPES OF ANTAGONISM

FEATURE	COMPETITIVE	NON-COMPETITIVE		PHYSIOLOGICAL	CHEMICAL
	REVERSIBLE	IRREVERSIBLE	ALLOSTERIC		
Definition	A pharmacologic antagonist that can be overcome by increasing the concentration of agonist	A pharmacologic antagonist that cannot be overcome by increasing agonist concentration	A drug that binds to a receptor molecule without interfering with normal agonist binding but alters response to normal agonist	A drug that counters the effects of another by binding to a different receptor and causing opposing effects	A drug that counters the effects of another by binding the agonist drug (not receptor)
Location	At receptor site	At receptor site	Other than receptor	Different receptor	With drug
Overcome	Yes (By agonists)	No	No	-	-
E_{max} ∝ Efficacy E_{max} Efficacy	-	↓ (Down Shift) ↓	↓ (Down Shift) ↓	-	-
EC_{50} ∝ 1/(Potency) EC_{50} Potency	↑ (Right shift) ↓	-	-	-	-
Examples	Diazepam (agonist) + flumazenil (antagonist) on GABA receptor	Norepinephrine (agonist) + phenoxybenzamine (noncompetitive antagonist) on α-receptors	Picroton + GABA linked Cl- channel	Epinephrine's antagonism of bronchoconstriction by histamine	Dimercaprol Pralidoxime
Graph					

DIFFERENCE BETWEEN TACHYPHYLAXIS & TOLERANCE

FEATURE	TACHYPHYLAXIS (PHARMACODYNAMIC TOLERANCE)	TOLERANCE (METABOLIC/ PHARMACOKINETIC TOLERANCE)
Definition	Rapid loss of drug effects caused by compensatory neurophysiological mechanisms	Decrease in clinical effects of drug after prolonged exposure to it
Onset	Rapid (few minutes)	Slow (days - months)
High Dose dependent	No	Yes
Effects with ↑ dose	Not Seen	Seen
Routine Practice	Not Seen	Seen
Examples	Ephedrine, Nitroglycerin (TD)	Barbiturates, Ethanol, Opium
Causes	• Blockage of access to G-proteins (β-arrestin) • Internalization of receptors (morphine receptor) • Sequestration of receptors (β receptors) • Depletion of essential substrate (thiol cofactors for nitroglycerin)	• Congenital (Negroes are resistant to mydriatic effect of ephedrine) • Acquired (morphine, ethyl alcohol, nitrates, ephedrine, and amphetamine)

CROSS TOLERANCE:

Tolerance between related drugs e.g. between ethyl alcohol and general anaesthesia.

1. Alteration in drug concentration that reaches the receptors due to an effect on absorption, distribution or elimination.
2. Variation in concentration of endogenous transmitters e.g. β- blockers will slow heart rate markedly in patients with excess endogenous catecholamines.
3. Alteration in the number or function of receptors, e.g. thyrotoxicosis increases the number and sensitivity of β-receptors.

DRUG DEVELOPMENT & REGULATION

Sale and use of drugs are regulated in almost all countries by governmental agencies.
In the United States, regulation is by the Food and Drug Administration (FDA).

NATURE/SOURCES OF DRUGS

SOURCES OF DRUG

- **Natural**
  - **Animals**
    - **Insulin** (pancreatic β-cells)
    - **Heparin** (Liver extract)
    - **Vitamin B12** (Liver)
    - **ADH** (hypothalamus)
  - **Plants**
    - **Digoxin** (Digitalis purpura)
    - **Quinine** (Cinchona bark)
    - **Atropine** (Atropa belladonna)
  - **Microorganisms**
    - **Penicillin** (P chrysogenum)
    - **Streptomycin** (S. griseus)
    - **Chloramphenicol** (S. venezuelae)
  - **Minerals**
    - **$MgSO_4$** (Laxative)
    - **Mg trisilicate** (Antacid)
- **Synthetic**
  - **Aspirin**
  - **Sulfonamide**
  - **Pethidine**
  - **Procaine**
- **Semisynthetic**
  - **Ampicillin** from penicillin

FORMS OF DRUGS

FORMS OF DRUG

- **SOLID**
  1. Tablets—Paracetamol
  2. Capsules—Ampicillin
  3. Powders—Dusting antiseptic powder
  4. Pressary—Antifungals
  5. Suppository—Analgesics.
- **LIQUID**
  1. Injections—Benzyl penicillin
  2. Mixtures—Potassium chloride
  3. Solution—Eyedrop
  4. Suspension—Antacid
  5. Emulsion—Cod liver oil
  6. Lotions—After shave lotions
  7. Enema—Barium enema
- **GASES**
  - Nitric Oxide

NOMENCLATURE OF DRUGS

NOMENCLATURE OF DRUG

- **Chemical Name**
  - Describes the chemistry of a drug
- **Official name or nonproprietary name**
  - Name chosen by the official bodies & used by pharmacopias
- **Proprietary name**
  - Name chosen by the firm manufacturing or marketing
- **Generic Name**
  - Forms or class or genus in which the drug in question falls

EXAMPLE:

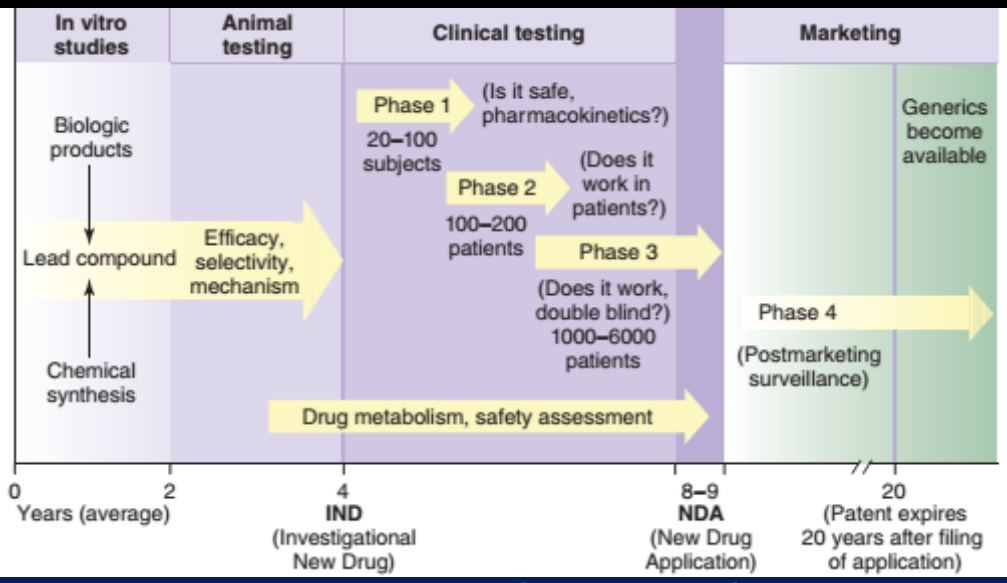
- Chemical name: 7 chloro 1,3 dihydro—1 methyl 5 phenyl 2H, 1,4 benzodiazepine—2.
- Official name: Diazepam
- Proprietary name: Valium
- Generic name: Benzodiazepine

DRUGS CLASSIFICATION

A drug class is group of medications having similar chemical structures, mechanism of action and mode of action.

1. **Prototypic/First-in-Class/Novel Drug:** An individual drug that represents a drug class
2. **Me-too Drugs:** Drugs similar to prototypic drugs having same mechanism of action with:
   - Faster onset of action
   - Improved selectivity
   - Increased potency
   - Longer duration of action
   - Less toxicity

DRUGS DEVELOPMENT



ANIMAL TESTING (PRE-CLINICAL)

One basis of two things evaluated:

1. **Function of proposed use:** Topical usage drugs require less testing than one for chronic systemic administration.
2. **Urgency:** Anticancer or anti-HIV drugs require less testing than one for life threatening diseases.

TEST	DETERMINATION	PERFORMANCE	EXAMPLES
Pharmacological profile	• All pharmacologic effects • Graded & quantal dose response data		Effects on CVS, GIT, Respiration, Hepatic, Renal, Endocrine and CNS intestinal
Acute toxicity	Acute dose that is lethal in approximately 50% animals.	Usually two species (1 rodent, 1 non-rodent), two routes.	Determine the no-effect dose and the maximum tolerated dose.
Subacute toxicity	• Biochemical effects • Physiologic effects	Three doses, two species for 2-4 weeks.	The longer the duration of expected clinical use, the longer the subacute test. 2 weeks - 3 months of testing may be required before clinical trials.
Chronic toxicity		Rodent & at least one nonrodent species for ≥ 6 months.	Required when drug is intended to be used in humans for prolonged periods. Usually run concurrently with clinical trials.
Teratogenic/ Reproductive Toxicity Teratogenesis is induction of development defects in somatic tissues of fetus (exposure to chemical, infection, or radiation).	Effects on: • Mating behavior • Reproduction • Parturition • Progeny • Birth defects • Postnatal development	Two species, (one rodent & rabbits) during early pregnancy (organogenesis take place) and by later (examining fetuses or neonates for abnormalities).	**Examples:** thalidomide, isotretinoin, valproic acid, ethanol, glucocorticoids, warfarin, lithium, and androgens.
Mutagenic Toxicity Mutagenesis is induction of changes in genetic material of animals of any age and therefore induction of heritable abnormalities.	• Genetic stability • Mutations	Test effects on genetic stability and mutations in: 1. **Sallmonella bacteria in culture (Ames test):** Aflatoxin, cancer drugs, and agents binding to DNA give this test positive 2. **Mammalian cells in culture** 3. **Mice (Dominant lethal test):** Clastogenicity in mice & exposure is before mating	
Carcinogenic Toxicity Carcinogenesis is the induction of malignant characteristics in cells.	• Gross pathology • Histologic pathology.	Two years, two species.	Required when drug is intended to be used in humans for prolonged periods. **Examples:** coal tar, aflatoxin, dimethylnitrosamine and other nitrosamines, urethane, vinyl chloride, and polycyclic aromatic hydrocarbons in tobacco smoke (eg, benzo[a]pyrene) and other tobacco products

REPRODUCTIVE SAFETY (FDA RATINGS)

CATEGORY	A (very safe)	B (safe)	C (may be safe)	D (teratogenic but used when serious)	X (teratogenic)
Animals	-	+/-	+/0	+	+
Humans	-	-/0	0	+	+

CLINICAL TESTING & MARKETING				
PRECLINICAL	**PHASE 1**	**PHASE 2**	**PHASE 3**	**PHASE 4**
2 different animal species	~ 20-100 healthy volunteers **(Exception: Cancer & toxic drugs to target patients)**	~ 100- 200 patients **(most drugs failed here)**	~ 1000-6000 patients	Post marketing surveillance (after FDA approval)
• Safety • Efficacy • Biological Activity	• Safety • Dosage • Pharmacokinetics	Effectiveness (check in monitored patients) **with placebo in single or double blind check**	Confirm effectiveness & common side effects **(double blind check)**	Common as wells as rare side effects

ORPHAN DRUGS

- An orphan drug is a drug for a rare disease (one affecting < 200,000 people in the United States).
- Study of such agents has often been neglected because profits from the sales of an effective agent for an uncommon ailment might not pay the costs of development.
- Some countries bestow certain commercial advantages on companies that develop drugs for uncommon diseases

2

AUTONOMIC NERVOUS SYSTEM PHARMACOLOGY

1 SEQ + 6 MCQs = 13 Marks

INTRODUCTION TO AUTONOMIC PHARMACOLOGY

CLASSIFICATION OF CHOLINERGIC RECEPTORS

	Mnemonic	Location	G Protein	Mechanism
M_1	**Nadia**	**N**erve Endings	G_q	↑IP_3, DAG cascade
M_2	**Have**	**H**eart	G_i	↓cAMP, K^+ channels activate
M_3	**Effective**	**E**ffector Cells: Smooth Muscle, Glands, Endothelium	G_q	↑IP_3, DAG cascade
M_4	**CNS**	**CNS**	G_i	↓cAMP, K^+ channels activate
M_5			G_q	↑IP_3, DAG cascade
N_N		Nerve Ganglia	-	Na^+/K^+ depolarizing current
N_M		NeuroMuscular Junction		

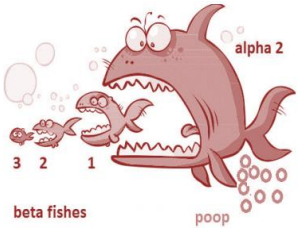
Anything that comes under parasympathetic control and not from **M_1 (Increased gastric secretions)** and **M_2 (Heart depression effects)** will come under **M_3**. Most of the functions are reverse of sympathetic control!

CLASSIFICATION OF ADRENERGIC RECEPTORS

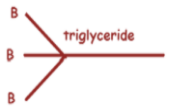
	Mnemonic	Location	G Protein	Mechanism
α_1	**England**	**E**ffector Cells: Smooth Muscle, Glands	G_q	↑IP_3, DAG cascade
α_2	**Never**	**N**erve Endings	G_i	↓cAMP
β_1	**Have**	**H**eart, JG apparatus	G_s	↑cAMP
β_2	**Some**	**S**mooth Muscle, Liver, Heart		
β_3	**Apology**	**A**dipocytes		
D_1 and D_5		Brain, Smooth Muscles of Renal Vasculature		
D_2 D_3 and D_4		Brain, Smooth Muscles, CVS	G_i	↓cAMP

- α_1-receptors are further classified to 1A, 1B & 1D while α_2-receptors are into 2A, 2B & 2C.
- α_1-receptors follow **BIG FISH BIG EYE** theory! Imagine a Fish made of rope with a big Eye. And you pulled rope and the Fish became smaller i.e. **α_1** has big eye (mydriasis) and other things generally constricted or contracted.

- α_2-receptors resemble a fish bigger than α_1-receptors. She was playing but some batameez betas (β receptors) start fighting with her. At the end, she won by eating the batameez betas but left some poop. So what happens is α_2-receptors have functions of opposing Batmez Betas. Poop represents platelets aggregation.



- β_1, β_2 and β_3 receptors resemble heart and kidney; relaxing wings of butterfly; triglyceride molecule respectively.



INNERVATIONS OF ORGAN SYSTEMS (Most by both SANS and PANS except)

- Only SANS supply; **Save Blood Save Human** (**S**weat Glands, **B**lood Vessels, **S**pleen, **H**air Follicles)
- Only PANS supply; **Punjab Group of Colleges** (**P**ancreatic Glands, **G**astric Glands, **C**iliary Muscle)

DRUGS MNEMONICS

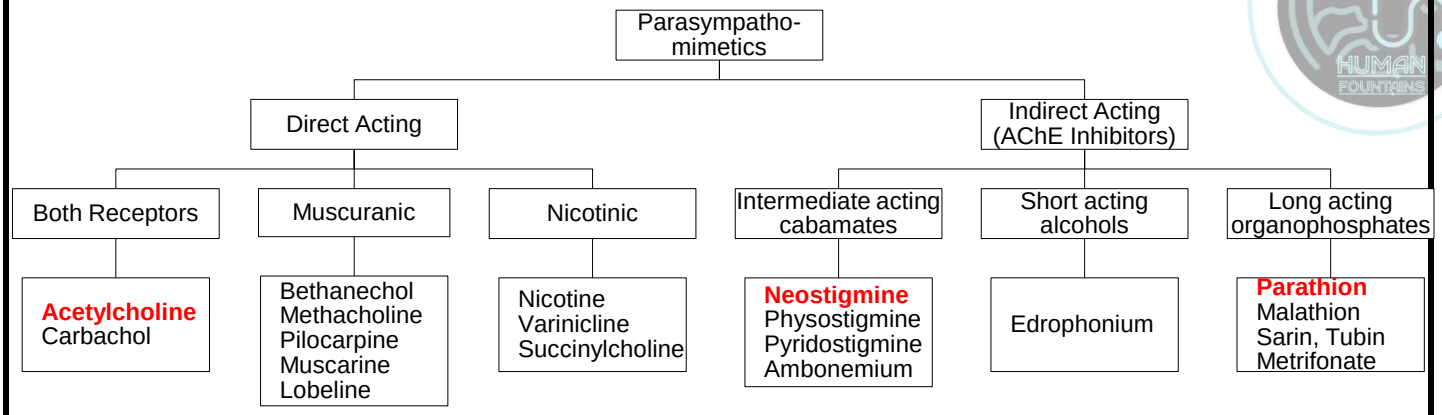
Cholinergic Transmission: **Hepatitis Virus B** = **H**emicholinium, **V**esamicol, **B**otulinum

Adrenergic Transmission: **MRGA (مرغا)** = **M**e-tyros-ine, **R**e-serp-ine, **G**ua-nethid-ine, **A**mphetam-ine

CT (کٹ) = **C**ocaine, **T**CA

ERECTION & EJACULATION: (Point & Shoot) i.e. PANS & SANS

PARASYMPATHOMIMETICS



WHY NEOSTIGMINE IS PREFERRED OVER PHYSOSTIGMINE IN TREATMENT OF MYASTHENIA GRAVIS?

Neostigmine has quaternary nitrogen; hence, it is more polar and cannot cross BBB to enter CNS, but cross the placenta. Physostigmine is lipid soluble and can cross BBB to enter CNS.

DIFFERENCE BETWEEN PARATHION AND MALATHION

FEATURE	PARATHION	MALATHION
Clinical Use	Insecticide	Insecticide + Scabicide
Duration	Days to Weeks	Days
Pharmacokinetics	Lipid Soluble	Metabolized to inactive form in mammals & birds
Danger	High	Less

ANTICHOLINERGIC DRUGS

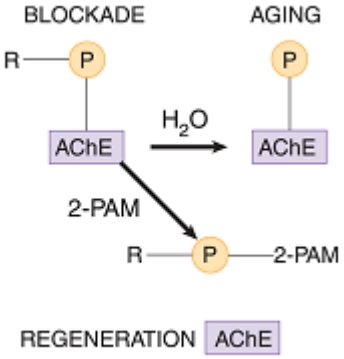
- Parasympatho-lytics
  - Anticholinergic Drugs
    - Anti-muscuranics
      - CNS → Antimotion Sickness (Scopolamine) → Antiparkinsonims & Dystonia when L-dopa is unresponsive (Benztropine, Biperiden, Trihexiphenidyl)
      - Eye (Mydriasis, Cycloplegia) → **Atropine** (72h), Homatropine (24h) Cyclopentolate (12h), Tropicamide (4h)
      - Bronchi (Asthma, COPD) → Ipratropium, Tiotropium, Aclidiunum
      - Gut → **Non Selective** (Dicycloamine, Glycopyrrolate) → **M1 Selective** (Pirenzepine, Telenzepine)
      - Bladder (Urinary Urgency) → **Non Selective** (Oxybutynin, Trospium) → **M3 Selective** (Tolterodine, Festerodine, Propiverine, Darifenancin, Solifenancin)
      - Intoxication of AChE inhibitors → **Atropine**
    - Anti-nicotinics
      - Ganglion Blockers → Hexamethonium Mecamylamine Trimethaphan
      - NMJ Blockers → **Depolarizing** Succinylcholine → **Nondepolarizing** Pan-curonium, **Tubo-curarine**, Ve-curonium, Cis-atra-curium, Ro-curonium, Atra-curium, Miva-curium
  - AChE Regenerators → Oximes → **Pralidoxime**

TREATMENT OF ORGANOPHOSPHATE POISONING

Irreversibly Acting Cholinomimetics:

These compounds phosphorylate the esteratic site on AChE, at serine hydroxyl groups

1. phosphorylation; reversible by pralidoxime (2-PAM)
2. removal of a part of the organophosphate molecule (aging); complex no longer reversible by 2-PAM



R = leaving group
P = organophosphate

1. Stabilize the patient vitally **ABC.**
2. Contaminated clothes should be removed and exposed skin should be washed with Na_2CO_3 solution.
3. Atropine 2 mg is given IM or IV at once and repeated every 15 min till mydriasis, tachycardia and dry mouth occurs.
4. Specific cholinesterase reactivator, Pralidoxime 1 gm in 100 ml normal saline or 5% glucose is given by IV infusion and repeated as indicated by patient's condition. It should be given as early as possible in order to be effective.
5. Artificial respiration with positive pressure device may be needed.
6. Airway should be kept clear as there is bronchoconstriction and excessive bronchial secretion. Endotracheal intubation or tracheostomy with suction may be required.
7. Diazepam may be needed for convulsions.

ATROPINE EFFECTS IN ORDER OF INCREASING DOSE

1. Decreased secretions (salivary, bronchiolar, sweat)
2. Mydriasis and cycloplegia
3. Hyperthermia (with vasodilation)
4. Tachycardia
5. Sedation
6. Urinary retention & constipation
7. Behavioral: excitation & hallucinations

SYMPATHOMIMETICS

- **Sympathomimetics**
  - **Direct Acting**
    - **α & β Agonists**
      - **Epinephrine (α,β)**
      - Norepinephrine (α,β except β_2)
      - Dopamine (D_1,α,β except β_2)
    - **α Agonists**
      - Nonselective: Oxymetazoline
      - α_1 selective: **Phenylephrine**, Tetrahydrozoline, Midodrine
      - α_2 selective: Clonidine, Methyldopa, Apraclonidine, Brimonidine
    - **β Agonists**
      - Nonselective: **Isoproterenol**
      - β_1 selective: Dobutamine
      - β_2 selective:
        - **SHORT ACTING:** Albuterol, Metaproterenol, Terbutaline, Ritrodrine
        - **LONG ACTING:** Salmeterol, Formoterol, Indacaterol, Vilanterol, Olodaterol
  - **Indirect Acting**
    - **Releasers:** Amphetamine, Methamphetamine, Tyramine
    - **Reuptake Inhibitors:** Cocaine, TCA
  - **Both**
    - **Ephedrine**

SYMPATHOMIMETIC EFFECTS ON CVS

Figure II-3-5a. Effect of Low-dose Epinephrine on Heart Rate and Blood Pressure

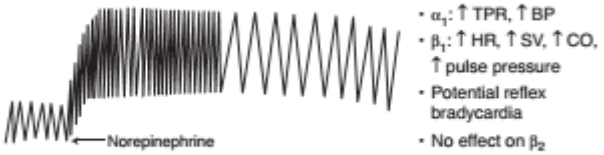


Figure II-3-4. Effect of Norepinephrine on Heart Rate and Blood Pressure

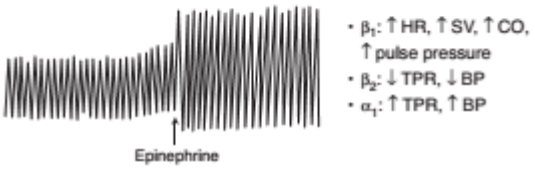


Figure II-3-5b. Effect of Medium-Dose Epinephrine on Heart Rate and Blood Pressure

Figure II-3-3. Effect of Beta Receptor Activation on Heart Rate and Blood Pressure

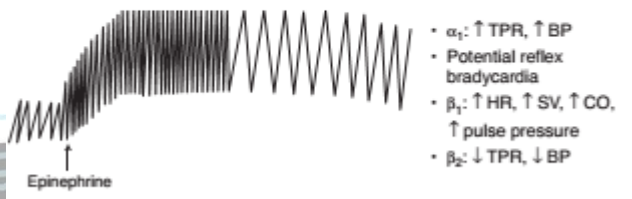


Figure II-3-5c. Effect of High-dose Epinephrine Is Similar to Norepinephrine

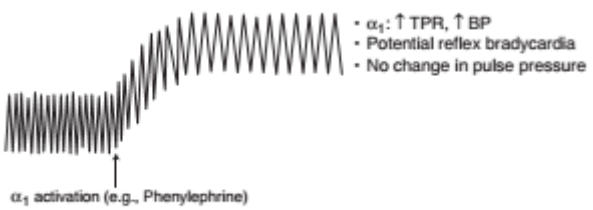


Figure II-3-2. Effect of Alpha Activators on Heart Rate and Blood Pressure

WHY NOR EPINEPHRINE IS NOT USED IN ANAPHYLACTIC SHOCK?

Epinephrine and norepinephrine are very similar neurotransmitters and hormones. While epinephrine has slightly more of an effect on your heart, norepinephrine has more of an effect on your blood vessels.

Pharmacological effects of adrenaline/epinephrine in the treatment of anaphylaxis*

Adrenergic receptor	Function
α_1 adrenergic receptor	– Increased vasoconstriction – Increased peripheral vascular resistance – Raised blood pressure – Reduction of tissue edema (e.g., larynx) – Nasal vasoconstriction
α_2 adrenergic receptor	– Lowering intraocular pressure
β_1 adrenergic receptor	– Raised heart rate (positive chronotropic) – Increased cardiac contraction (positive inotropic) – Vasoconstriction in skin and mucosa
β_2 adrenergic receptor	– Bronchodilation – Vasodilation – Inhibition of mediator release – Lowering peripheral blood pressure
β_3 adrenergic receptor	– Promotion of lipolysis

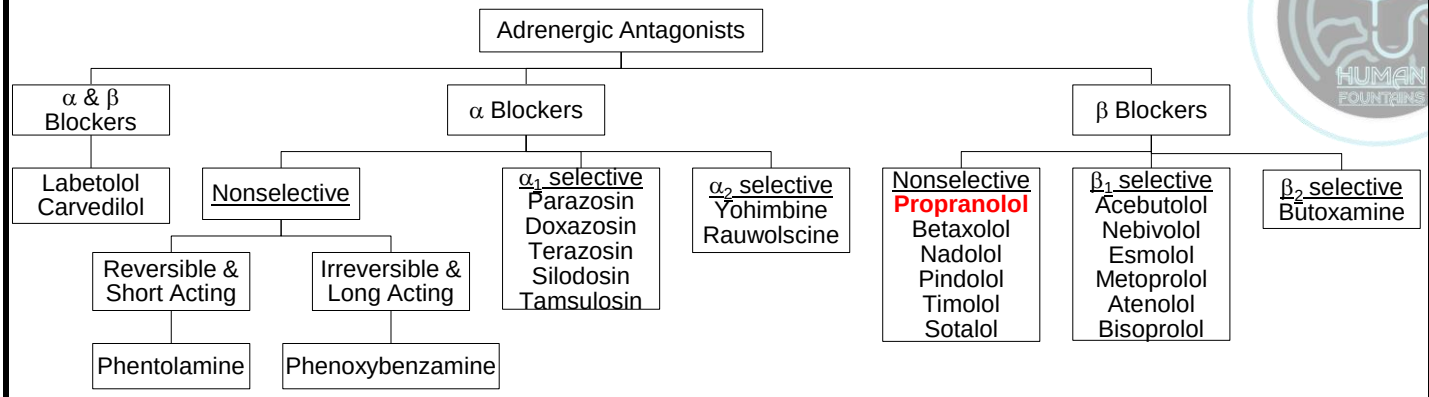
WHY DOPAMINE IS GIVEN IV ONLY?

Since the half-life of dopamine in plasma is short—approximately one minute in adults, two minutes in newborn babies and up to five minutes in preterm babies—it is usually given as a continuous intravenous drip rather than a single injection.

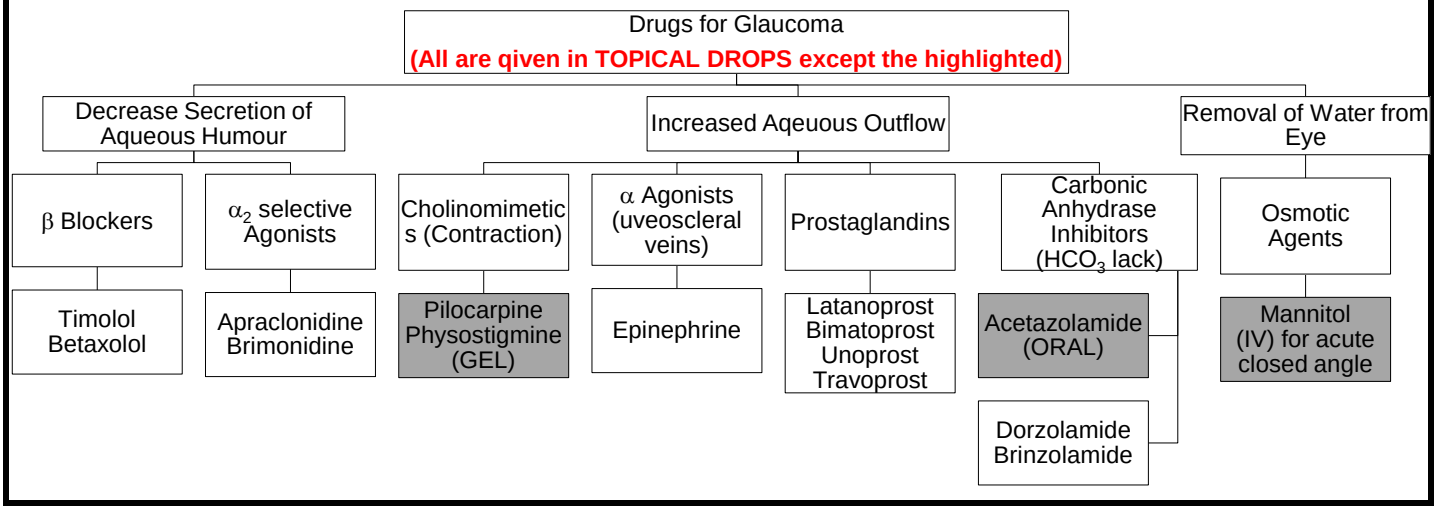
USES OF CLONIDINE IN DIABETIC DIARRHEA

Activate uninnervated α_2 receptors and cause water and salt absorption in GIT that relieves diarrhea

ADRENERGIC ANTAGONISTS



DRUGS USED IN GLAUCOMA



3

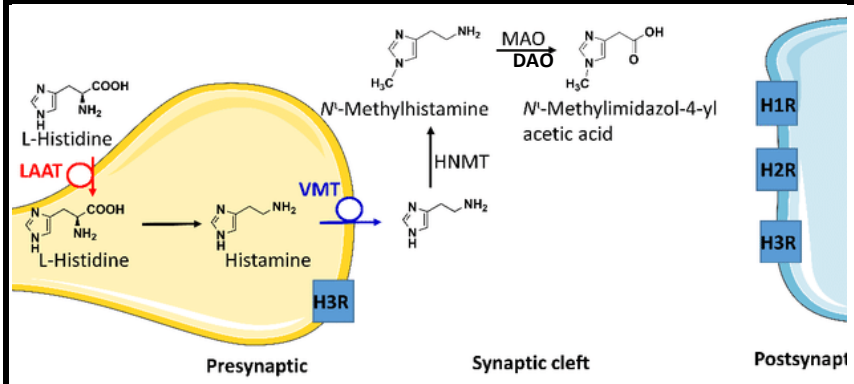
AUTOCOIDS & NSAIDS PHARMACOLOGY

1 SEQ + 7 MCQs = 14 Marks

AUTOCOIDS

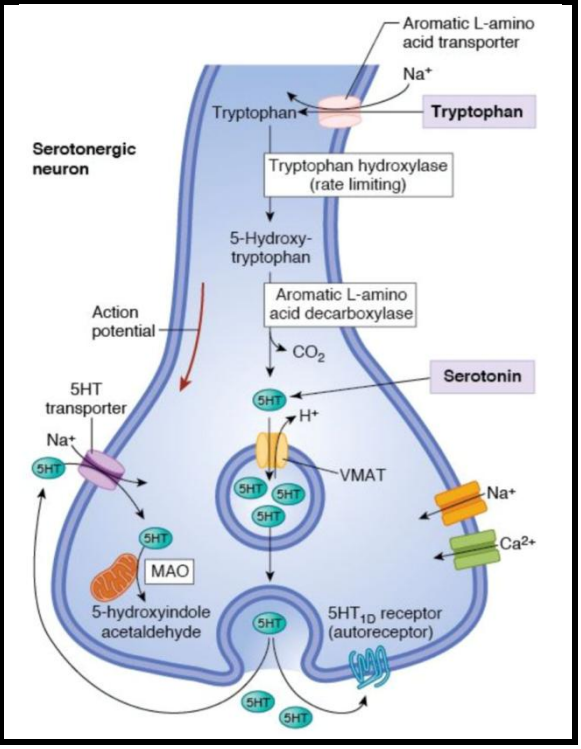
- Drugs for Unit 16
  - Histamine Antagonists
    - H1 Antagonists
      - 1st Generation
        - **Diphenhydramine**
        - Dimenhydrinate
        - Doxylamine
        - Promethazine
        - **Cyclizine**
        - **Chlorpheniramine**
      - 2nd Generation
        - Cetirizine
        - Fexofenadine
        - Loratadine
        - Des-loratadine
    - H2 Antagonists
      - **Cimetidine**
      - Famotidine
      - Ranitidine
      - Nizatidine
  - Serotonin
    - Serotonin Agonists
      - 5-HT1 Agonist
        - **Suma-triptan**
        - Riza-triptan
        - Frova-triptan
        - Almo-triptan
        - Ele-triptan
        - Zolmi-triptan
        - Nara-triptan
      - 5-HT2 Agonist
        - Locaserin
        - Fenfluramine
        - Dex-fenfluramine
      - 5-HT4 Agonist
        - **Tegaserod**
    - Serotonin Antagonists
      - 5-HT2 Antagonist
        - **Ketanserin**
        - Cycloheptadine
        - Phenoxybenzamine
      - 5-HT3 Antagonist
        - **Ondan-steron**
        - Grani-steron
        - Dola-steron
        - Palono-steron
        - Alo-steron
  - Ergot Alkaloids
    - Vessels
      - **Ergotamine**
    - Uterus
      - **Ergonovine**
    - Brain
      - **Lysergic Acid Diethylamide (LSA)**
      - Bromocriptine
      - Pergolide
      - Cabergoline
      - Methylsergide

HISTAMINE METABOLISM

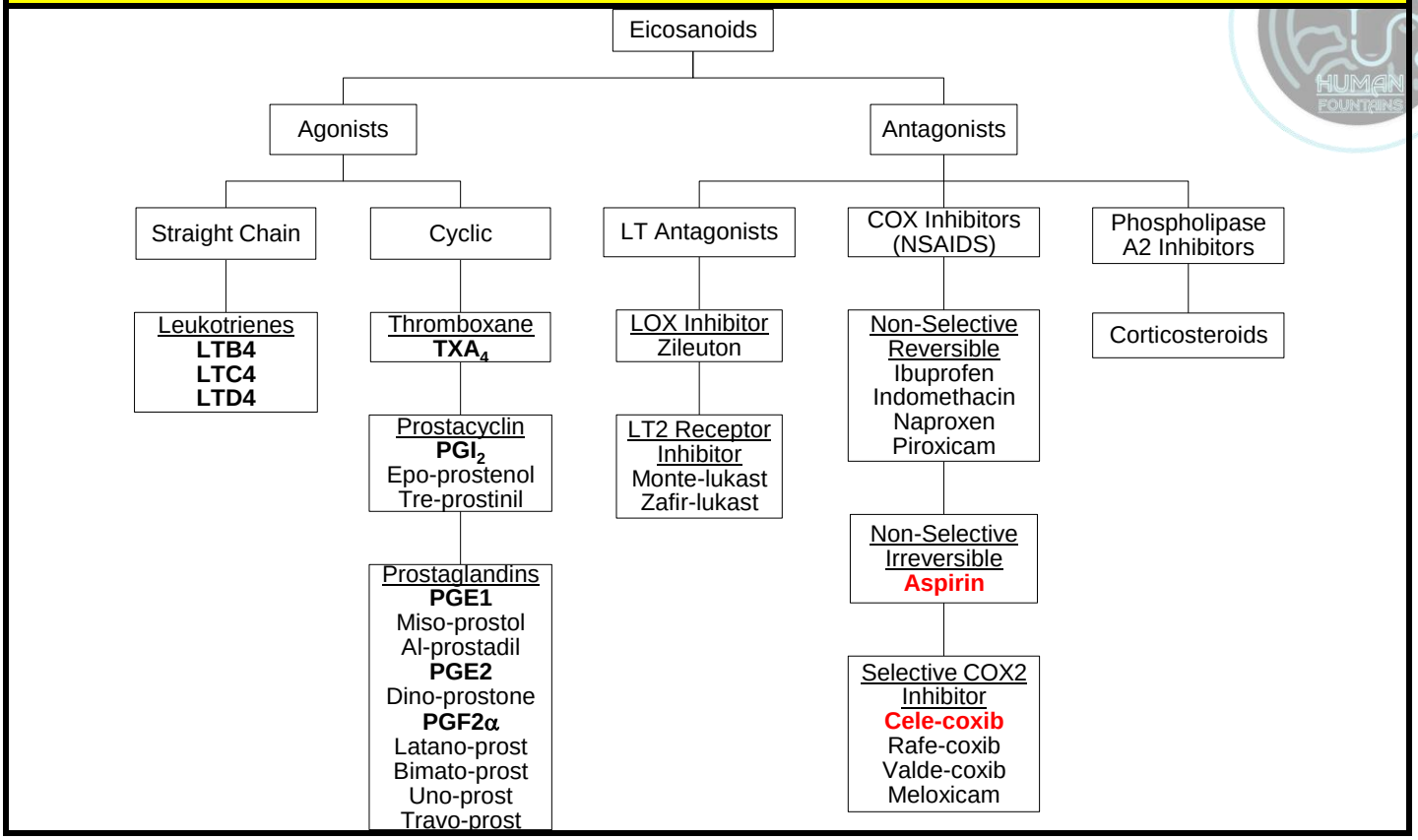


HCl secretion in stomach
Inflammation
Strong Vasodilation (due to NO release)
Thepeuratic Value (none)
Allergy
Mast Cells (production)
IgE
Neurotransmitter or **N**arrow Airways (Bronchoconstriction)
E (x)

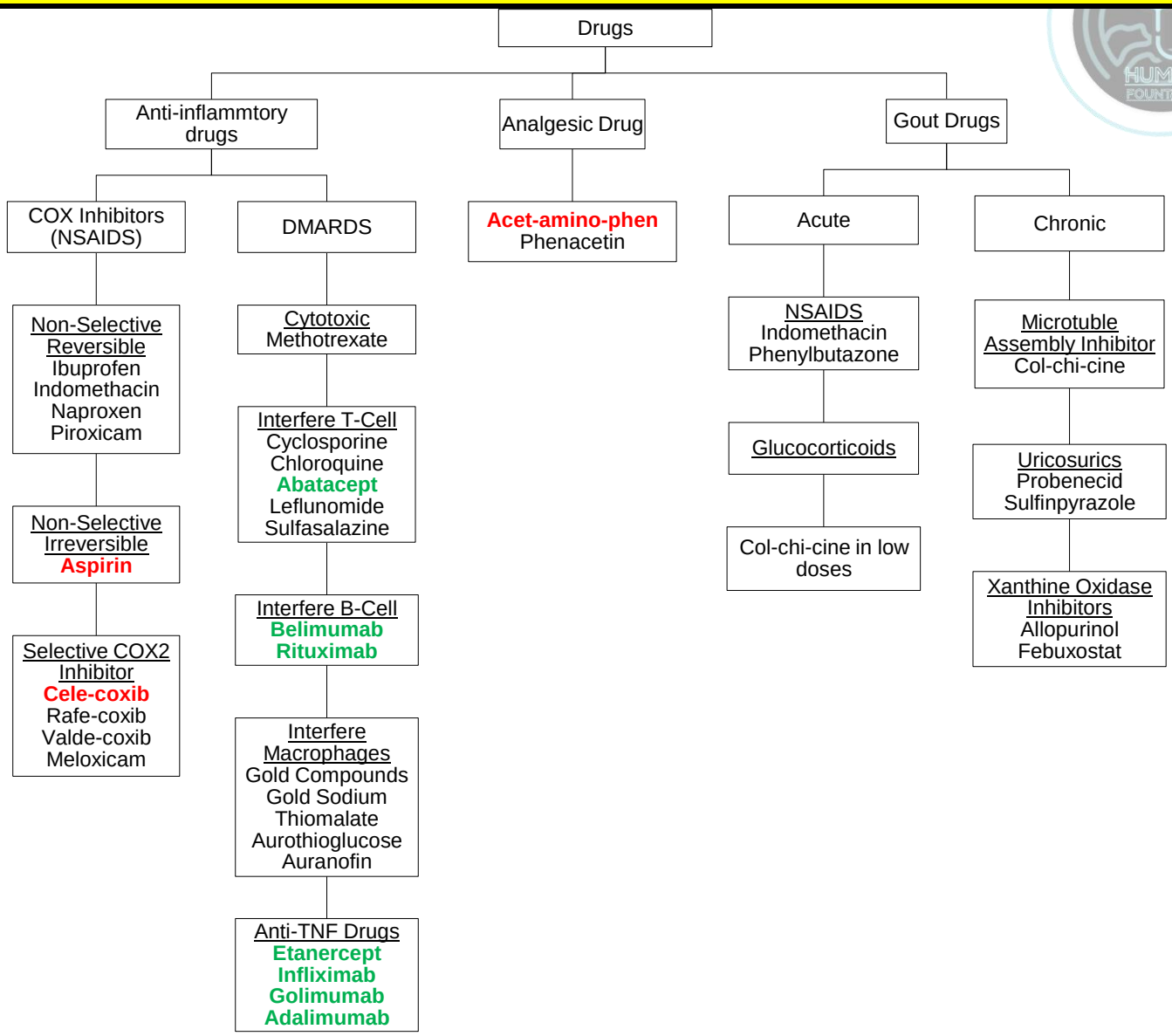
SEROTONIN METABOLISM



EICOSANOID AGONISTS & ANTAGONISTS



NSAIDS, DMARDS & ANTI-GOUT DRUGS



***Biological DMARDS

PHARMACOLOGICAL EFFECTS OF ASPIRIN

DOSE	MAJOR EFFECT	URIC ACID ELIMINATION	ACID & ELECTROLYTE BALANCE
Low: (300 mg/d)	Antiplatelet	↓ tubular secretion → hyperuricemia	
Moderate: (300-2400 mg/d)	Analgesic + Antipyretic		
High: (2400-4000 mg/d)	Anti-inflammatory	↓ tubular reabsorption → uricosuria	Mild uncoupling of oxi. Phosphorylation → ↑ respiration →↓ pCO_2→ **respiratory alkalosis** → renal compensation →↑ HCO_3^- elimination →**compensated** respiratory alkalosis (pH = normal, ↓ HCO_3–, ↓ pCO_2)
Toxic Dose			Inhibits respiratory center →↓ respiration→↑pCO_2→ **respiratory acidosis** (↓ pH, ↓ HCO_3–, normalization of pCO_2) plus inhibition of Krebs cycle and severe uncoupling of oxi. phosphorylation (↓ ATP) →**metabolic acidosis**, hyperthermia, and hypokalemia **TOXICITY MANAGEMENT** 1. No specific antidote. 2. Gastric lavage (± activated charcoal) 3. Ventilatory support 4. Symptomatic management of acid-base/ electrolyte imbalance, & hyperthermia & dehydration. 5. ↑Urine volume & its alkalinization facilitate salicylate renal elimination. **(zero-order elimination)**

NSAIDS vs ASPIRIN

1. Analgesia: ketorolac > ibuprofen/naproxen > ASA
2. Gastrointestinal irritation: < ASA
3. Minimal effects on acid-base balance
4. No effects on uric acid elimination
5. Allergy: common, possible cross-hypersensitivity with ASA
6. Renal: chronic use may cause nephritis, nephritic syndrome, acute failure (via ↓ formation of PGE2 and PGI2, which normally maintain GFR and RBF)

SELECTIVE COX-2 INHIBITORS vs NSAIDS

1. Less gastrointestinal toxicity
2. Less antiplatelet action
3. Not effective as an antiinflammatory agent.
4. Exert prothrombotic effects via inhibition of endothelial cell function (MI and strokes).
5. Increased risk of Arterial Thrombosis

ACETAMINOPHEN IS PREFERRED OVER ASPIRIN

1. Renal Disease
2. Duodenal Ulcer
3. Viral Infections
4. Aspirin Allergies
5. Bleeding Disorder
6. Late Pregnancy

ACETAMINOPHEN vs ASPIRIN

1. No antiplatelet effect
2. No implication in Reye Syndrome
3. No effects on uric acid
4. Low GUT distress
5. Not bronchospastic

4

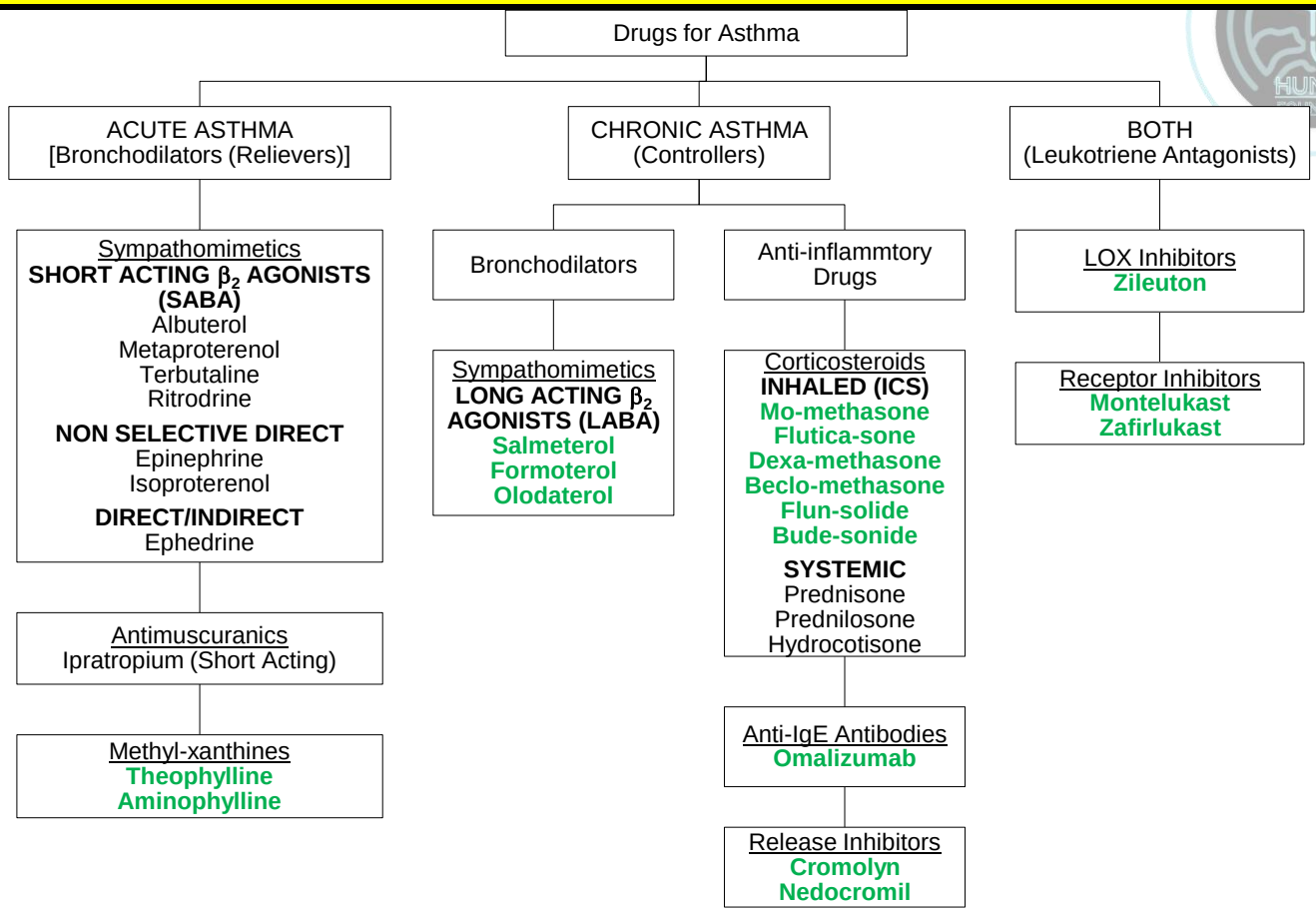
RESPIRATORY PHARMACOLOGY

0.5 SEQ + 2 MCQs = 5.5 Marks

GASTROINTESTINAL PHARMACOLOGY

0.5 SEQ + 3 MCQs = 6.5 Marks

DRUGS FOR ASTHMA

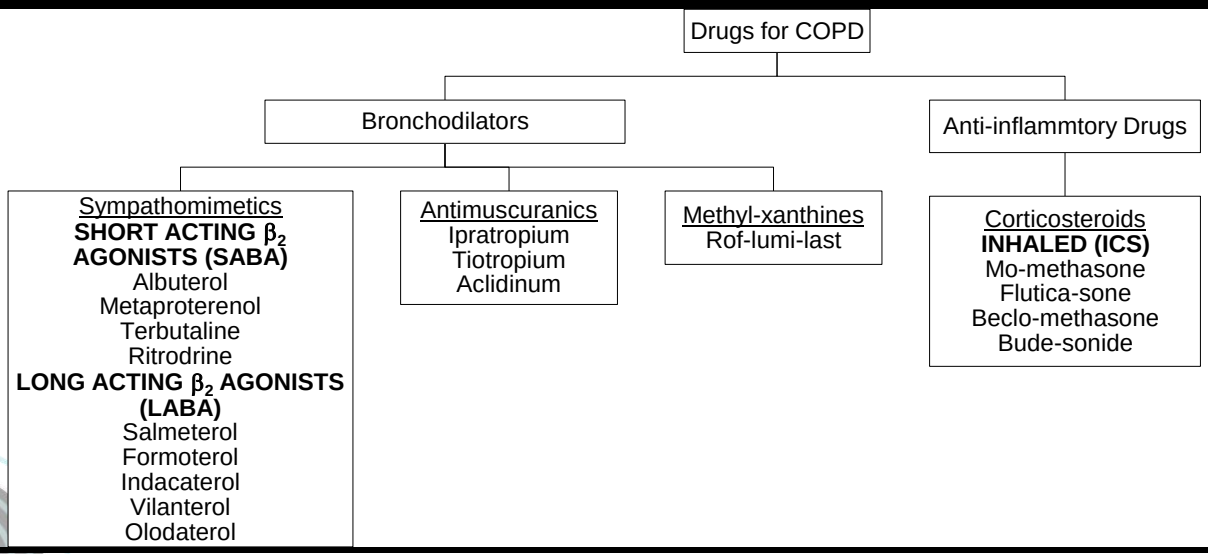


***Porphylaxis of Asthma

MANAGEMENT OF ASTHMA

Classification	Bronchoconstrictive episodes	Results of peak flow or spirometry	Long-term control	Quick relief of Symptoms
Intermittent	< 2 days per week	Near normal*	No daily medication	SABA
Mild persistent	> 2 days per week, not daily		Low-dose ICS	
Moderate persistent	Daily	60% to 80% of normal	Low-dose ICS + LABA **OR** Medium-dose ICS	
Severe persistent	Continual	< 60% of normal	Medium-dose ICS + LABA **OR** High-dose ICS + LABA	

DRUGS FOR COPD



DRUGS FOR GASTROINTESTINAL DISORDERS

Drugs for GIT Disorders

ACID PEPTIC DISEASE
1. Antacids: $Mg(OH)_2$; $Al(OH)_3$
2. H_2 Blockers: **Cimetidine**; Famotidine; Ranitidine; Nizatidine
3. Proton Pump Inhibitors: **Ome-prazole**; Panto-prazole; Rabe-prazole; Dex-lanso-parazole; Lanso-prazole; Es-ome-prazole
4. Mucosal Protective Agents: Sucralfate; Misoprostol; Colloid Bismuth
5. Antibiotics: Amoxicillin, Metronidazole, Clarithromycin

PROKINETIC AGENTS (↑MOTILITY)
1. D_2 Blockers: Metoclopramide; Domperidone
2. Macrolides: Erythromycin
3. Cholinomimetics: Neostigmine

LAXATIVES/ PURGATIVES
1. Bulk Forming: Psyllium, Methylcellulose, Polycarbophil
2. Osmotic: MgO, $Mg(OH)_2$, Sorbitol, Lactulose, Mg citrate, Na_3PO_4, Polyethylene glycol
3. Stool Softening/Lubricating/Surfactants: Docusate, Glycerin, Mineral oil
4. Stimulant: Aloe, Bisacodyl, Cascara, Castor oil, Senna
5. Chloride Channel Activator: Lubiprostone, Linaclotide (cGMP)
6. Opioid Antagonists: Methylnaltrexone, Alvimopan

ANTI-DIARRHEALS
1. Opoid Agonists: Loperamide; Diphenoxylate
2. Colloid Bismuth Compounds: Subsalicylate; Citrate
3. Adsorbents: Kaolin + Pectin

IRRITABLE BOWEL SYNDROME
1. $5\text{-}HT_3$ Blockers: **Alo-setron**
2. Anticholinergics: Dicycloamines, Hyoscyamine
3. Chloride Channel Activators: Lubiprostone
4. $5\text{-}HT_4$ Agonist: Tegaserod

ANTIEMETICS
1. Antimuscuranics: Scopolamine, Phenothiazines
2. Corticosteroids: Dexamethasone
3. Cannabinoids: Dronabinol; Nabilone
4. D_2 Blockers: Phenothiazines; Metoclopramide
5. $5\text{-}HT_3$ Blockers; Ondan-steron; Grani-steron; Dola-steron; Palono-steron
6. H_1 Blockers: Diphenhydramine, Dimenhydrinate, Cyclizine
7. NK_1 Blockers: Apre-pitant, Netu-pitant, Rowa-pitant

INFLAMMATORY BOWEL DISEASE
1. Aminosalicylates (5-ASA): Me-salamine, Pentasa, Asacol, Lialda, Rowasa, Canasa
2. AZO Compounds: Bal-salazide, Ol-salazine, Sulfa-salazine
3. Glucocorticoids: Budesonide
4. Immunosuppressive Antimetabolites: 6-Mercaptopurine, Azathioprine, Methotrexate
5. Anti-TNF Drugs: Infliximab, Golimumab, Adalimumab
6. B-Cell Intregrin Blocker: Natalizumab

PANCREATIC SUPPLEMENTS
Pancrelipase
Pancreatin

BILE ACID THERAPY
Ursodiol

5

CARDIOVASCULAR, DIURETIC & BLOOD PHARMACOLOGY

1.5 SEQ + 10 MCQs = 20.5 Marks

ANTI-HYPERTENSIVE DRUGS

Anti-Hypertension Drugs

Diuretics (Blood Volume ↓)

Thiazide Diuretics (mild-moderate hypertension)
Hydro-choloro-thiazide
Chlorothiazide
Metolazone
Chlorthalidone

Loop Diuretics (severe hypertension)
Furosemide
Bumetanide
Torsemide
Ethacrynic Acid

Sympathoplegics

Baroreceptor Sensitizing Agents (↓SANS, ↑Heart Vagal tone)
Veratrum Alkaloids (Natural)

CNS Acting (α_2 Agonists) (↓CO, ↓TPR)
Clonidine
Methyldopa

Ganglion Blockers
Hexamethonium
Mecamylamine
Trimethaphan

Postganglionic Neuron Blockers
Reserpine
Guanethidine
Guanadrel
MAO inhibitors

Adrenoceptor Blockers
α_1 Blockers (↓TPR)
Para-zosin
Doxa-zosin
Tera-zosin
β Blockers (↓CO, ↓TPR)
Propranolol
β_1 Blockers (↓CO, ↓TPR)
Atenolol
Nebivolol
Esmolol
Metoprolol
Acebutalol
α/β Blockers (↓CO, ↓TPR)
Labetolol
Carvedilol

Vasodilators

Calcium Channel Blockers
Dihydropyridines
Felo-dipine
Isra-dipine
Nicar-dipine
Nisol-dipine
Nife-dipine
Amlo-dipine
Verapa-mil
Dilti-azem

NO Releasers
Hydrala-zine
Nitroprusside

Postassium Channel Openers
Minoxidil Sulfate
Diazoxide

D_1 Agonist
Fenoldopam

Angiotension Antagonists

ACE Inhibitors
Capto-pril
Benaze-pril
Lisino-pril
Enala-pril

ARBs
Cande-sartan
Lo-sartan
Irbe-sartan
Val-sartan

Renin Antagonist

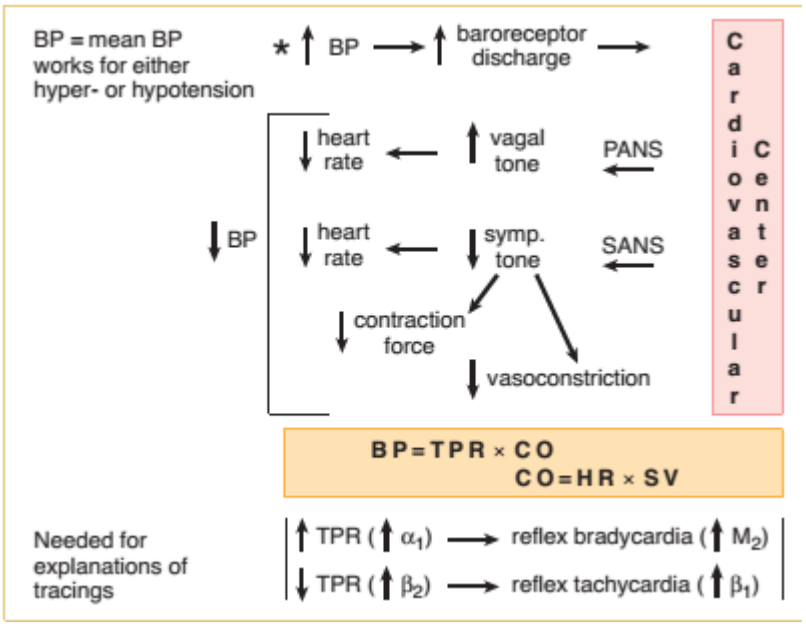
Aliskiren

HYPERTENSION DRUG STRATEGY:

1. ↓TPR
2. ↓CO
3. ↓Body Fluid Volume

COMPENSATORY RESPONSE:

1. Reflex Tachycardia (↑SANS) - Baroreceptors
2. Edema (↑Renin)



▶ COMBINATION OF DRUGS IN CO-MORBID DISEASES

INDICATION (Hypertension +)	DRUG(S)
Angina	β-blockers, CCBs
Diabetes, Chronic Kidney Disease	ACEI, ARBs, CCBs (-dipines)
Heart failure	ACEIs, ARBs, β-blockers
Post-MI	β-blockers
BPH	α-blockers
Dyslipidemias	α-blockers, CCBs, ACEIs/ARBs
Pregnancy (Chronic Hypertension)	Methyldopa/ Labetolol
Pregnancy (Preeclampsia)	Hydralazine/Labetolol

▶ LOSARTAN IS PREFERRED OVER CAPTOPRIL?

It has lower incidence of cough i.e. by inhibiting kininase II (which normally prevents degradation of histamine).

▶ DOES CCBs AFFECT SKELETAL MUSCLE?

No, as contraction in skeletal muscles is mediated by Ca^{2+} release from sarcoplasmic reticulum and CCBs affects L- type Ca^{2+} channel located in plasma membranes of smooth and cardiac muscles most effectively.

ANTI-ANGINAL DRUGS

- Anti-Anginal Drugs
  - Vasodilators
    - Nitrates
      - Ultrashort Acting (Inhalational): Amyl nitrite
      - Short Acting (Sublingual): Nitroglycerin, Isosorbide dinitrate
      - Intermediate Acting (Oral): Nitroglycerin, Isosorbide dinitrate, Isosorbide mononitrate, Pentaerythritol tetranitrate
      - Long Acting (Transdermal): Nitroglycerin
    - Calcium Channel Blockers
      - Dihydropyridines (Oral): Felo-dipine, Isra-dipine, Nicar-dipine, Nisol-dipine, **Nife-dipine**, Amlo-dipine
      - Verapa-mil (Oral & Parenteral)
      - Dilti-azem (Oral & Parenteral)
  - Cardiac Depressents
    - β-Blockers
      - Non-Selective β Blockers: **Propranolol**
      - β_1 Blockers: Atenolol, Nebivolol, Esmolol, Metoprolol, Acebutalol
  - Others
    - pFOX Inhibitors: Ranolazine, Trimetazidine
    - Selective HR↓: Ivabradine

ERECTILE DYSFUNCTION

Nitrates + "-afils"
- i. Silden-afil
- ii. Tadal-afil
- iii. Varden-afil

TREATMENT STRATEGIES FOR ANGINA

TYPE OF ANGINA	TREATMENT STRATEGY	COMPENSATORY
Atherosclerotic/ Stable/ Classic Angina/ Angina of Effort	**↓Oxygen Requirement by ↓TPR, ↓CO or Both** **↑ Coronary Blood Flow** Acute Attack: Nitrates + Rest (Repeat in recurrence); Nifedipine can also be given Prophylaxis: CCBs, β-blockers	From action of nitrates: 1. Reflex Tachycardia (↑SANS) – Baroreceptors 2. ↑ Heart Force
Vasospastic/ Rest/ Variant/ Prinzmetal's Angina	**↑Oxygen Delivery by reversing vasospasm** **↑ Coronary Blood Flow** Nitrates Prophylaxis: CCBs	
Unstable/ Crescendo Angina/ Acute Coronary Syndrome	I/V nitrates (nitroglycerin) given Definite: Myocardial Revascularization (Coronary Artery Bypass Grafting CABG, Percutaneous Transluminal Coronary Angioplasty PTCA)	-

TREATMENT OF CYANIDE POISONING

TREATMENT 1

(3 step procedure)
1. **Immediate inhalation of amyl nitrite & IV administration of sodium nitrite** promotes formation of MetHb, which binds CN− ions, forming cyanoMetHb which prevents inhibitory action of CN− (complex IV of ETC)
2. CyanoMetHb is reconverted to MetHb by treatment with **IV sodium thiosulfate**, forming MetHB and the less toxic thiocyanate ion (SCN−) excreted by kidney.
3. MetHb is converted to OxyHb with **methylene blue.**

TREATMENT 2

Hydroxocobalamin (preferred now)

HEART FAILURE DRUGS (A: ACUTE; C: CHRONIC)

Heart Failure Drugs

Positive Inotropic Drugs

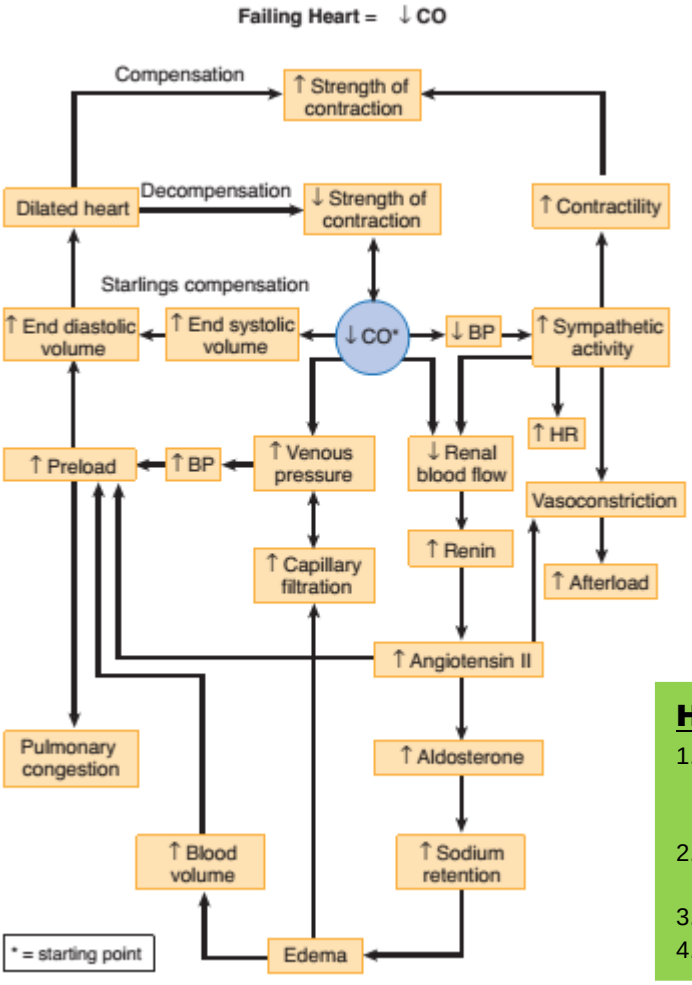
- Cardiac Glycosides (CHF)
  - Digoxin
  - Digitoxin (long duration)
- β-Agonists (AHF)
  - Dobutamine
  - Dopamine
- PDE Inhibitors/Bipyridines (AHF)
  - Milrinone
  - Theophylline

Vasodilators

- NO Releasers (AHF)
  - Nitroprusside
  - Nitroglycerin
- NO Releasers (CHF)
  - Nitrates
  - Hydralazine
- ADH Antagonists
  - Coni-vaptan
  - Tol-vaptan

Miscellanous drugs for CHF

- Loop Diuretics (AHF + CHF)
  - **Furosemide**
  - Bumetanide
  - Torsemide
  - Ethacrynic Acid
- Thiazide Diuretics (CHF)
  - **Hydrochloro-thiazide**
  - Chlorothiazide
  - Metolazone
  - Chlorthalidone
- ACE Inhibitors (CHF)
  - Capto-pril
  - Benaze-pril
  - Enala-pril
  - Lisino-pril
- ARBs (CHF)
  - Irbe-sartan
  - Cande-sartan
  - Lo-sartan
  - Val-sartan
- Natriuretic Peptide (AHF)
  - Ne-siri-tide
- β-Blockers (CHF)
  - Bisoprolol
  - Carvedilol
  - Metoprolol
  - Nebivolol
- K+ Sparing Diuretics (CHF)
  - Spironolactone
  - Eplerenone



** Yellow Highlighted for AHF
** Blue Highlighted for both AHF & CHF

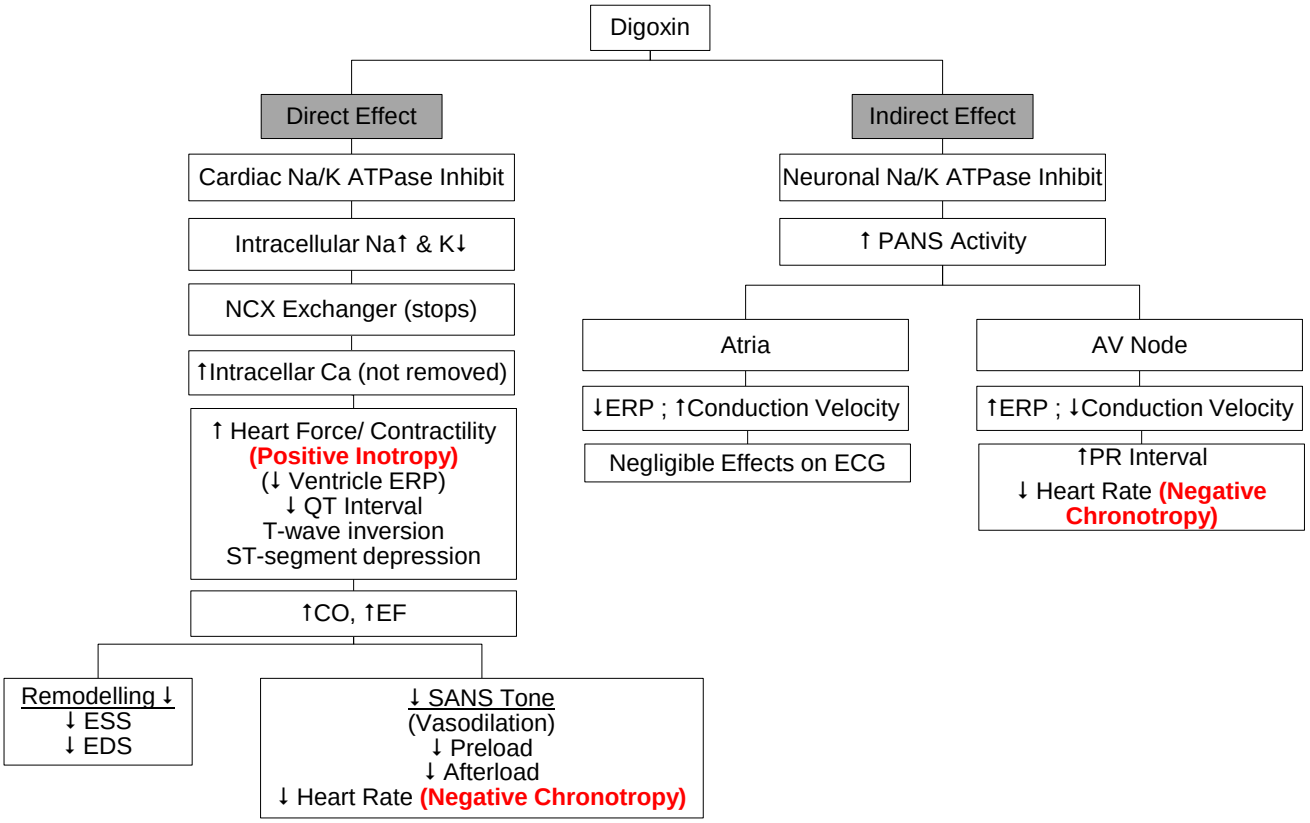
HEART FAILURE DRUGS STRATEGY

1. ↓Preload (Blood Volume x Venous Tone)
   a. ↓Blood Volume by Diuretics, ACEIs, ARBs
   b. ↓Venous Tone by Venodilators
2. ↓Afterload (TPR or BP) by ACEIs, ARBs, β-blockers , Arteriodilators
3. ↑Contractility by Positive Inotropic Drugs
4. ↓Remodeling of Heart Muscles by ACEIs, ARBs, β-blockers,

DIGOXIN MECHANISM OF ACTION & EFFECTS

TABLE 13–2 Effects of digoxin on electrical properties of cardiac tissues.

Tissue or Variable	Effects at Therapeutic Dosage	Effects at Toxic Dosage
Sinus node	↓ Rate	↓ Rate
Atrial muscle	↓ Refractory period	↓ Refractory period, arrhythmias
Atrioventricular node	↓ Conduction velocity, ↑ refractory period	↓ Refractory period, arrhythmias
Purkinje system, ventricular muscle	Slight ↓ refractory period	Extrasystoles, tachycardia, fibrillation
Electrocardiogram	↑ PR interval, ↓ QT interval	Tachycardia, fibrillation, arrest at extremely high dosage



TYPES OF HEART FAILURE & TREATMENT

TABLE 13–3 Classification and treatment of chronic heart failure.

ACC/AHA Stage[1]	NYHA Class[2]	Description	Management
A	Prefailure	No symptoms but risk factors present[3]	Treat obesity, hypertension, diabetes, hyperlipidemia, etc
B	I	Symptoms with severe exercise	ACEI/ARB, β blocker, diuretic
C	II/III	Symptoms with marked (class II) or mild (class III) exercise	Add aldosterone antagonist, digoxin; CRT, ARNI, hydralazine/nitrate[4]
D	IV	Severe symptoms at rest	Transplant, LVAD

[1]American College of Cardiology/American Heart Association classification.

[2]New York Heart Association classification.

[3]Risk factors include hypertension, myocardial infarct, diabetes.

[4]For selected populations, eg, African Americans.

ACC, American College of Cardiology; ACEI, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor inhibitor plus neprilysin inhibitor; CRT, cardiac resynchronization therapy; LVAD, left ventricular assist device; NYHA, New York Heart Association.

HEART FAILURE DIFFERENCES

TABLE 13–4 Differences between systolic and diastolic heart failure.

Variable or Therapy	Systolic Heart Failure	Diastolic Heart Failure
Cardiac output	Decreased	Decreased
Ejection fraction	Decreased	Normal
Diuretics	↓ Symptoms; first-line therapy if edema present	Use with caution[1]
ACEIs	↓ Mortality in chronic HF	May help to ↓ LVH
ARBs	↓ Mortality in chronic HF	May be beneficial
ARNI	↓ Symptoms and NT-proBNP	↓ Symptoms and NT-proBNP
Aldosterone inhibitors	↓ Mortality in chronic HF	May be useful
Beta blockers[2], ivabradine	Beta blocker ↓ mortality in chronic HF, ivabradine reduces hospitalizations	Useful to ↓ HR, ↓ BP
Calcium channel blockers	No or small benefit[3]	Useful to ↓ HR, ↓ BP
Digoxin	May reduce symptoms	Little or no role
Nitrates	May be useful in acute HF[4]	Use with caution[1]
PDE inhibitors	May be useful in acute HF	Very small study in chronic HF was positive
Positive inotropes	↓ Symptoms, hospitalizations	Not recommended

[1]Avoid excessive reduction of filling pressures.

[2]Limited to certain β blockers (see text).

[3]Benefit, if any, may be due to BP reduction.

[4]Useful combined with hydralazine in selected patients, especially African Americans.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor inhibitor plus neprilysin inhibitor; BP, blood pressure; HF, heart failure; HR, heart rate; LVH, left ventricular hypertrophy; NT-proBNP, N-terminal pro-brain natriuretic peptide; PDE, phosphodiesterase.

ANTI-ARRHYTHMIC DRUGS

Anti-Arrhythmic Drugs

- **Group 1 I_{Na} Blockers**
  - **Group 1A** — Prolong AP, Moderate Kinetics: **Procain-amide**, Disopyr-amide, Quini-dine, **Amio-darone**
  - **Group 1B** — Shorten AP, Fast Kinetics: **Lidoca-ine**, Mexilet-ine, Phenytoin
  - **Group 1C** — No effect on AP, Slow Kinetics: **Flecain-ide**
- **Group 2** — β-Blockers: **Propranolol**, Metoprolol, Timolol, **Esmolol**, **Sota-lol**, **Amio-darone**
- **Group 3** — I_K Blockers, Prolong AP: **Sota-lol**, **Ibu-tilide**, **Dofe-tilide**, **Amio-darone**, Drone-darone
- **Group 4** — L-type I_{Ca} Blockers: **Verapamil**, Diltiazem, **Amio-darone**
- **Group 5** — Misc.: Adenosine, Potassium, Magnesium, Ranolazine, Ivabradine

***Sotalol Effect: I_K blocker > β-blocker

***Amiodarone Effect: I_K blocker > I_{Na} blocker > β-blocker > I_{Ca} blocker

PROPERTIES OF PROTOTYPIC ANTI-ARRHYTHMIC DRUGS (PM: PACE MAKER)

Group	Drug	AP	I_{Na} Block		ER Period		β-Block	I_{Ca} Block	PR Interval	QRS Duration	QT Interval	PM Activity
			Normal	Ischemic	Normal	Ischemic						
1A	Procaineamide Disopyramide Quinidine	↑	+	+++	↑	↑↑↑	+	- + -	↑/↓	↑↑	↑↑	↓
1B	Lidocaine Mexiletine	↓	-	+++	↓	↑↑	-	-	-	-	-/↓	↓↓
1C	Flecainide	-	+	+++	-	↑	-	-	↑	↑↑	-	↓↓
2	Propranolol Esmolol	-	-	+	↓	↑↑	+++	-	↑↑	-	-	↓↓
3, 1A, 2, 4	Amiodarone Dronedarone	↑	+	+++	↑↑	↑↑	+	+	↑	↑↑	↑↑↑↑	↓↓
3	Ibutilide Dofetilide	↑	-	-	↑	?	-	-	-	-	↑↑↑	-
3, 2	Sotalol	↑	-	-	↑↑	↑↑↑	+++	-	↑↑	-	↑↑↑	↓↓
4	Verapamil Diltiazem	-	-	+	-	↑	+	+++	↑↑	-	-	↓↓
5	Adenosine	-	-	-	-	-	+	+	↑↑↑	-	-	-

ANTI-ARRHYTHMIC DRUGS THERAPY

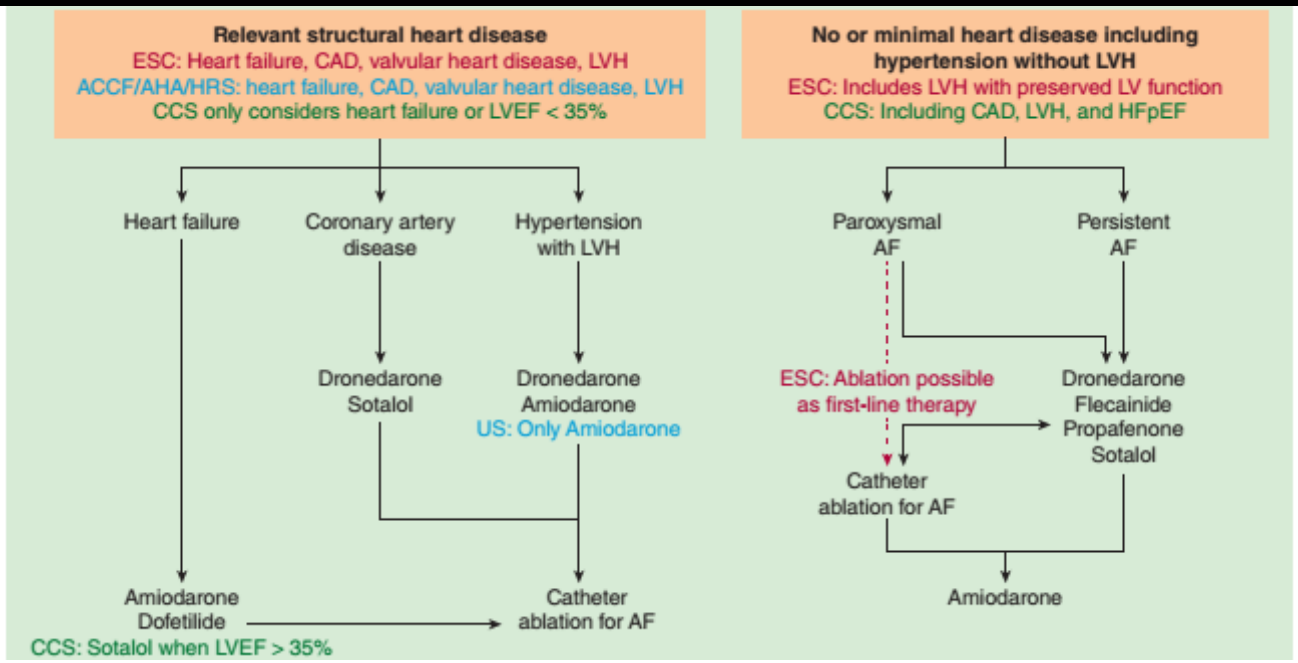
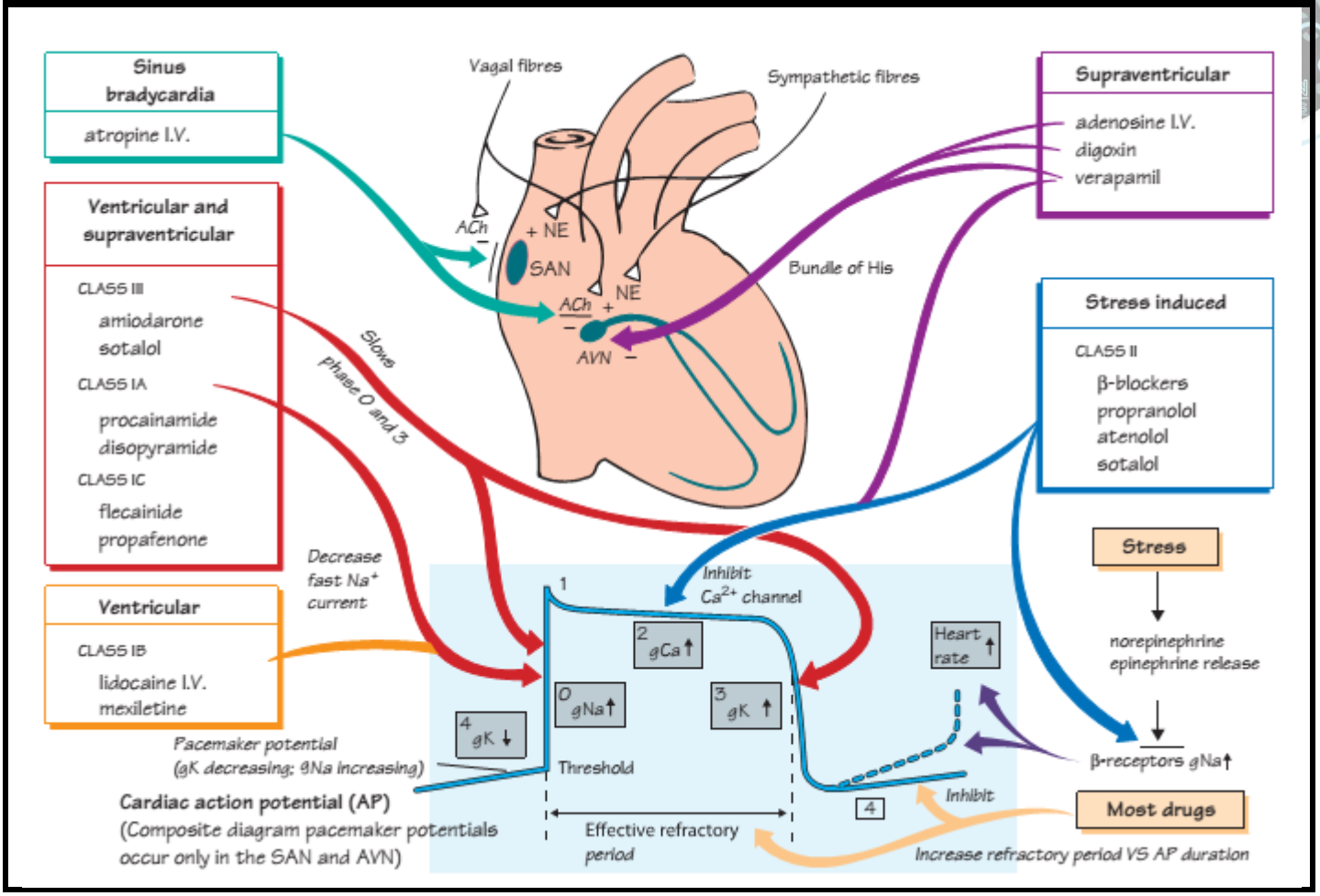


FIGURE 14–11 Selection of rhythm control therapies depends on presence and nature of any underlying heart disease. Patients may be divided into two broad categories: those with and those without underlying heart disease. Patient with heart failure, left ventricular ejection fraction (LVEF) less than 35%, coronary artery disease (CAD), valvular heart disease, and left ventricular hypertrophy (LVH) fall into the first category. The second category includes patients with mild LVH and with heart failure but a preserved ejection fraction (HFpEF). The recommendations are based on the guidelines of the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), the Heart Rhythm Society (HRS), and the Canadian Cardiology Society (CCS). AF, atrial fibrillation; ESC, European Society of Cardiology;

CLINICAL USES OF ANTI-ARRHYTHMIC DRUGS



DIURETICS

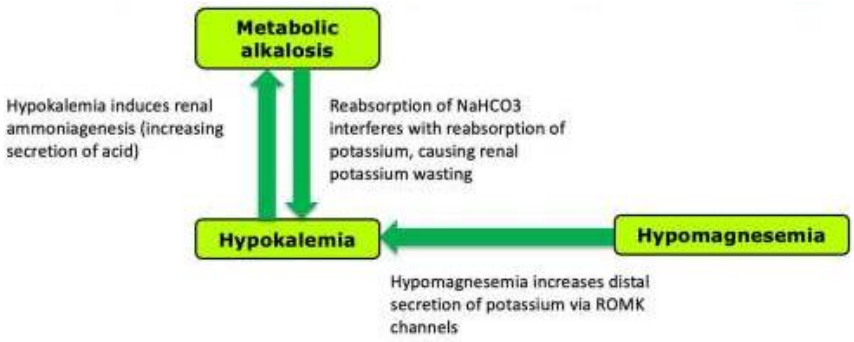
- **Diuretics**
  - **Drugs that modify salt excretion**
    - **PCT**
      - Carbonic Anhydrase Inhibitors
        - **Aceta-zolamide**
        - Dor-zolamide
        - Brin-zolamide
      - SGLT2 Inhibitors
        - Can-agliflozin
        - Dap-agliflozin
        - Emp-agliflozin
        - Ipr-agliflozin
    - **TAL**
      - Loop Diuretics
        - **Furosemide**
        - Torsemide
        - Bumetanide
        - **Ethacrynic Acid**
    - **DCT**
      - Thiazides Diuretics
        - **Hydrochloro-thiazide**
        - Chlorothiazide
        - Metolazone
        - Chlorthalidone
    - **CCT**
      - K+ Sparing Diuretics
        - Spironolactone
        - Eplerenone
        - Amiloride
        - Triamterene
  - **Drugs that modify water excretion**
    - Osmotic Diuretics
      - **Mannitol**
      - Glycerin
      - Isosorbide
      - Urea
    - ADH Agonists
      - **Desmo-pressin**
      - **Vaso-pressin**
    - ADH Antagonists
      - Coni-vaptan
      - Tol-vaptan
      - Demeclocylcine
      - Lithium

ACIDOSIS & ALKALOSIS

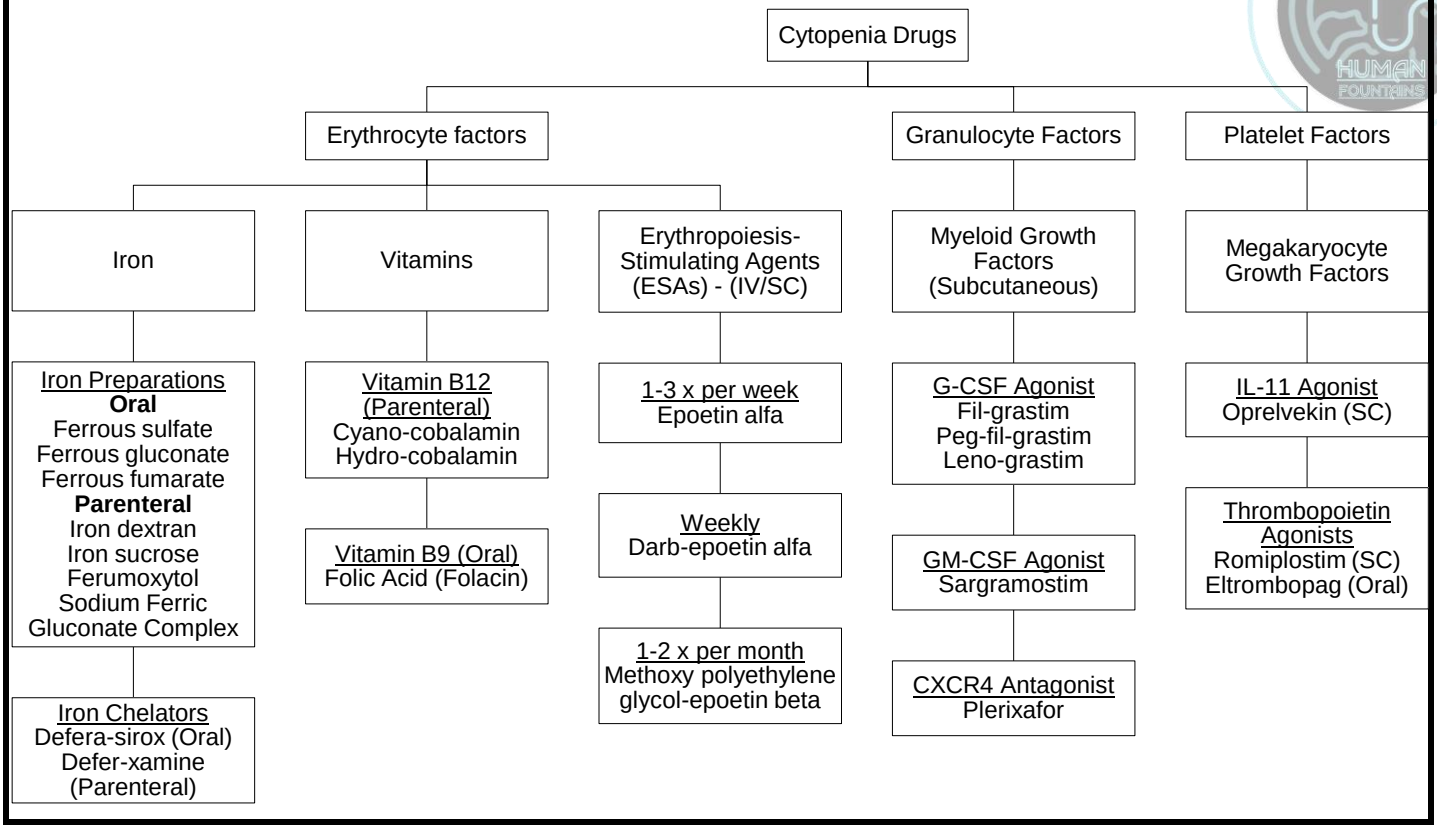
pH: Acidosis or Alkalosis?

- pH < 7.35 → **Acidosis:** CO_2 is high or HCO_3^- is low
  - **CO_2 is high:** Respiratory acidosis
    - **HCO_3^- normal:** No renal compensation
    - **HCO_3^- is high:** Renal compensation
  - **HCO_3^- is low:** Metabolic acidosis
    - **CO_2 normal:** Respiratory compensation
    - **CO_2 is low:** No respiratory compensation
- *Which reading fits with the change in pH?*
- pH > 7.45 → **Alkalosis:** CO_2 is low or HCO_3^- is high
  - **CO_2 is low:** Respiratory alkalosis
    - **HCO_3^- normal:** No renal compensation
    - **HCO_3^- is low:** Renal compensation
  - **HCO_3^- is high:** Metabolic alkalosis
    - **CO_2 normal:** No respiratory compensation
    - **CO_2 is high:** Respiratory compensation

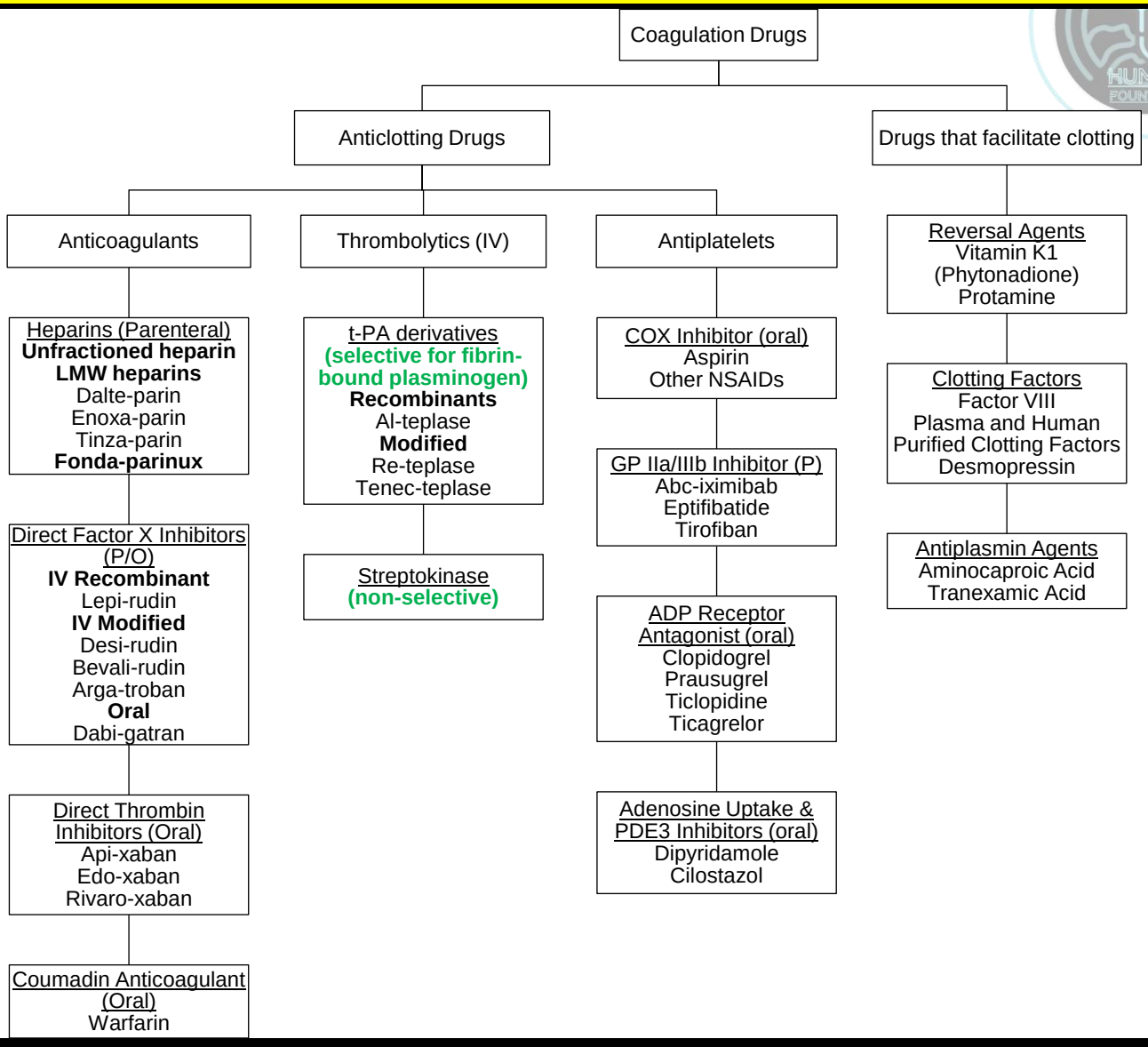
HYPOKALEMIA & METABOLIC ALKALOSIS



DRUGS USED IN CYTOPENIAS/ ANEMIAS



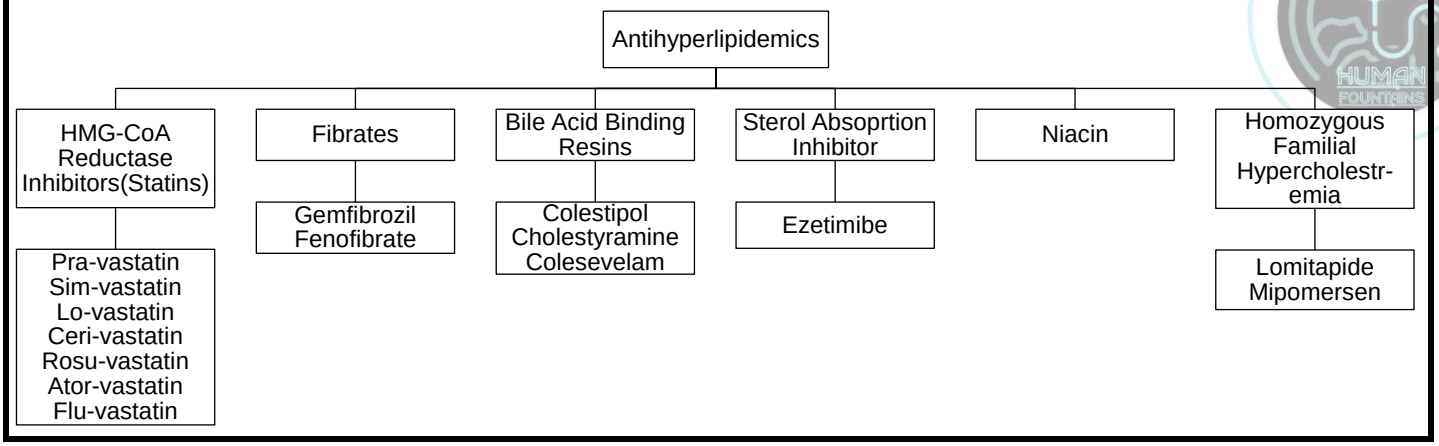
DRUGS USED IN COAGULATION DISORDERS



DIFFERENCE BETWEEN LMW HEPARINS & HMW HEPARINS

Feature	HMWH	LMWH
Molecular Weight	15000-20000 Daltons	2000-6000 Daltons
Bioavailability	Low	High (90%)
Half Life	Short (Dose dependent)	Long (Dose independent)
Mode of Action	Inactivates both factor IIa & Xa	Inactivates only Xa
Anticoagulant Effect	More effective	Less Effective
Monitoring	By aPTT	Not required (given once/twice a day)
Protamine Reversal	More Effective	Partially Effective
Heparin Induced Thrombocytopenia	More risk	Less risk
Osteroporosis	More risk	Less risk
Excretion	Less reliable	More reliable

ANTIHYPERLIPIDEMICS

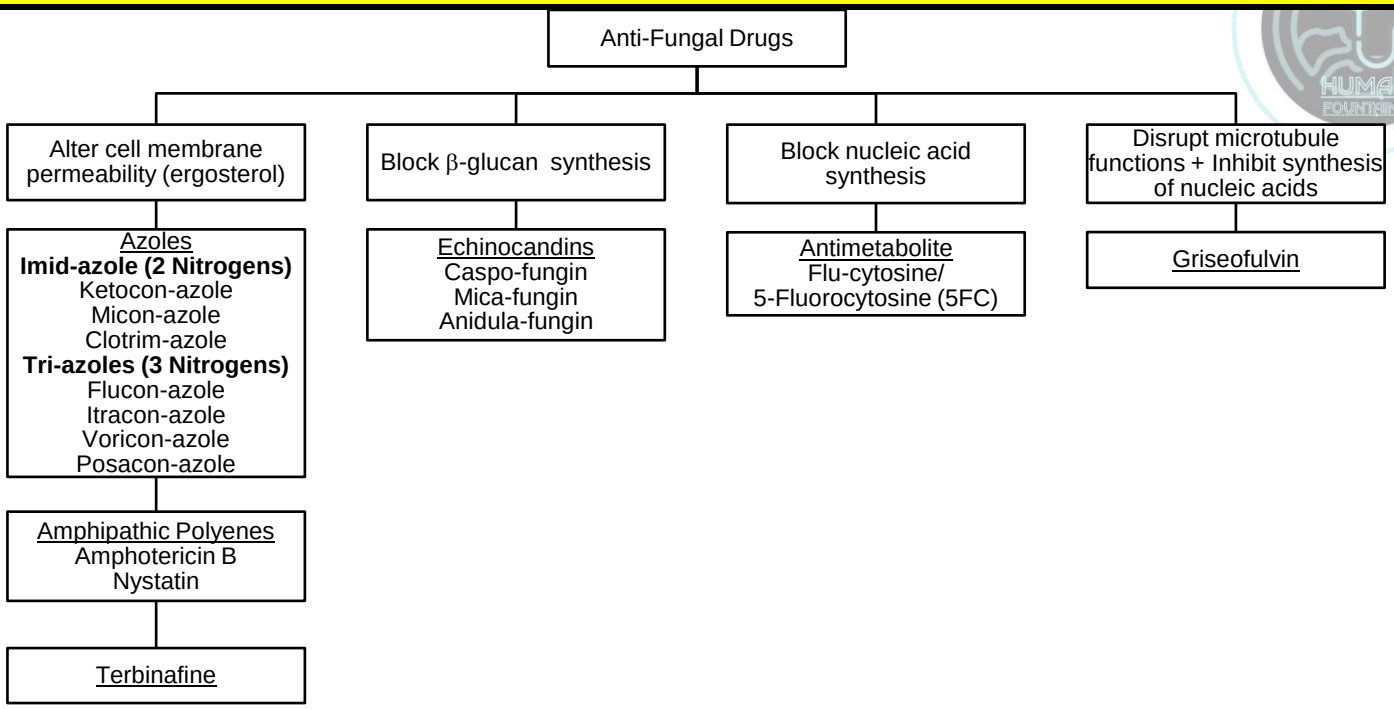


6

ANTIFUNGAL, ANTIVIRAL & ANTICANCER PHARMACOLOGY

0.5 SEQ + 5 MCQs = 8.5 Marks

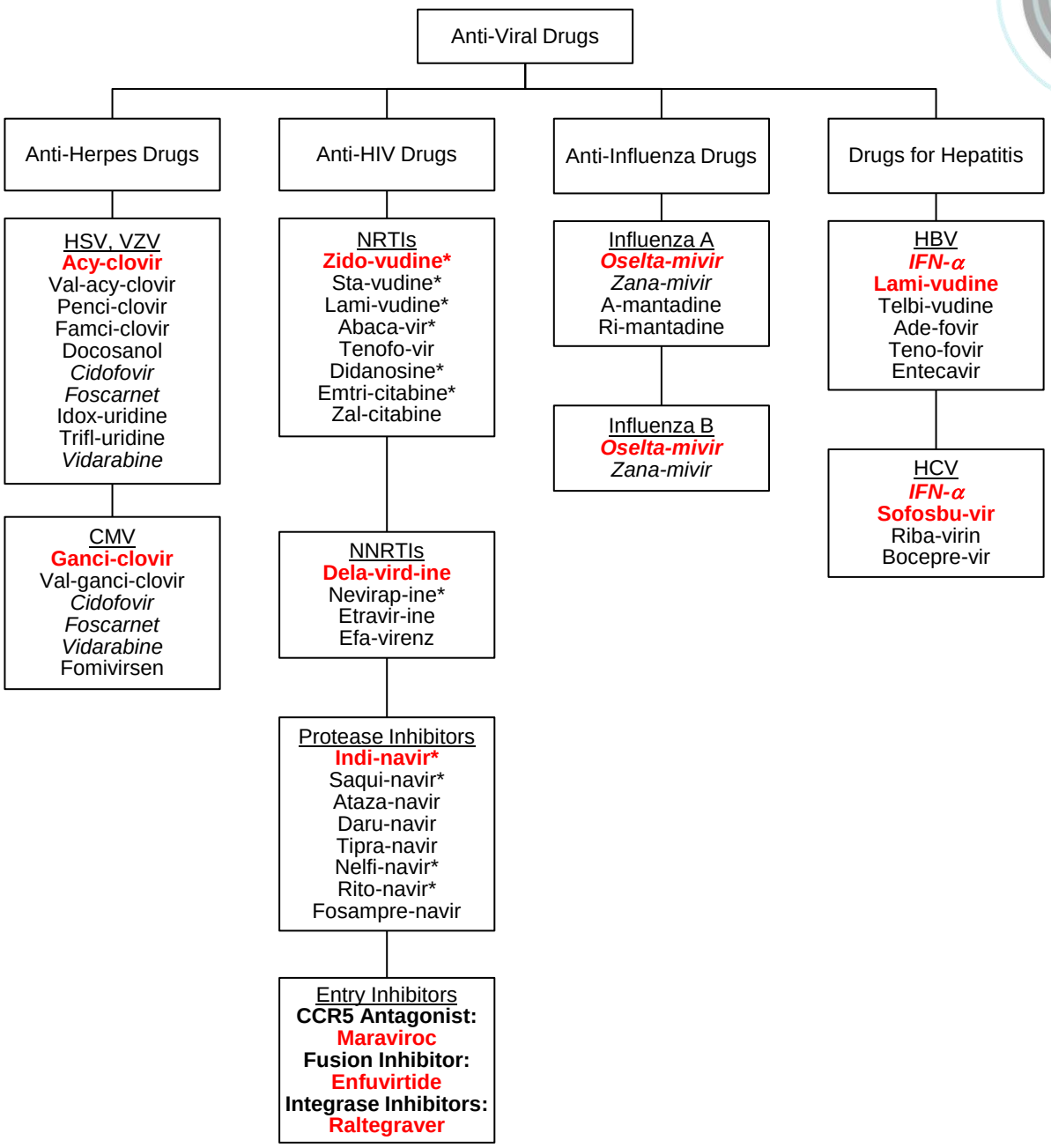
ANTI-FUNGAL DRUGS



SPECTRUM OF AZOLES

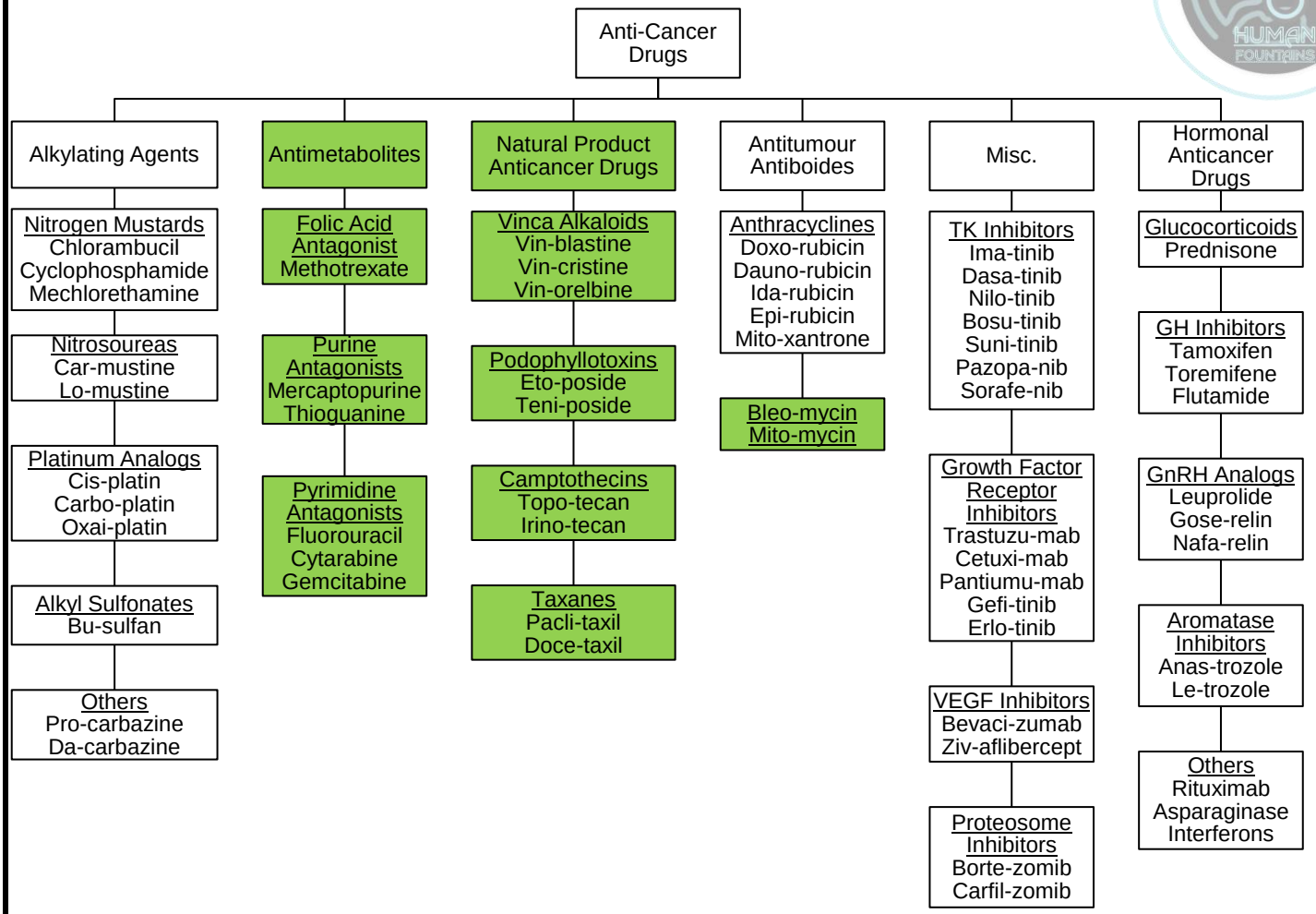
Name	Spectrum	Cutaneous Mycoses	Subcutaneous Mycoses	Systemic Mycoses	Opportunistic Mycoses
Ketoconazole Miconazole Clotrimazole	+ > Ketokonzaole > Ketokonzaole	Dermatophytes			Candida (CMC)
Fluconazole	++	Dermatophytes		Coccidioides Blastomyces	Candida Cryptococcus
Itraconazole	+++	Dermatophytes	Sporothrix **Chromomycosis**	Coccidioides Histoplasma Blastomyces Paracoccidioides	Cryptococcus Aspergillus
Voriconazole	+++				Candida Aspergillus
Posaconazole	++++				Candida Aspergillus Rizopus

ANTIVIRAL DRUGS



***Anti-retroviral drugs used in pregnancy**

ANTICANCER DRUGS



*Green Highlighted are CCS (Cell Cycle Specific) Drugs

7

ANTI-MYCOBACTERIAL & PARASITIC PHARMACOLOGY

1 SEQ + 6 MCQs = 13 Marks

ANTI-PROTOZOAL DRUGS

Anti-Protozoal Drugs for Intestinal & Urogneital Protozoans

- **Amebiasis**
  - Tissue Amebicides (act on GIT wall & Liver): Metronidazole, Tinidazole, Chloroquine, Emetines
  - Luminal Amebicides (act on GIT wall): Diloxanide furoate, Iodoquinol, Paromomycin
- **Giardiasis**: Metronidazole, Tinidazole
- **Cryptosporidiosis**: Paromomycin, Nitazoxanide
- **Trichomoniasis**: Metronidazole, Tinidazole

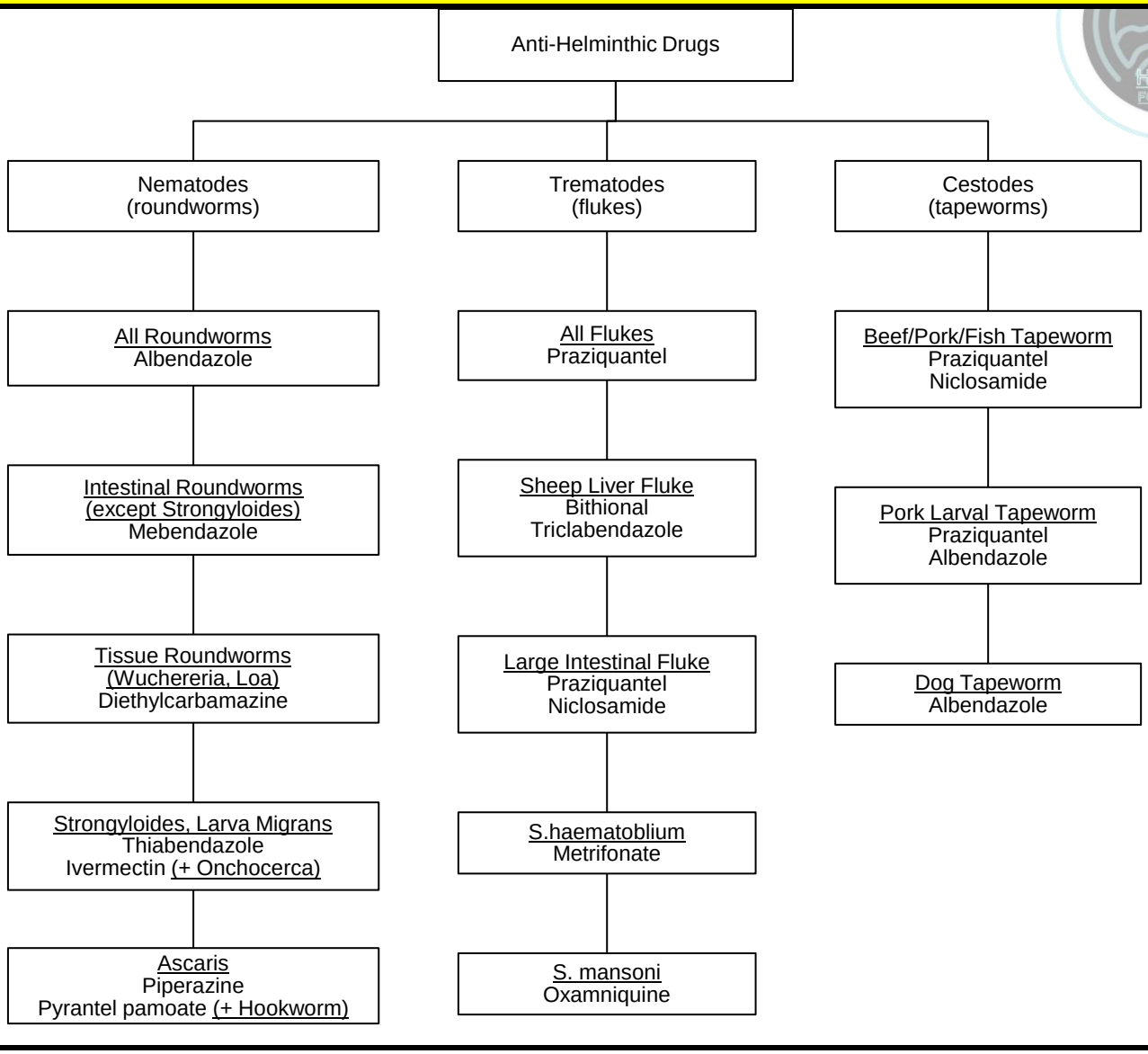
Anti-Protozoal Drugs for Blood & Tissue Protozoans

- **Malaria**
  - Tissue Schizonticides (kill schizonts in liver): Prima-quine
  - Blood Schizonticides (kill schizonts in RBCs): Chloro-quine, Meflo-quine, Qui-nine, **Artemisi-nins** (Artesunate, Artemether, Dihydro-artemisinin)
  - Sporonticides (prevent sporogony): **Antifolates** (Sulfonamide, Proguanil, Pyrimethamine)
  - Other Malarial Drugs: Doxycycline, Atovaquone, Halofantrine, Amodiaquine, Lumefantrine
- **Toxoplasmosis**: TMP-SMZ Antifolates (Pyrimethamine + Clindamycin + Folinic Acid)
- **Pneumocystis Pneumonia**: TMP-SMZ, Pentamidine, Atovaquone, Primaquine + Clindamycin, Trimetrextae + Leucovorin, Trimethoprim + Dapsone
- **Trypanosomiasis**
  - American type (Chagas Disease): Nifurtimox
  - African type: Suramin, Pentamidine, Melarsoprol, Eflornithine, Nifurtimox
- **Leishmaniasis**
  - Visceral type: Pentamidine, Paromomycin, Miltefosine
  - Cutaneous type: Metrodinazole, Fluconazole
  - Mucocutaneous type: Amphotericin B
  - All types: Sodium stibogluconate

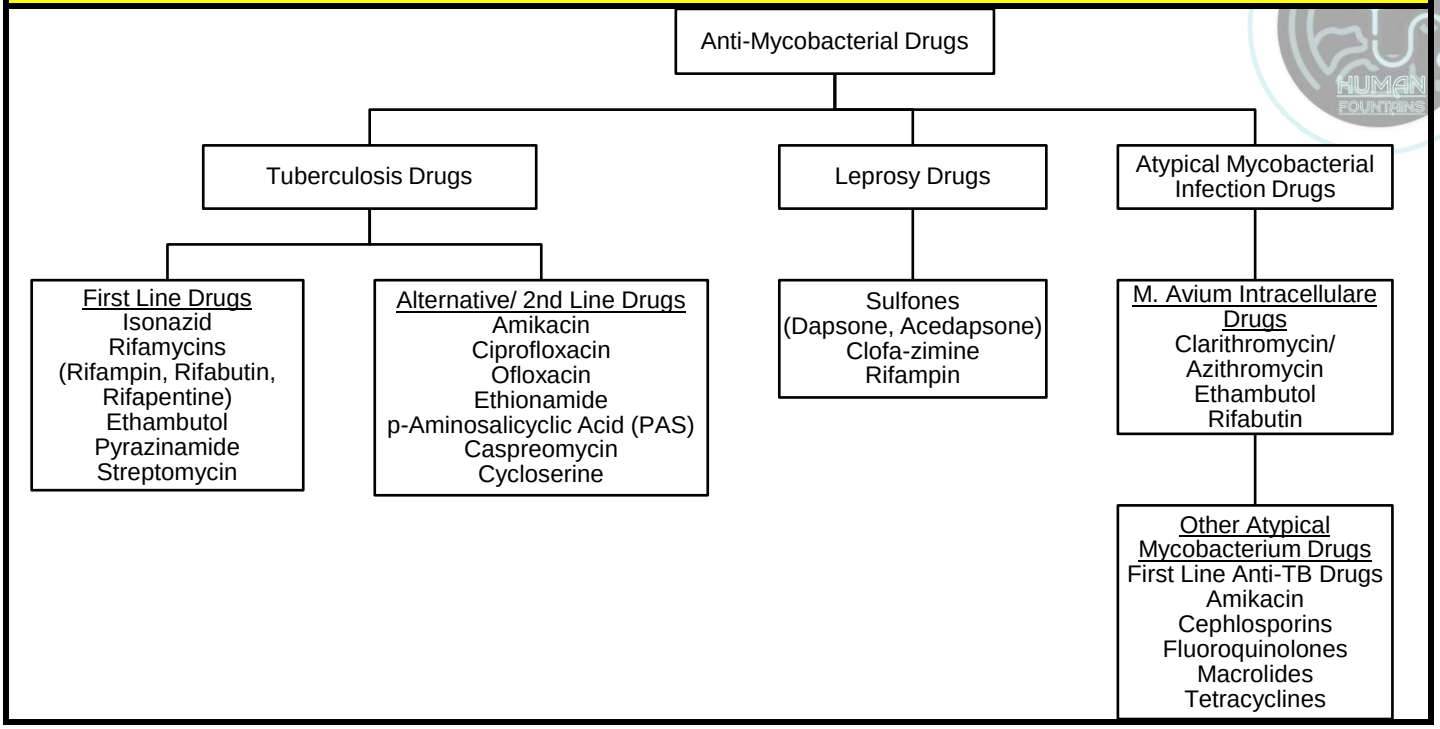
DRUG REGIMEN IN TREATMENT OF MALARIA

DESCRIPTION	DRUG
All Plasmodium species (except Chloroquine-resistant P. falciparum)	**Chloroquine**
Chloroquine-resistant P. falciparum	**Mefloquine** Quinine + Doxycycline Quinine + Clindamycin Artemisinins + Lumefantrine Artemisinins + Amodiaquine Fansidar (Primethamine + Sulfadoxine)
Prevention of relapses in case of P. vivax & P. ovale only	**Primaquine**
Prevention of malaria (Prophylaxis) in Chloroquine-sensitive geographic areas	**Chloroquine**
Prevention of malaria (Prophylaxis) in Chloroquine-resistant geographic areas	**Malarone** (Atovaquone + Proguanil) Mefloquine
Prevention of malaria in pregnancy	Doxycycline Mefloquine

ANTI-HELMINTHIC DRUGS



ANTI-MYCOBACTERIAL DRUGS



8

ANTI-BACTERIAL PHARMACOLOGY

1 SEQ + 10 MCQs = 17 Marks

GENERAL CONSIDERATIONS

BASIS OF CLASSIFICATION OF ANTIMICROBIAL AGENTS

A. NATURE

- Antimicrobials are of two types:
  - ⇒ -cidal drugs = kills
    - ***Be****ta-Lactams (Cell wall synthesis Inhibitors)*
    - ***Va****ncomycin & relatives*
    - ***F****luoroquinolones*
    - ***A****minoglycosides*
    - ***Co****trimoxazole*
    - ***St****reptogramins*
  - ⇒ -static drugs = inhibit growth
    - ***All other then –cidal drugs***
- Usage
  - ⇒ Immunocompetent person = Both types
  - ⇒ Immunocompromised person = Only – cidal drugs

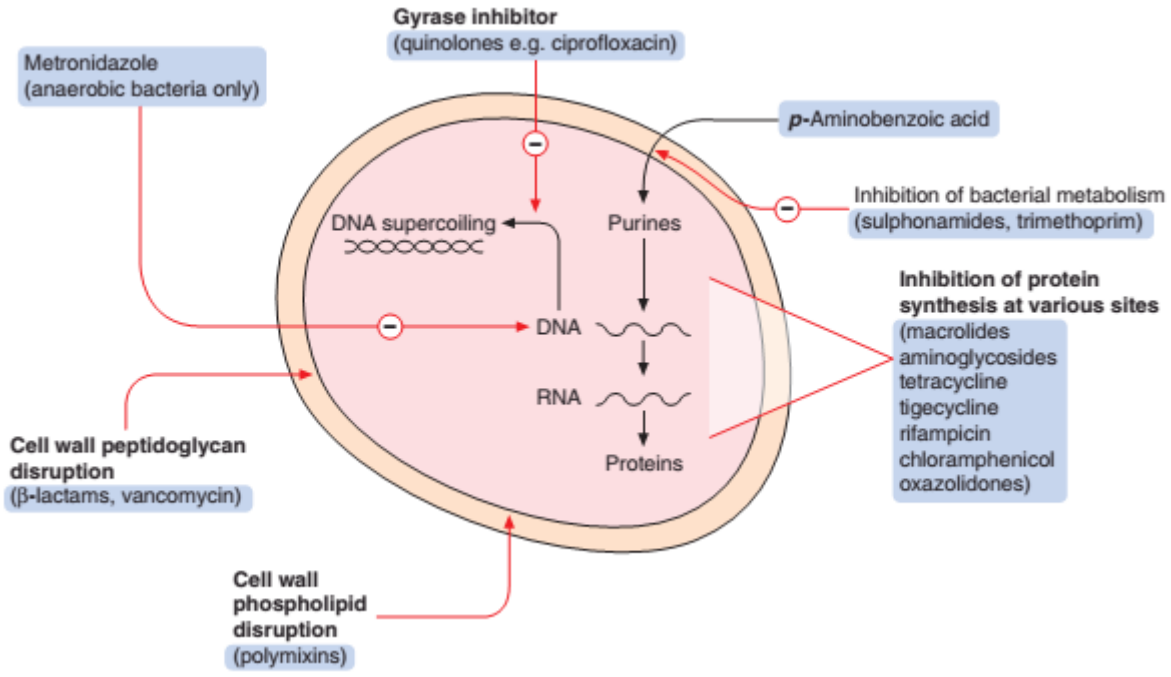
B. TYPE OF MICRORGANISMS

C. CHEMICAL STRUCTURE

D. SOURCE

- Antibiotics
- Non-antibiotic

E. MECHANISM OF ACTION

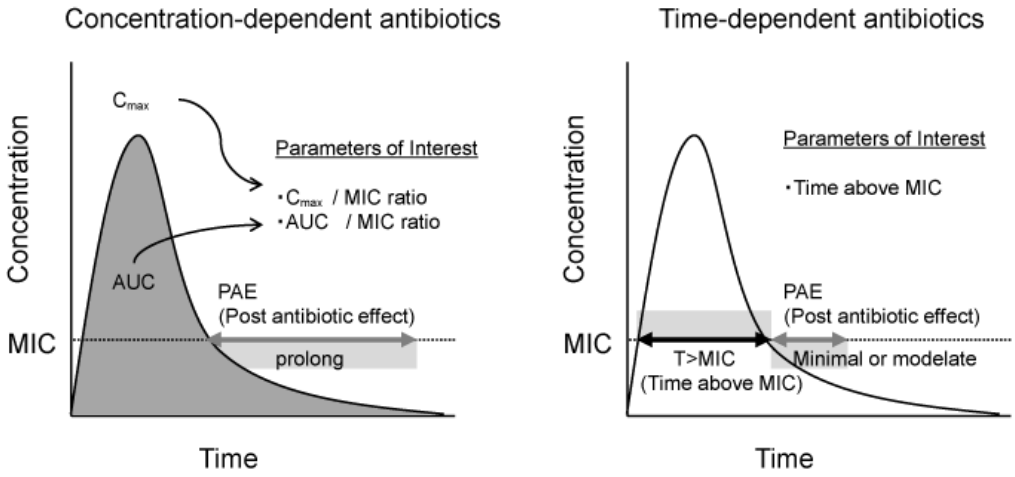


DIFFERENT PATTERNS OF ANTIMICROBIAL ACTION

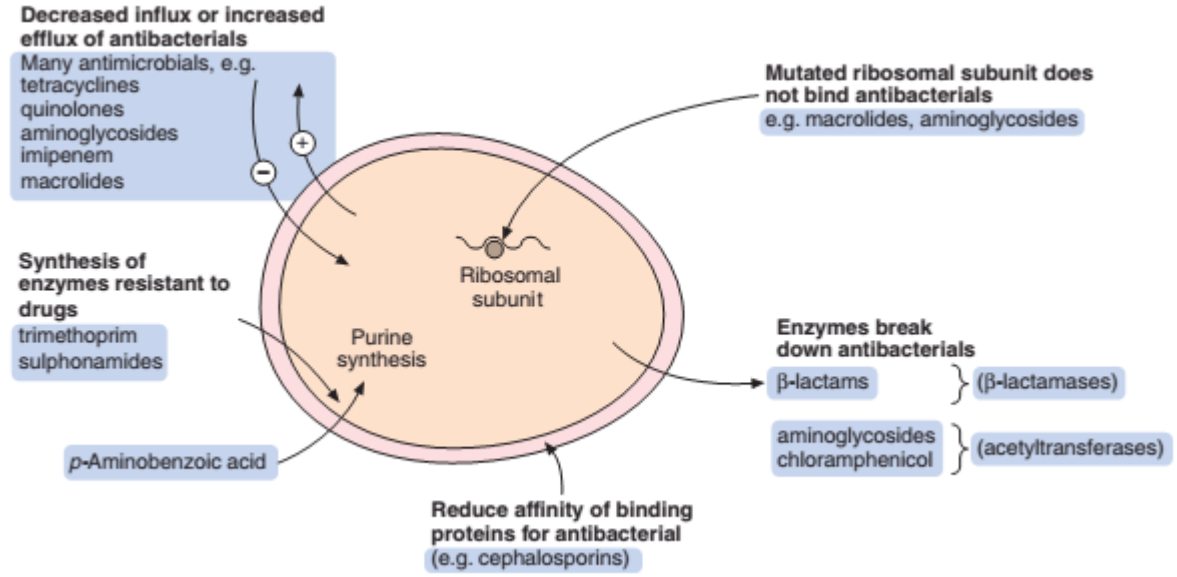
FEATURE	TYPE – I = CDK	TYPE – II = TDK	TYPE – III = Both CDK & TDK
Pattern of Activity	Concentration dependent with prolonged PAE	Time dependent with minimal PAE	Time dependent with prolonged PAE
PK/PD Parameter	AUC/MIC C_{max}/MIC	T > MIC	AUC/MIC
Goal of therapy	Maximize concentration	Maximize duration of exposure	Maximize amount of drug
Dosing	Less frequent (Single High Dose)	More frequent (Multiple Small Doses)	Depends
Examples	Aminoglycosides Flouroquinilones	Beta Lactams Vancomycin	Macrolides Tetracycline

- ***MIC****:* Minimal Inhibitory Concentration:
  An estimate of the drug sensitivity of pathognes for comparison with anticipated levels in blood or tissue
- ***PAE****:* Post Antibiotic Effect:
  Antibacterial effect that persists after drug concentration falls below the MIC
- ***AUC****:* Area Under Curve

GRAPHS FOR PATTERNS OF ANTIMICROBIAL ACTION



GENERAL MECHANISMS OF RESISTANCE TO ANTIMICROBIAL ACTION



Drug resistance due to altered targets	Drug resistance due to decreased accumulation: ↓ Permeability	Drug resistance due to decreased accumulation: ↑ Efflux	Drug resistance due to enzymatic inactivation
Aminoglycosides			Aminoglycosides
Chloramphenicol			*Chloramphenicol*
Clindamycin			
Fluoroquinolones	Fluoroquinolones	Fluoroquinolones	
β-Lactams	β-Lactams		β-Lactams
Macrolides		Macrolides	Macrolides
Rifampin			
Sulfonamides			
Tetracycline	*Tetracycline*	*Tetracycline*	*Tetracycline*
Trimethoprim			
Vancomycin			

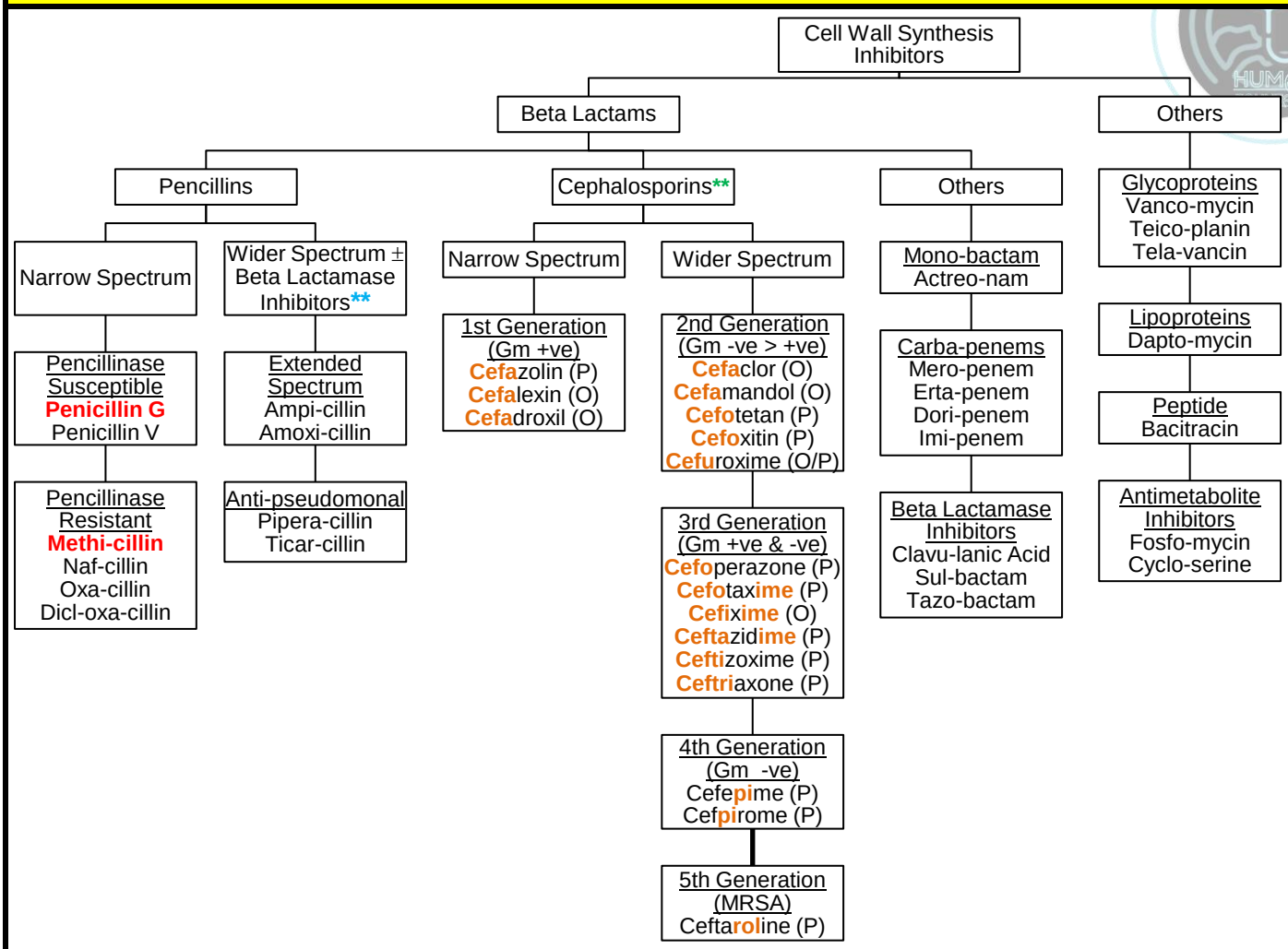
Alteration in the target enzyme, DNA gyrase, has resulted in resistance to fluoro-quinolones.

β-Lactams enter gram-negative cells through porin channels. Enterobacter is largely resistant to cephalo-sporins by producing β-lactamases. However, resistant organisms may also have altered porin channels through which cephalosporins do not pass.

Tetracycline was effective against gyne-cologic infection due to Bacteroides, but now these organisms are resistant due to the presence of plasmid-mediated protein that promotes efflux of the drug.

β-Lactamases (penicillinases) destroy antibiotic with the β-lactam nucleus. Neisseria gonorrhoeae is now largely resistant to *penicillin* because of penicillinase activity.

CELL WALL SYNTHESIS INHIBITORS



** Extended & Antipseudomonal spectrum of Pencillins + Carbapenems = Stable to Pencillinases

** All cephalosporins can cross BBB except 1st generation, 2nd generation, Cefoperazone & Cefixime.

SPECTRUM OF PENICILLIN

DRUG	GRAM + COCCI	GRAM - COCCI	GRAM + RODS	GRAM - RODS	SPIROCHETES
NARROW SPECTRUM					
Pencillinase Susceptible Penicillin G Penicillin V	• *Streptococcus pyogenes* • *Streptococcus viridians* • *Streptococcus pneumoniae*	• *Neisseria gonorrhoeae*[A] • *Neisseria meningitidis*[A]	• *Bacillus anthracis* • *Clostridium perfringens* • *Corynebacterium diphtheriae*	✗	• *Treponema pallidum* • *Leptospira interrogans*
Pencillinase Resistant Methi-cillin Naf-cillin Oxa-cillin	• *Staphylococci*[B]	✗	✗	✗	✗
BROAD SPECTRUM					
Extended Spectrum ± Beta Lactamase Inhibitors Ampi-cillin Amoxi-cillin	• *S. pyogenes* • *S. viridians* • *S. pneumonia* • *Staphylococci*[B] • *Enterococci*	• *N. gonorrhoeae*[C] • *N. meningitidis*[C]	• *Listeria monocytogenes*	• *Escherichia coli* • *Haemophilus infuenzae* • *Proteus mirabilis* • *Salmonella typhi*	✗
Anti-pseudomonal ± Beta Lactamase Inhibitors Pipera-cillin Ticar-cillin	Less potent than prototypes			• *E. coli* • *H. infuenzae* • *P. mirabilis* • *Pseudomonas aeruginosa* • *Klebsiella* • *Enterobacter*	✗

A. Non-penicillinase-producing.
B. Not effective against methicillin-resistant staphylococcal infections (MRSA). Only MSSA
C. Penicillinase producing.

SPECTRUM OF CEPHALOSPORINS

DRUG	GRAM + COCCI	GRAM - COCCI	GRAM + RODS	GRAM - RODS	OTHERS
NARROW SPECTRUM					
1st Generation (Gm +ve) Cefazolin Cefalexin Cefadroxil	• *Streptococcus pyogenes* • *Streptococcus (anerobes)* • *PRSP*[A] • *MSSA*[B] • *Staphylococcus epidermidis*	✗	✗	• *Escherichia coli* • *Proteus mirabilis* • *Klebsiella*	✗
BROAD SPECTRUM					
2nd Generation (Gm -ve > +ve) Cefaclor Cefamandol Cefotetan Cefoxitin Cefuroxime	• *S. pyogenes* • *Streptococcus (anerobes)* • *PRSP*[A] • *MSSA*[B]	• *Neisseria gonorrhoeae* • *Moraxella catarrhalis*	✗	• *E. coli* • *Haemophilus infuenzae* • *P. mirabilis* • *Klebsiella* • *Enterobacter*	• *Bacteroides fragilis (anaerobe)*- ***Cefo drugs***
3rd Generation (Gm +ve & -ve) Cefoperazone Cefotaxime Cefixime Ceftazidime Ceftizoxime Ceftriaxone	• *S. pyogenes* • *Streptococcus (anerobes)* • *PRSP*[A] • *MSSA*[B]	• *N. gonorrhoeae* – ***Cefixime, Ceftriaxone***	✗	• *E. coli* • *H. infuenzae* • *P. mirabilis* • *Klebsiella* • *Enterobacter* • *Serratia* • *Pseudomonas aeruginosa*	• *Bacteroides fragilis (anaerobe)*- ***Ceftizoxime***
4th Generation/ Anti-pseudomonal (Gm -ve) Cefepime Cefpirome	• Combines the gram (+) activity of 1st generation with gram (-) activity of 3rd generation cephalosporins. • Used in *P. aeruginosa* mainly				
5th Generation (MRSA) Ceftaroline (P)	• *MRSA*[C]	✗	✗	✗	✗

A. ***PRSP: Pencillin resistant pneumococci***
B. ***MSSA: Methicillin suspectible staphylococci***
C. ***MRSA: Methicillin resistant staphylococci***

SPECTRUM OF OTHER BETA LACTAMS

DRUG	GRAM + COCCI	GRAM - COCCI	GRAM + RODS	GRAM - RODS	OTHERS
Monobactam Aztreonam	✗	✗	✗	• *Klebsiella* • *Serratia* • *Pseudomonas*	✗
Carbapenems Mero-penem Erta-penem[C] Dori-penem Imi-penem	• *Streptococci* • *MSSA*[A] • *Enterococci*	• *Neisseria gonorrhoeae*[B] • *Neisseria meningitidis*[B]	• *Listeria monocytogenes* • *Clostridium sp.* • *Gardnerella vaginalis*	<u>Pathogens inside & outside enteric tract</u> • *Salmonella* • *Escherichia coli* <u>Pathogens outside enteric tract</u> • *Klebsiella* • *Serratia* • *Enterobacter* • *Proteus* • *Providencia* • *Pseudomonas* <u>Respiratory Tract</u> • *H. influenzae* <u>Others</u> • *Acinetobacter sp.* • *Citrobacter sp.*	• *Bacteroides fragilis (anaerobe)* • *Fusobacterium (anaerobe)* • *Actinomyces* • *Nocardia*
Beta Lactamase Inhibitors Clavu-lanic Acid Sul-bactam tazo-bactam	• *Good inhibitors of Plasmid encoded beta-lactamases i.e. Streptococci, Gonococci, E. coli, H. influenza* • *Bad inhibitors of Chromosome encoded beta-lactamases i.e. Serratia, Enterobacter , Pseudomonas*				

A. ***MSSA: Methicillin suspectible staphylococci***
B. ***Penicillinase producing strains***
C. ***Not effective against P. auruginosa and Acinetobacter spp.***

SPECTRUM OF OTHER AGENTS

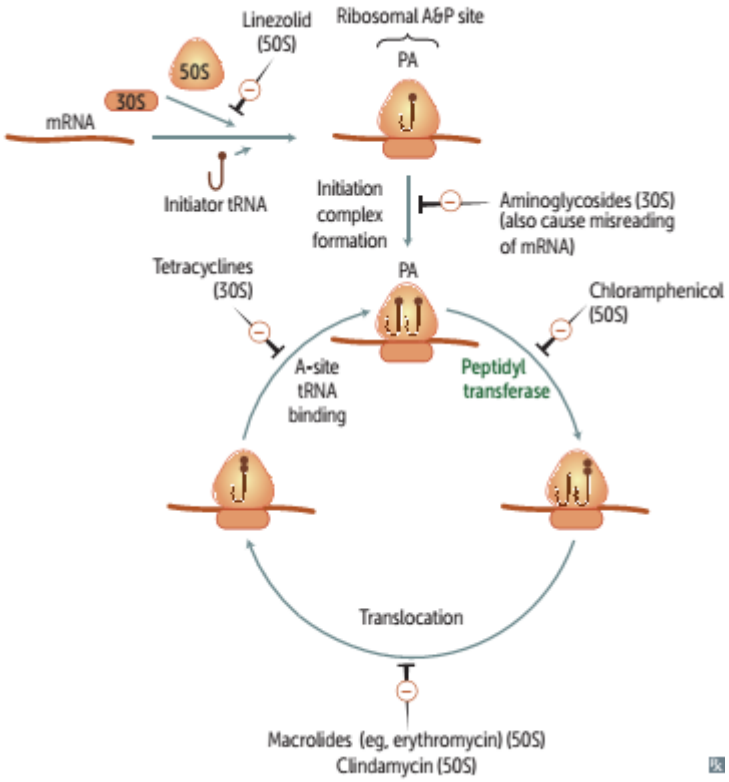
DRUG	GRAM + COCCI	GRAM - COCCI	GRAM + RODS	GRAM - RODS	OTHERS
Glycoproteins Vanco-mycin Teico-planin Tela-vancin	• *Streptococci* • *PRSP* • *MSSA/ MRSA* • *S. epidermidis* • *Enterococci*	✗	• *Listeria monocytogenes* • *Clostridium difficile (Orally)* • *Clostridium sp.* • *Coryneabacterium*	✗	• *Actinomyces*
Lipoprotein Dapto-mycin	• *Streptococci* • *PRSP* • *MSSA/ MRSA* • *S. epidermidis* • *Enterococci* • *VRE* [A] • *VISA* [B]*/VRSA* [C]	✗	• *Coryneabacterium*	✗	✗
Beta Lactamase Inhibitors Clavu-lanic Acid Sul-bactam tazo-bactam	• *Good inhibitors of Plasmid encoded beta-lactamases i.e. Streptococci, Gonococci, E. coli, H. influenza* • *Bad inhibitors of Chromosome encoded beta-lactamases i.e. Serratia, Enterobacter , Pseudomonas*				

A. VRE: Vancomycin resistant enterococci
B. VISA: Vancomycin intermediate staphylococci aureus
C. VRSA: Vancomycin resistant staphylococci aureus

PROTEIN SYNTHESIS INHIBITORS & AMINOGLYCOSIDES

- Protein Synthesis Inhibitors
  - Inhibitors of 30S Subunit
    - Broad Spectrum
      - Tetracyclins: Tetra-cycline, Doxy-cycline, Mino-cycline, Demeclo-cycline
      - Glycylcycline: Tige-cycline
      - Aminoglycosides: Genta-micin, Tobra-mycin, Amika-cin, Strepto-mycin, Neo-mycin, Netil-micin, Kana-mycin, Spectino-mycin
  - Inhibitors of 50S Subunit
    - Broad Spectrum
      - Chloramphenicol
    - Moderate Spectrum
      - Macrolides: Azi-thro-mycin, Clari-thro-mycin, Ery-thro-mycin
      - Ketolides: Teli-thro-mycin
    - Narrow Spectrum
      - Lincosamides: Clindamycin
      - Streptogramins: Quinupristin-dalfopristin
      - Oxazolidinone: Linezolid

MECHANISM OF ACTIONS



DRUG CLASS	MECHANISM OF ACTION	EFFECT
Aminoglycosides	Blocks functioning of initiation complex and causes misreading of mRNA	Bactericidal
Tetracyclines	Blocks tRNA binding to ribosome	Bacteriostatic
Chloramphenicol	Blocks peptidyltransferase i.e. transpeptidation blocked	Both*
Macrolides	Blocks translocation	Bacteriostatic
Telithromycin		Both*
Clindamycin		Bacteriostatic
Linezolid	Blocks early step in ribosome formation	Both*
Streptogramins	Causes premature release of peptide chain	Both*

**Primarily bacteriostatic but can be bacteriocidal depending on dose.*

SPECTRUM OF AMINOGLYCOSIDES

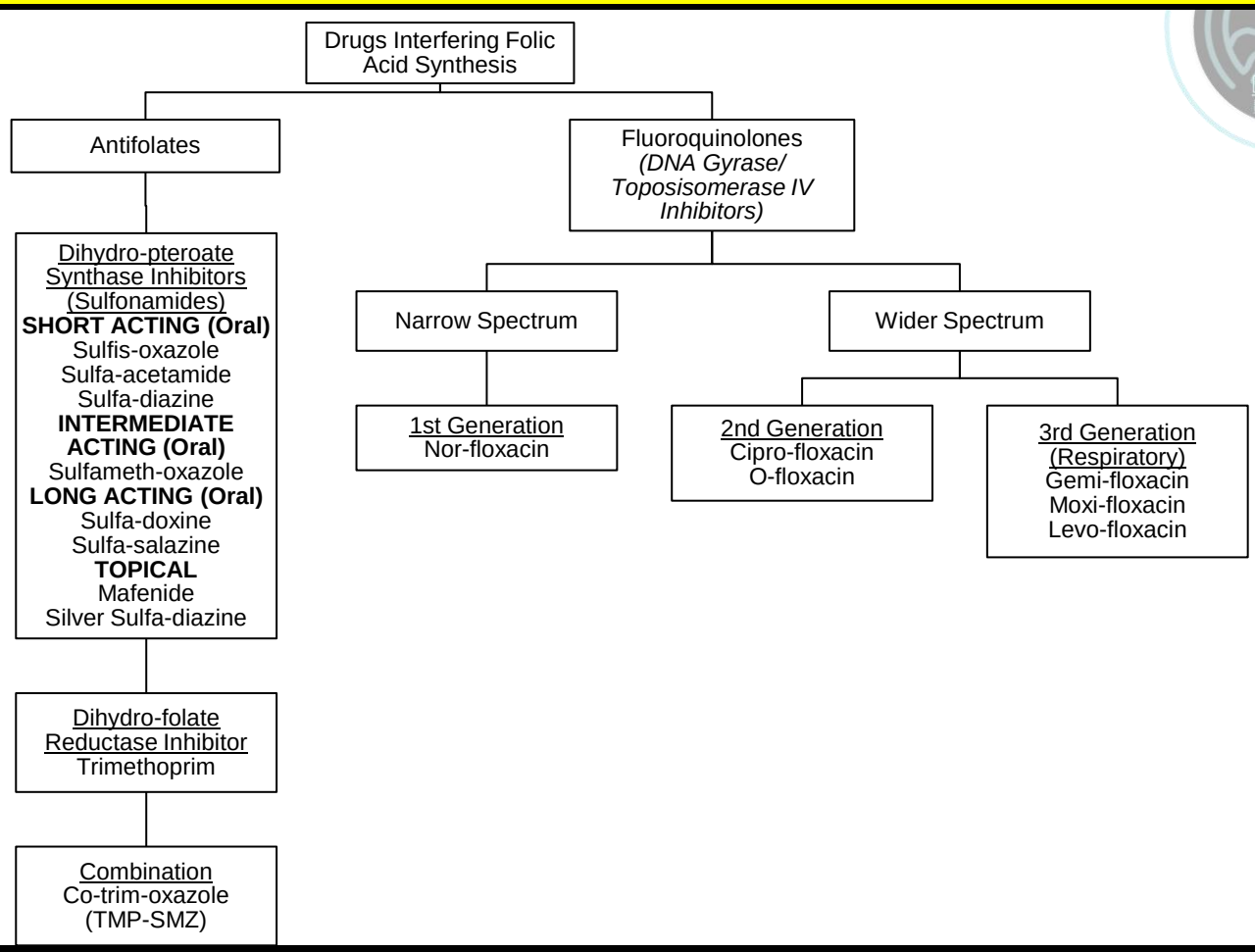
DRUG	CLASS	ORGANISMS/USES	Route
Genta-micin Tobra-mycin Amika-cin	Aerobic Gram Negative Rods (causing UTI or Sepsis) Ref: Levinson Microbiology 15th Ed. Page 145	*E. coli Enterobacter Klebsiella Serratia Proteus Pseudomonas*	IV
	Aerobic Gram Negative Rods	*H. influenzae M. catarrhalis Shigella*	IV
Aminoglycosides + Cell Wall Synthesis Inhibitors	Aerobic Gram Negative Rods (causing UTI or Sepsis)	*Pseudomonas* (pneumonia)	IV
	Gram Positive Cocci	*Enterococci* (carditis)	IV
	Gram Positive Rods	*Listeria*	IV
Strepto-mycin + Cell Wall Synthesis Inhibitors	Aerobic Gram Negative Rods (associated with animal sources)	*F. tularensis* (tularemia) *Yersenia pestis* (plague)	IV
	Acid Fast Rods	*Mycobacterium tuberculosis*	IM
Amika-cin + Cell Wall Synthesis Inhibitors	Acid Fast Rods	Multidrug Resistant Strain of *Mycobacterium tuberculosis* resistant to Streptomycin	IM
Neo-mycin Kana-mycin Genta-micin	-	Eliminate bowel flora	Topical/ Oral
Netil-micin	-	Infections resistant to other AGs	IV
Spectino-mycin	-	Gonorrhea in patients allergic to beta-lactams	IM

SPECTRUM OF OTHER PROTEIN SYNTHESIS INHIBITORS

DRUG	GRAM + COCCI	GRAM - COCCI	GRAM + RODS	GRAM - RODS	OTHERS
Chloramphenicol	• *Streptococcus pneumoniae*	• *Neisseria meningitidis*	✗	• *Salmonella* • *H. influenzae*	• *Chlamydiae* • *Rrickettsiae* • *Spirochetes* • *Anaerobes (Bacteroides fragilis)*
Tetracyclines Tetra-cycline (T) Doxy-cycline Mino-cycline (M) Demeclo-cycline	• *Streptococcus pneumoniae* • *MSSA*	• *Neisseria meningitides* **(M)**	• *Bacillus anthracis* • *Clostridium perfringens* • *Clostridium tetani*	• *Brucella sp.* • *Vibrio cholerae* • *Yersinia pestis* • *Helicobacter pylori* **(T)**	**Doxycycline** • *Mycoplasma* • *Chlamydiae* • *Rickettsiae* • *Spirochetes* ⇒ *Borrelia burgdorferi* ⇒ *Leptospira interrogans* ⇒ *Treponema pallidum*
Glycylcycline Tige-cycline	• *MRSA* • *VRE* • *Multidrug resistant streptococci*	*Extended spectrum gram negative beta lactamase producing bacteria*	✗	*Extended spectrum gram negative beta lactamase producing bacteria*	• *Acinetobacter*
Macrolides Azi-thro-mycin (A) Clari-thro-mycin (C) Ery-thro-mycin (E) Fidaxo-micin (F)	• *Streptococcus pneumonia* • *Streptococcus pyogenes*	• *Neisseria gonorrhoeae* **(A)** • *Moraxella catarrhalis* **(A)**	• *Clostridum difficile* **(F)** • *Coryne-bacterium diphtheria* **(E)**	• *Bordetella pertussis* • *Campylobacter jejuni* • *H. infuenzae* **(A)** • *Helicobacter pylori* **(C)** • *Legionella pneumophila* **(A)**	• *Spirochetes* **(A)** ⇒ *Treponema pallidum* • *Chlamydia* **(A)** ⇒ *C. pneumoniae* ⇒ *C. psittaci* ⇒ *C. trachomatis* • *Mycoplasma* **(A)** ⇒ *M. pneumonia* ⇒ *Ureaplasma urealyticum* • *Other* ⇒ *Mycobacterium avium complex* **(C)**
Ketolide Teli-thro-mycin	• *Same as macrolides* • *Also effective against multidrug resistant organisms and macrolide resistant organisms*				
Lincosamides Clindamycin	• *Streptococci* • *MRSA*	✗	✗	✗	• *Anaerobes (Bacteroides fragilis)*
Streptogramins Quinupristin-dalfopristin	• *PRSP* • *MRSA* • *VRSA* • *VRE (only E. faecium)*	✗	✗	✗	✗

Oxazolidinone Linezolid	• *PRSP* • *MRSA* • *MRSE* • *VRSA* • *VRE* • *Streptococci*	x	• *Coryne-bacterium sp.* • *Listeria monocytogenes* • *Clostridium perfringens*	x	• *Mycobacterium tuberculosis*

ANTIFOLATES & FLUOROQUINOLONES



SPECTRUM OF DRUGS

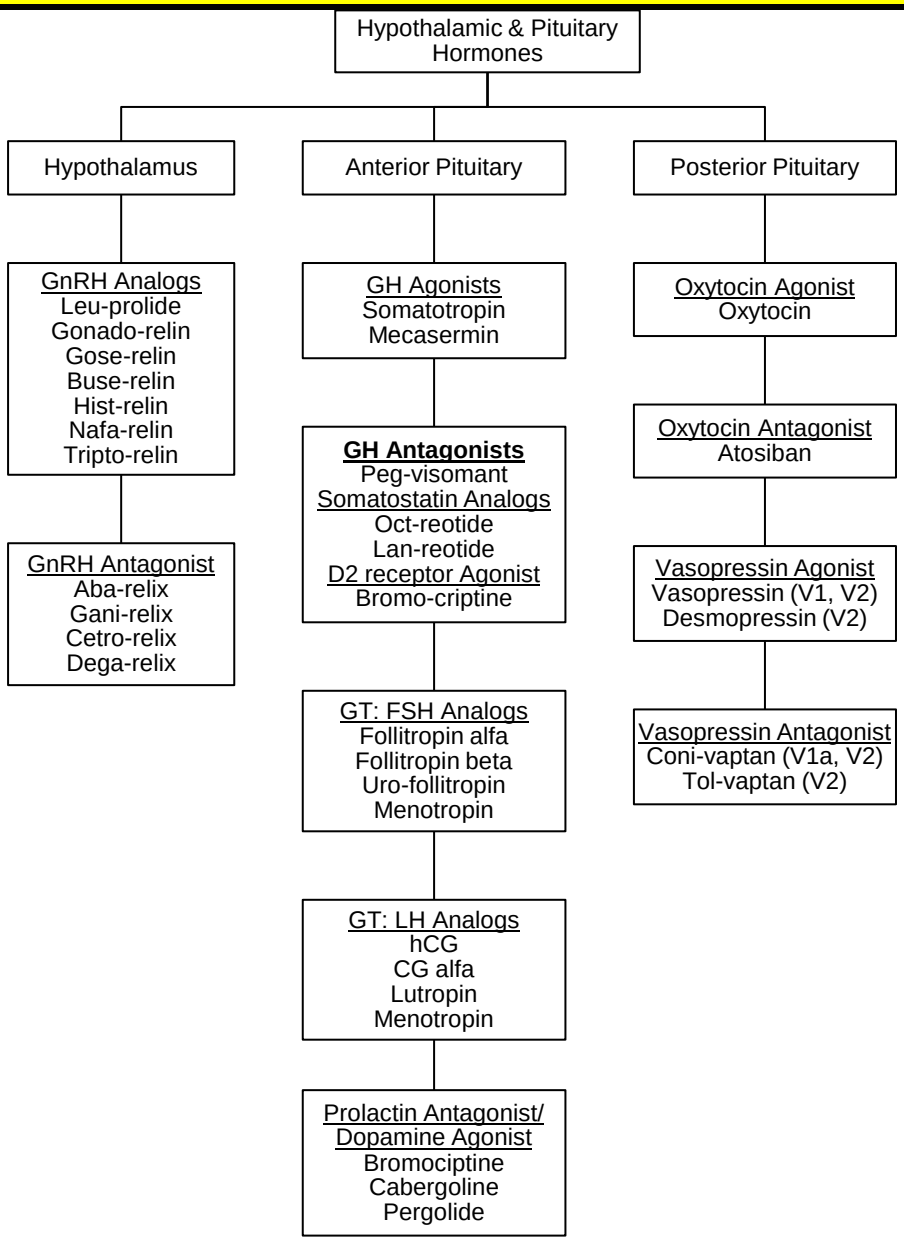
DRUG	GRAM + COCCI	GRAM - COCCI	GRAM + RODS	GRAM - RODS	OTHER ORGANISM
Co-trim-oxazole	• *S. aureus*	✗	• *Listeria monocytogenes*	• *E. coli* • *H. infuenzae* • *Legionella* • *P. mirabilis* • *S. typhi* • *Shigella*	PARASITES • *P. jirovecii* • *Toxoplasmosis gondii*
Fluoroquinolones	• *S. pneumoniae*	✗	• *Bacillus anthracis*	• *E. coli* • *H. infuenzae* • *Legionella* • *P. mirabilis* • *Shigella* • *P. aeruginosa* • *Serratia* • *Klebsiella* • *Enterobacter*	• *M. tuberculosis*

9

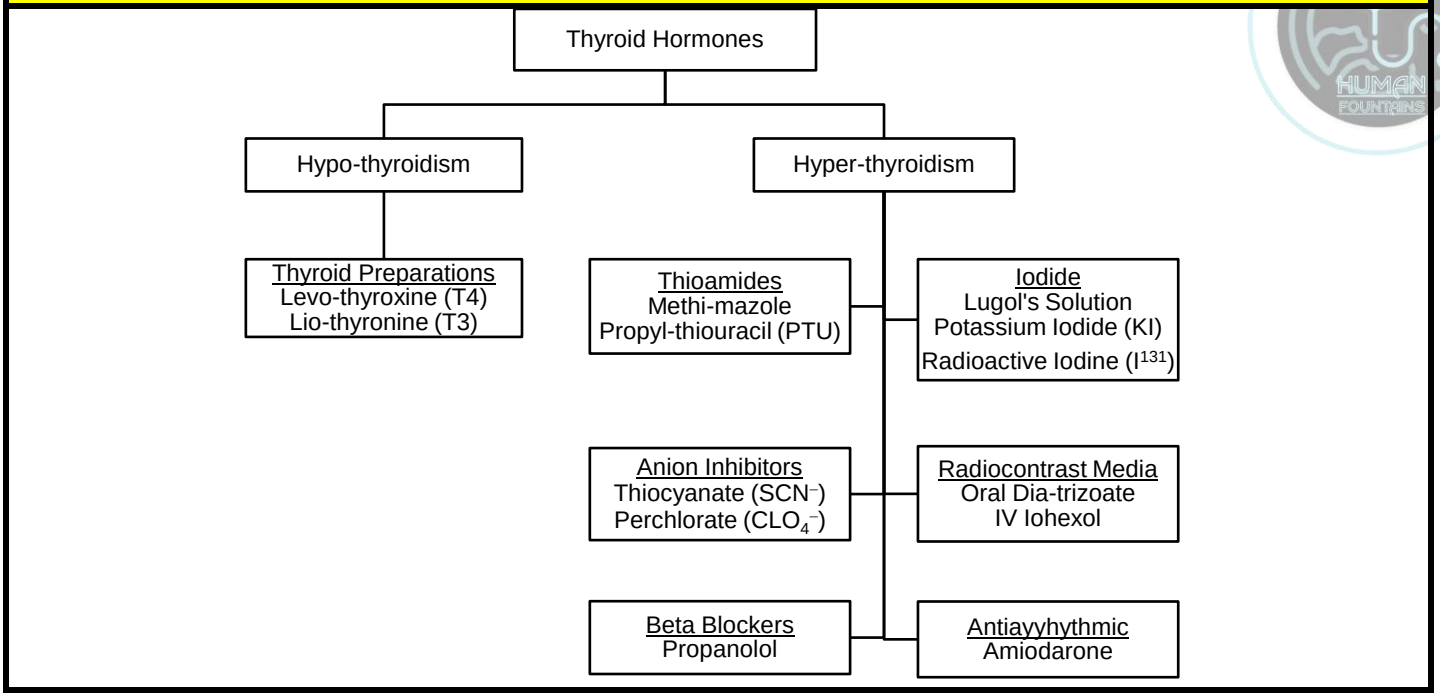
ENDOCRINE PHARMACOLOGY

1 SEQ + 6 MCQs = 13 Marks

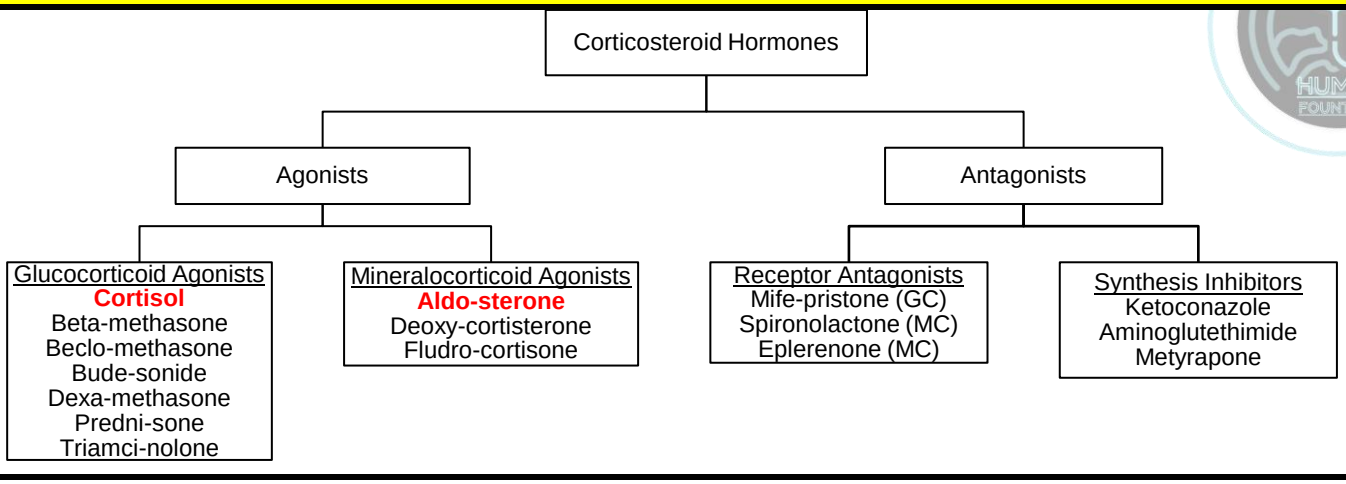
HYPOTHALAMIC & PITUITARY HORMONES



THYROID HORMONES



CORTICOSTEROID HORMONES

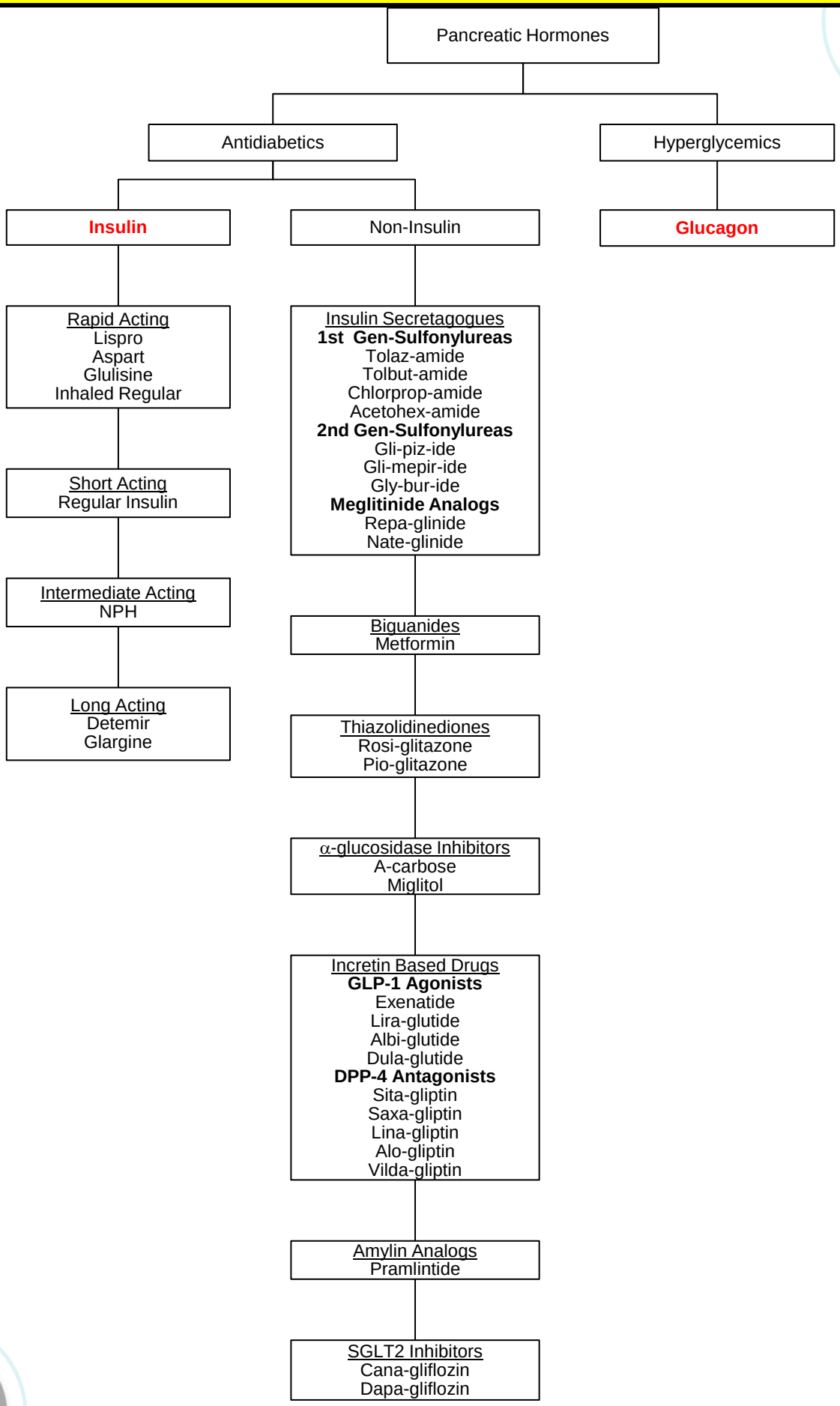


GONADAL HORMONES

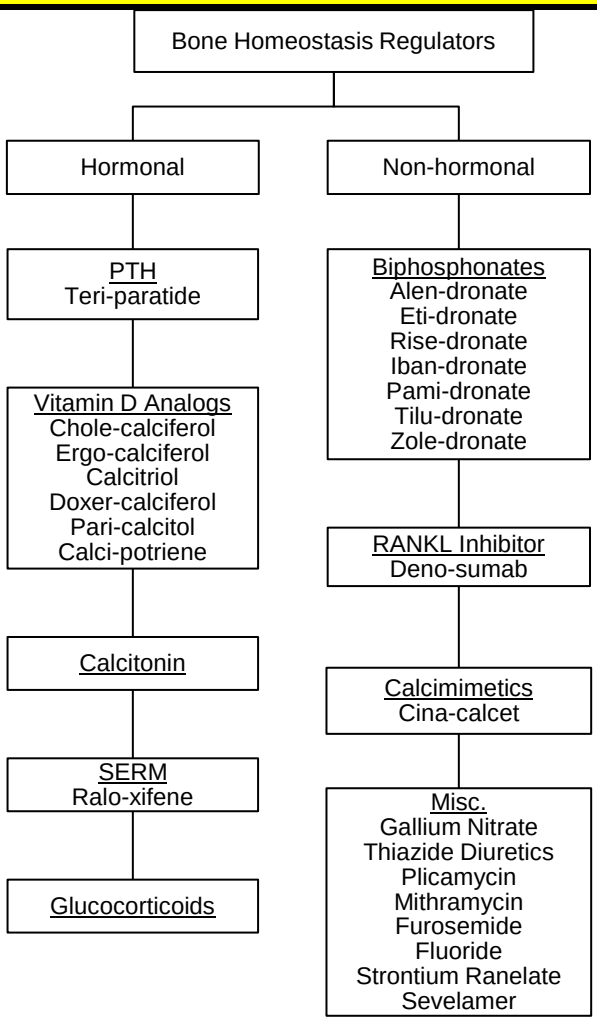
- Ovarian Hormones
  - Estrogens
    - Agonists
      Estradiol
      Ethinyl estradiol
      Estradiol cypionate
      Estrone
      Diethyl-stil-bestrol
      Mestranol
    - Antagonists
      - **SERMS**
        Tamo-xifen
        Tore-mifene
        Ralo-xifene
        Bazedo-xifene
        Clo-miphene
      - **Full Receptor Antagonist**
        Fulve-strant
      - **Synthesis (Aromatase) Inhibitors**
        Anas-trozole
        Le-trozole
        Exemestane
      - **GnRH Agonists**
        Leu-prolide
      - **GnRH Antagonists**
        Gani-relix
        Cetro-relix
  - Progestins
    - Agonists
      Progesterone
      - **Synthetic Progestins**
        Medroxy-progesterone acetate
        Megestrol acetate
      - **Older 19-Nortestosterone Compounds**
        L-Nor-gestrel
        Nor-ethindrone
      - **Newer 19-Nortestosterone Compounds**
        Nor-gestimate
        Nor-elgestromin
        Deso-gestrel
        Etono-gestrel
      - **Spironolactone Derivatives**
        Dor-spirenone
    - Antagonists
      Mifepristone (RU 486) in combination with PGE analog Misoprostol

- Androgen Hormones
  - Agonists
    Testosterone
    - **Oral Androgens**
      Fluoxy-me-sterone
      Methyl-testosterone
    - **Esters**
      Testosterone cypionate
    - **Anabolic Steroids**
      Ox-androlone
      N-androlone
  - Antagonists
    - **Receptor Antagonist**
      Fl-utamide
      Bical-utamide
      Nil-utamide
      Spironolactone
    - **5∝-reductase Inhibitors**
      Fin-asteride
      Dut-asteride
    - **GnRH Agonists**
      Leu-prolide
    - **GnRH Antagonists**
      Aba-relix
      Dega-relix
    - **Synthesis Inhibitors**
      Ketoconazole

PANCREATIC HORMONES



DRUGS AFFECTING BONE MINERAL HOMEOSTASIS

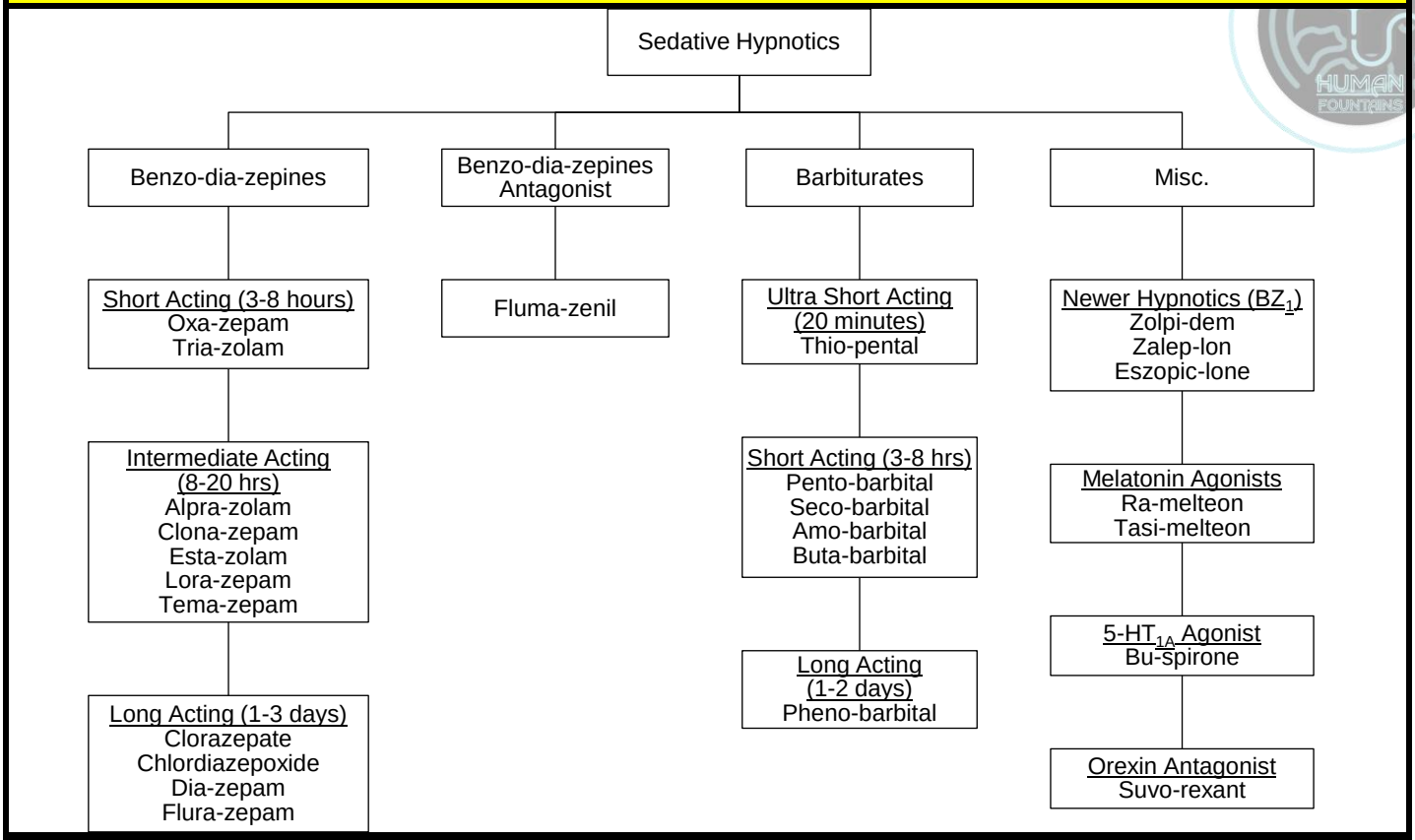


10

CENTRAL NERVOUS SYSTEM PHARMACOLOGY

1 SEQ + 5 MCQs = 12 Marks

SEDATIVE HYPNOTICS



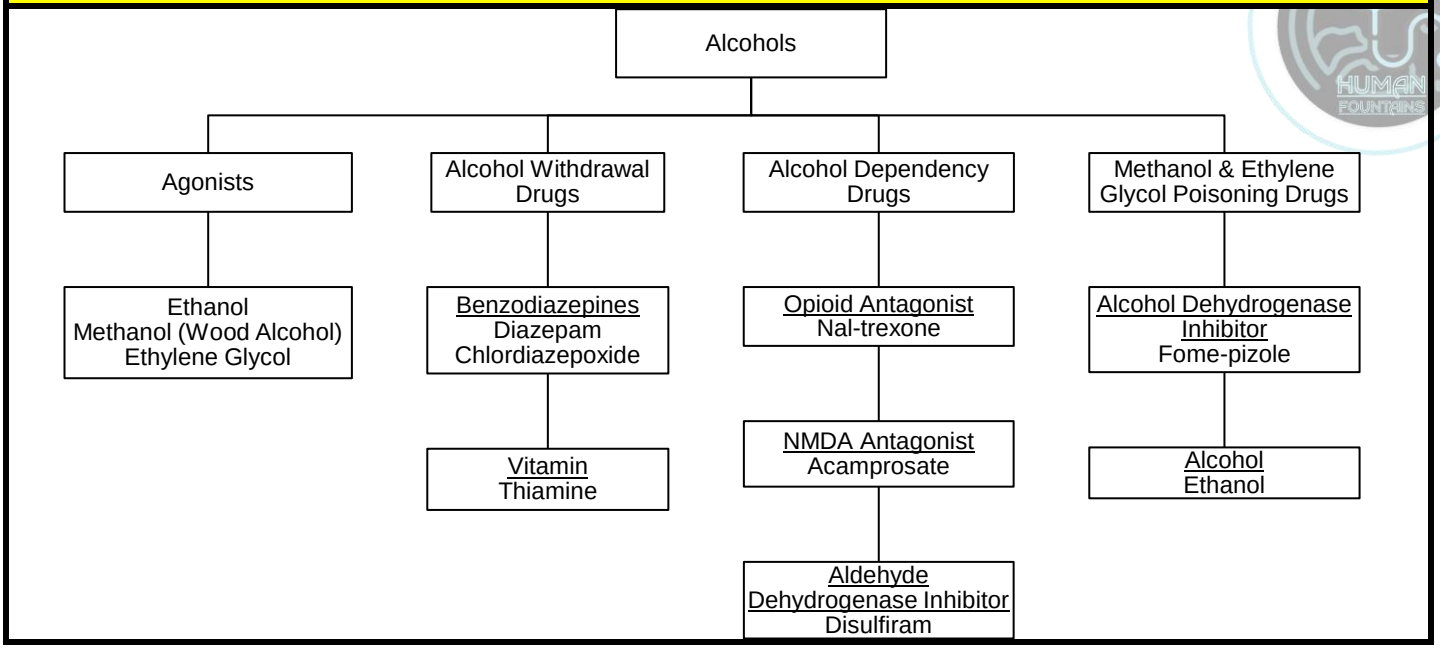
CLINICAL INDICATIONS OF BARBITURATES

NAME OF DRUG	CLINICAL INDICATIONS
Alpra-zolam	Anxiety (Panic, Phobias)
Clona-zepam	Anxiety, Bipolar disorder, Seizures disorder
Dia-zepam	Anxiety, Anesthesia IV, Muscle Relaxation, Status epilepticus, Withdrawal states
Lora-zepam	Anxiety, Status epilepticus
Chlordiazepoxide	Withdrawal states
Mida-zolam	Anesthesia IV
Flura-zepam	Sleep disorders
Esta-zolam	
Tria-zolam	
Tema-zepam	
Oxa-zepam	

DIFFERENCE BETWEEN BENZODIAZEPINES & BARBITURATES

FEATURE	BENZODIAZEPINES	BARBITURATES
Mode of Action	Potentiate GABA	Prolong GABA activity
	↑ the frequency of Cl− channel opening	↑ duration of Cl− channel opening
	Have no GABA mimetic activity	Have GABA mimetic activity at high doses
Receptors	Act through BZ receptors	Do not act through BZ receptors
	These receptors are part of $GABA_A$ complex	Have their own binding sites on $GABA_A$ complex
Dependence Liability	Less	High
Half lives	2-4 hours	4-60 hours
Antagonism	By Fluma-zenil	No

ALCOHOLS


Alcohols
Agonists
Alcohol Withdrawal Drugs
Alcohol Dependency Drugs
Methanol & Ethylene Glycol Poisoning Drugs
Ethanol
Methanol (Wood Alcohol)
Ethylene Glycol
Benzodiazepines
Diazepam
Chlordiazepoxide
Vitamin
Thiamine
Opioid Antagonist
Nal-trexone
NMDA Antagonist
Acamprosate
Aldehyde Dehydrogenase Inhibitor
Disulfiram
Alcohol Dehydrogenase Inhibitor
Fome-pizole
Alcohol
Ethanol

ANTISEIZURE/ANTIEPILEPTIC DRUGS

Antiseizure Drugs (Clinical Uses)

Tonic-Clonic (Grand Mal) Seizures
- Drug of Choice: Phenytoin, Fos-phenytoin, Carbama-zepine, Ox-carba-zepine, **Valproate**
- Drug of Choice (infants): Phenobarbital, Primidone
- Back up & Adjunctives: Gabapentin, Lamotrigine, Levetiracetam, Topiramate, Zonisamide

Partial Seizures
- Drug of Choice: Phenytoin, Fos-phenytoin, Carbama-zepine, Ox-carba-zepine, Lamotrigine
- Back up & Adjunctives: Gabapentin, Felbamate, Pregabalin, Phenobarbital, Topiramate, **Valproate**

Absence (Petit Mal) Seizures
- Drug of Choice: Ethosuximide, **Valproate**
- Back up & Adjunctives: Clona-zepam, Lamotrigine, Levetiracetam, Zonisamide

Myoclonic Seizures
- Drug of Choice: **Valproate**
- Back up & Adjunctives: Felbamate, Clona-zepam, Lamotrigine, Levetiracetam, Topiramate, Zonisamide

Status Epilepticus
- Short Acting: Diazepam (IV), Lorazepam (IV), Phenobarbital (child)
- Long Acting: Phenytoin, Fos-phenytoin

OTHER USES:
1. **Manic Phase of Bipolar Disorder**: Valproate
2. **Migraine**: Phenytoin, Topiramate
3. **Neuropathic pain**: Gabapentin, Pregabalin
4. **Neuralgia (trigeminal)**: Carbamazepine, Oxcarbazepine
5. **Bipolar disorders**: Carbamazepine, Lamotrigine

Mechanism of Actions of Anti-seizure Drugs

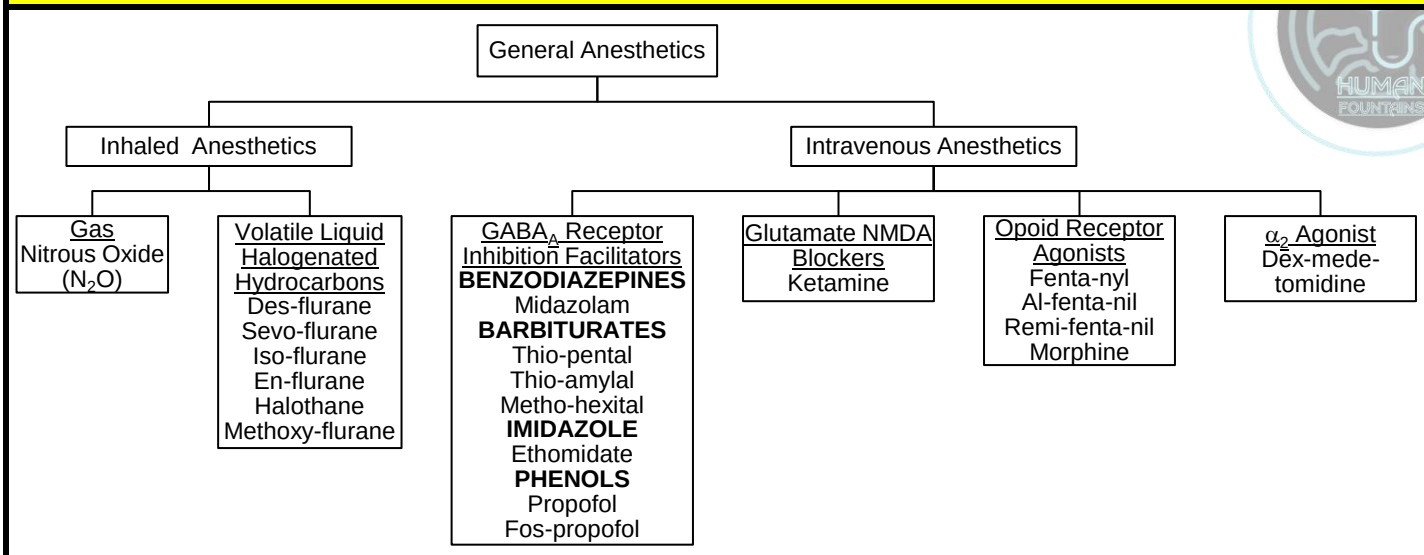
Sodium Channel Blockade
- Therapuetic Doses: Phenytoin, **Topiramate**, Car bama-zepine, Lamo-trigine, Zonis-amide
- High Doses: Pheno-barbital, Valproate

GABA Related Targets
- $GABA_A$ Receptor Agonist
  - **Benzodiazepines** *(increase frequency of Cl^- channel opening)*: Dia-zepam, Clona-zepam, Lora-zepam
  - **Barbiturates** *(increase duration of Cl^- channel opening)*: Phenobarbital
- GABA Transaminase Inhibitor: Vigabatrin, Valproate
- GABA Reuptake Inhibitor: Tiagabine
- GABA Analog: Gabapentin
- GABA Facilitators: Felbamate, **Topiramate**, Valproate

Calcium Channel Blockade (T type)
Etho-suximide, Valproate, Gabapentin, **Topiramate**, Pregabalin

Glutamate Receptor Blockade
Phenobarbital, **Topiramate**, Felbamate

GENERAL ANESTHETICS



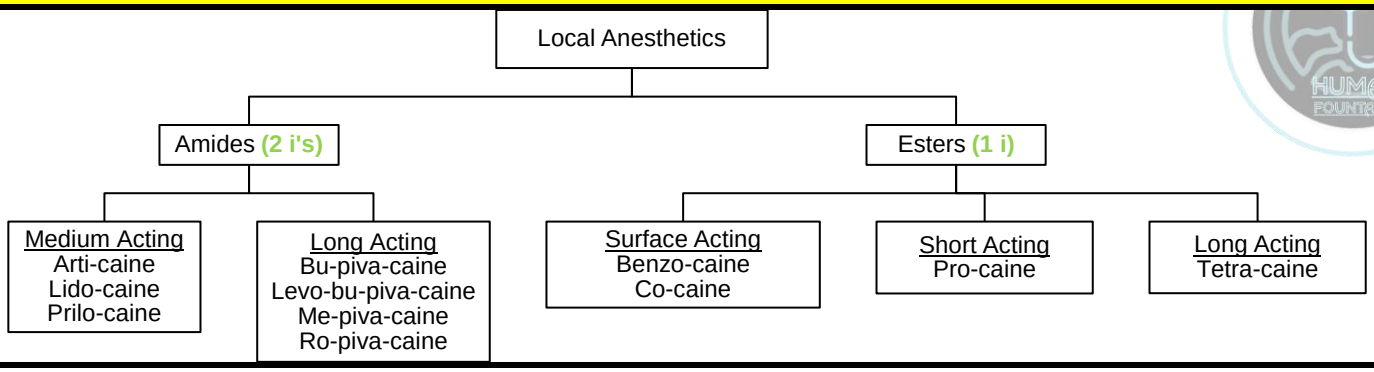
DIFFERENCE BETWEEN NITROUS OXIDE & HALOTHANE

FEATURE	HALOTHANE	NITROUS OXIDE
Potency	High	Low
Induction	Slow	Rapid
Recovery	Slow	Rapid
Blood Gas Coefficient	2.30	0.47
MAC	0.75%	> 100%
Metabolism	> 40%	None
Arrhythmia	Increased risk	None
Hepatotoxic	Increased risk (not in children)	None
Therapeutic Actions	DOC in children Good for asthmatic bronchodilation	Rapid onset and recovery Good analgesia

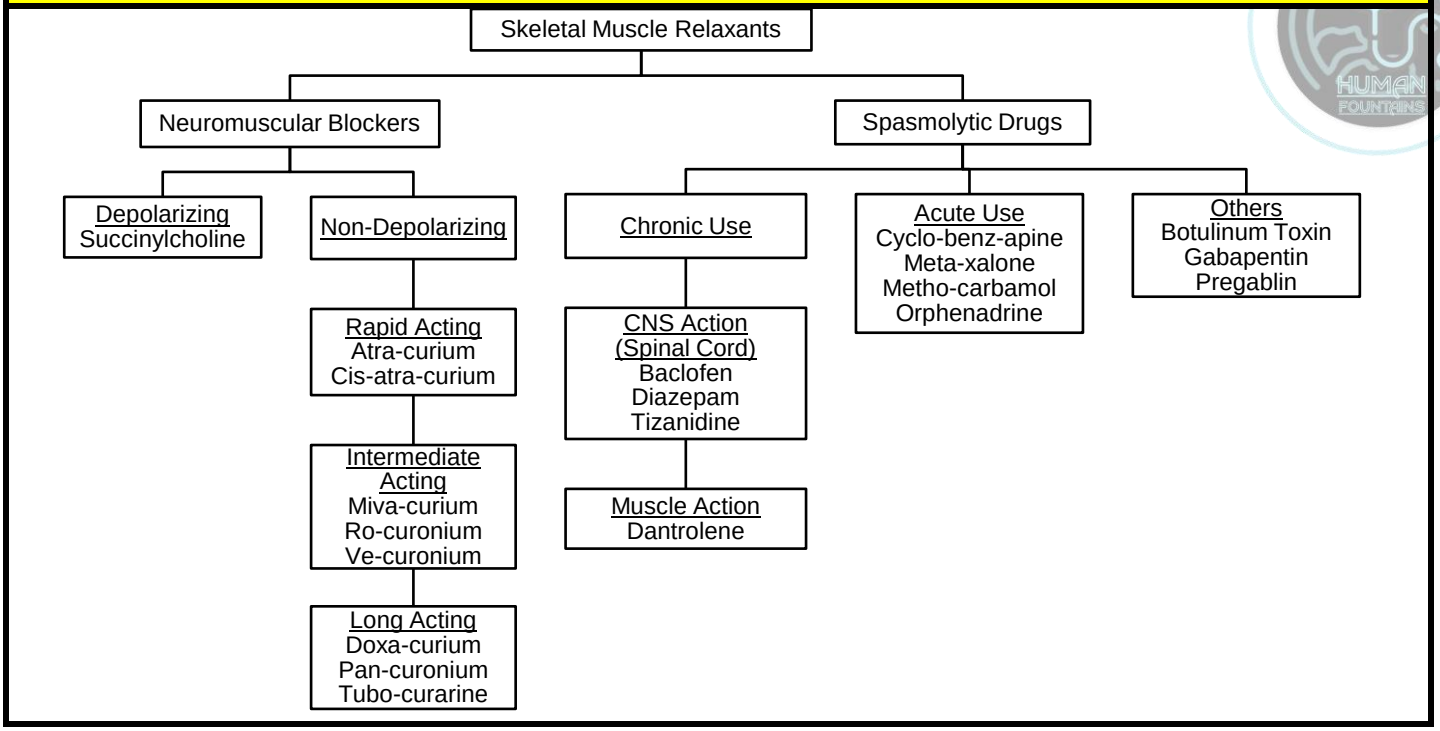
MERITS & DEMERITS OF HALOTHANE

MERITS	DEMERITS
Potent	Hypotension and Bradycardia
Less irritant	Arrhythmiogenic
Smooth and rapid induction	Hepatotoxic
Smooth and rapid recovery	Shivering during recovery
Non inflammable	Not an analgesic
Bronchodilator	Variable muscle relaxation

LOCAL ANESTHETICS



SKELETAL MUSCLE RELAXANTS



DRUGS FOR MOVEMENT DISORDERS

Drugs for Movement Disorders

Parkisonism (Paralysis Agitans)
- Drug of Choice: Levodopa ± Carbidopa
- Dopamine Agonists: **D_2 AGONIST** Apo-morphine, Ropinirole, Bromocriptine; **D_3 AGONIST** Pramipexole
- MAO_B Inhibitors: Rasa-giline, Sele-giline
- COMT Inhibitors: Tol-capone, Enta-capone
- Antimuscuranic: Benzotropine, Biperiden, Orphenadrine
- Others: Amantadine

Physiological & Essential Tremor
- β-Blockers: Propran-olol, Metopr-olol
- Antiseizure Drugs: Gabapentin, Topiramatee, Primidone
- Others: Botulinum Toxin

Huntington's Disease
- Amine Depletors: Reserpine, Tetrabenazine
- D_2 Antagonists: Haloperidol, Perphenazine
- Atypical Antipsychotic: Olanzapine

Touretter's Syndrome
- D_2 Antagonists: Haloperidol, Pimozide
- α_2 Agonist: Clonidine
- Benzodiazepine: Clonazepam
- Antiseizure Drugs: Carbamazepine
- Atypical Antipsychotic: Molindone

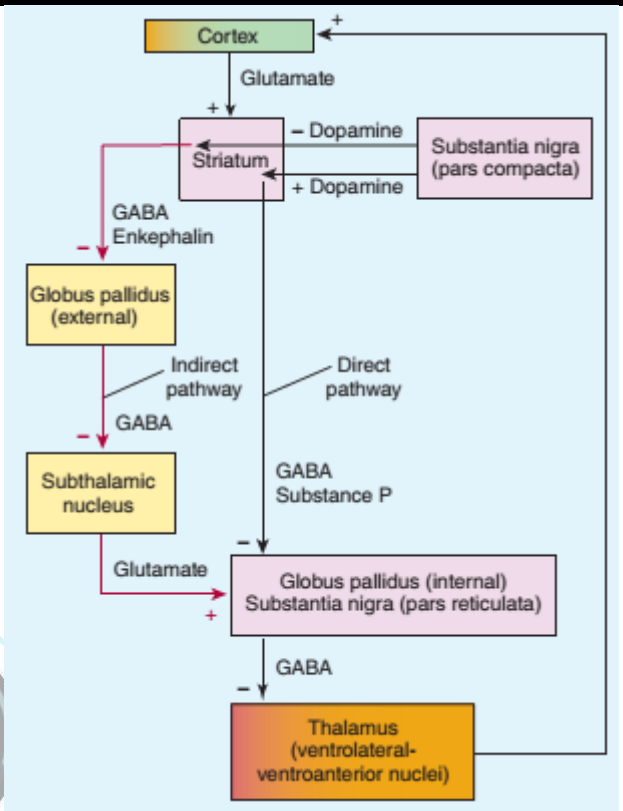
Drug Induced Dyskinesias
- Benzotropine, Diphenhydramine

Wilson's Disease
- Pencillamine, Tri-entine, Tetrathiomolybdate

Restless Legs Syndrome
- Dopamine Agonists: Ropinirole, Pramipexole
- Opoid Analgesics
- Benzodiazepine
- Antisezure Drugs: Gabapentin

Increase Dopamine Function
Increase Dopamine
Decrease ACh Function

FUNCTIONAL CIRCUITRY BETWEEN CORTEX, BASAL GANGLIA AND THALAMUS



In Parkinson's disease, there is degeneration of pars compacta of substantia nigra, leading to overactivity in indirect pathway (red) and increased glutamatergic activity by subthalamic nucleus.

ANTIPSYCHOTIC & BIPOLAR DRUGS

- Antipsychotic & Bipolar Drugs
  - Antipsychotics (Neuroleptics)
    - Classic Drugs (D_2 receptor affinity)
      - Phenothiazines
        - **PROPYLAMINE SIDE-CHAIN**
        - Chlorprom-azine
        - **PIPERIDINE SIDE-CHAIN**
        - Thiorid-azine
        - **PIPERAZINE SIDE-CHAIN**
        - Trifluoper-azine
        - Fluphen-azine
        - Prochlorper-azine
        - Perphen-azine
      - Thioxanthenes
        - Thiothixene
      - Butyrophenonones
        - **Haloperidol**
    - Newer Drugs ($5HT_2$ receptor affinity)
      - **Aripipr-azole**
      - Cloz-apine
      - Lox-apine
      - Olanz-apine
      - Queti-apine
      - Molin-done
      - Risperi-done
      - Ziprasi-done
  - Bipolar Drugs
    - Classic Drug
      - Lithium
    - Newer Drugs
      - Acute Mania
        - Olanz-apine
        - Queti-apine
        - Valproate
      - Acute Mania ± Prophylaxis
        - Carbama-zepine
        - Clona-zepam
        - Lamo-trigine

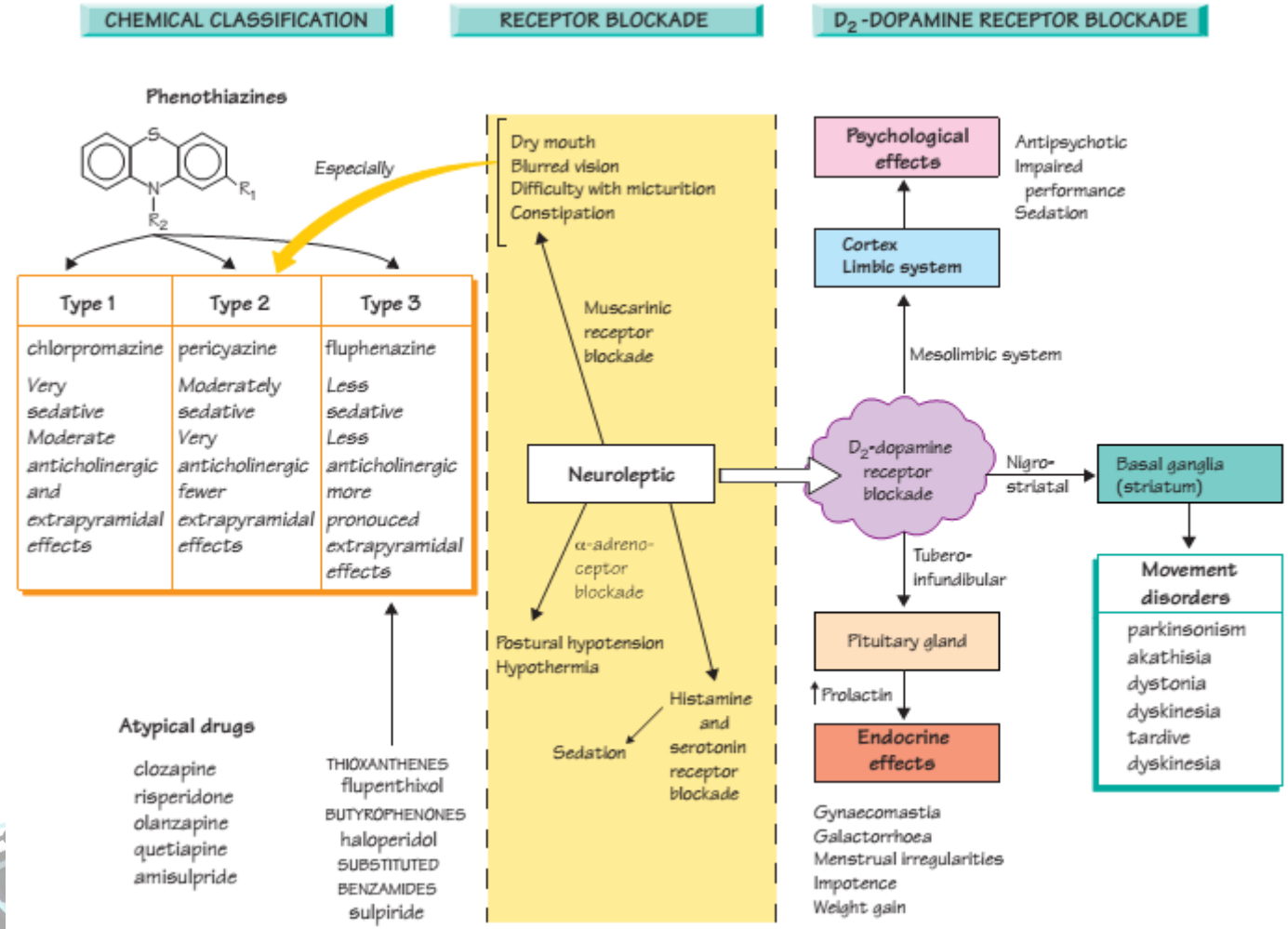
**Sedation & anti-cholinergic effects decreases from top to bottom subclasses.

** Extrapyramidal effects increases from top to bottom subclasses.

** Extrapyramidal effects are maximum in this class of drugs.

** Least sedating of newer antipsychotics.

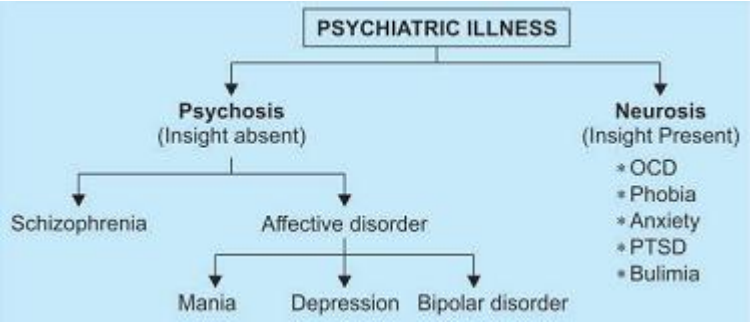
ANTIPSYCHOTICS ADVERSE EFFECTS



DIFFERENCE BETWEEN TYPICAL & ATYPICAL ANTIPSYCHOTICS

FEATURE	TYPICAL ANTIPSYCHOTICS	ATYPICAL ANTIPSYCHOTICS
Receptor Affinity	$D_2 > 5\text{-}HT_2$	$5\text{-}HT_2 > D_2$
Schizophrenia Symptoms	↓ Positive Symptoms	↓ Positive & Negative Symptoms
Extrapyramidal Side Effects	↑ tendency (maximum in Haloperidol)	↓ tendency
Tardive Dyskinesias	High risk	Low risk
Metabolic Disturbances	None	May produce
Agranulocytosis	None	May produce (Cloz-apine)
QT Interval Prolongation	None	May produce (Queti-apine & Ziprasi-done)
Withdrawal Symptoms	Less	High

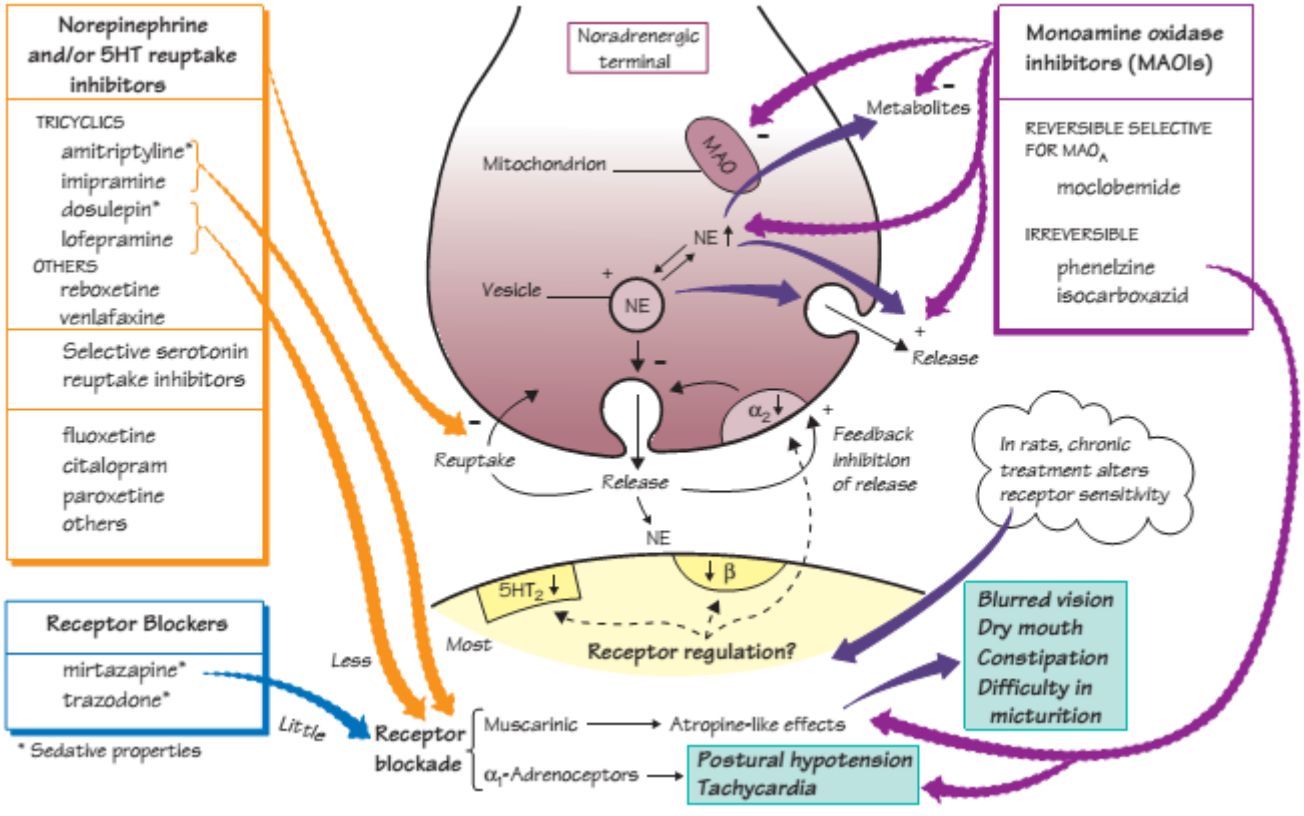
TYPES OF PSYCHIATRIC ILLNESS



ANTIDEPRESSANTS

- Antidepressants
  - TCAs
    - Ami-triptyline
    - Clo-mipramine
    - I-mipramine
  - SSRIs
    - Fluo-xetine
    - Paro-xetine
    - Fluvo-xamine
    - Ser-traline
    - Citalo-pram
    - Es-citalo-pram
  - Heterocyclics
    - SNRIs
      - Levo-milna-cipran
      - Dulo-xetine
      - Venla-faxine
      - Des-venla-faxine
    - 5-HT_{2A} Antagonists
      - Net-azodone
      - Tr-azodone
    - Others
      - Amoxa-pine
      - Mirtaze-pine
      - Bu-pro-pion
      - Ma-pro-tiline
  - MAO Inhibitors
    - MAO_A & MAO_B Inhibitor
      - Phenel-zine
      - Tranyl-cy-promine
    - MAO_B Inhibitor
      - Sele-giline

ANTIDEPRESSANTS ADVERSE EFFECTS



ADVANTAGES OF SSRIs OVER TCAs

1. ↓ Sedation
2. Not interfere with cognitive and anticholinergic effects
3. No postural hypotension (Suitable for elders)
4. Wide safety margin
5. Better patient acceptability
6. Preferred for porphylaxis of recurrent depression.
7. Additional use in NEUROSIS psychiatric illnesses

OPIOID ANALGESICS & ANTAGONISTS

- **Opioid Drugs**
  - **Agonists**
    - Full Agonists: Fentanyl, Morphine, Oxy-morphone, Hydro-morphone, Methadone, Meperidine, Heroin, Levor-phanol, Loper-amide (Antidiarrheal), Diphenoxylate (Antidiarrheal)
    - Partial Agonists: Codeine, Oxy-codone, Hydro-codone
    - Weak Agonists: Prop-oxy-phene
  - **Mixed Agonist-Antagonists**
    - κ Agonist & μ Antagonist: Butor-phanol, Nal-buphine, Penta-zocine
    - μ Agonist & κ Antagonist: Bupre-norphine
    - μ Agonist & 5-HT Reuptake Inhibitor: Tramadol
    - μ Agonist & NE Reuptake Inhibitor: Tapentadol
  - **Antagonists**
    - Older Agents (Crosses BBB): Nalo-xone, Nalme-fene, Naltre-xone
    - Newer Agents/ Antidiarrheals (Do not cross BBB): Methyl-naltre-xone, Alvimopan
  - **Others**
    - Antitussives: Codeine, Dextro-meth-orphan

Overdose reversed by Naxolone
Overdose cannot be reversed by Naxolone

OPIOID RECEPTORS

RECEPTOR	FUNCTIONS	ENDOGENOUS OPIOID PEPTIDE AFFINITY
μ (mu)	Supraspinal and spinal analgesia Respiratory inhibition Hormone modulation Neurotransmitter release Sedation Slowed GIT transit	**Endorphins** > enkephalins > dynorphins
δ (delta)	Supraspinal and spinal analgesia Hormone modulation Neurotransmitter release Tolerance development	**Enkephalins** > endorphins = dynorphins
κ (kappa)	Supraspinal and spinal analgesia Sedation Slowed GIT transit Psychotomimetic effects	**Dynorphins** > > endorphins = enkephalins

PHARMACOLOGICAL & ADVERSE EFFECTS OF OPIOIDS

ACUTE EFFECTS (BAD AMERICANS Hormones Imbalanced)

1. **B**radycardias & hypotension
2. **A**nalgesia *(treatment of moderate to severe pain)*
3. **D**ependence
4. **A**norexia *(poor appetite)*
5. **M**iosis *(characteristic of all opioids except meperidine)*
6. **E**uphoria *(state of excitement)*
7. **R**espiratory depression
8. **I**ncrease smooth muscles activity *(characteristic of all opioids except meperidine)*
   - Biliary tract constriction → Biliary Colic
   - ↑ Ureteral & bladder sphincter tone
   - ↓ Uretrine tone → Prolongation of labor
9. **C**onstipation *(atidiarrheal agents)*
10. **A**ntitussive *(suppression of cough reflex by inhibiting respiratory centres with decrease response to CO_2 challenge)*
11. **N**ausea and vomiting *(activate chemoreceptor trigger zone)*
12. **S**edation and mental clouding (at higher doses)
13. **Hormones Imbalanced**
    - ↑ Release of ADH & Prolactin
    - ↓ Release of LH
    - Exaggerate response in adrenal insufficiency & hypothyroidism

CHRONIC EFFECTS (TD)

1. **T**olerance
2. **D**ependance → Abstinence Syndrome → **GLARY De CMH** (**G**ooseflesh, **L**acrimation, **A**nxiety, **R**hinorrhea, **Y**awning, **D**iarrhea, **C**hills, **M**uscle aches, **H**ostility)

ADVERSE EFFECTS OF OPIOIDS

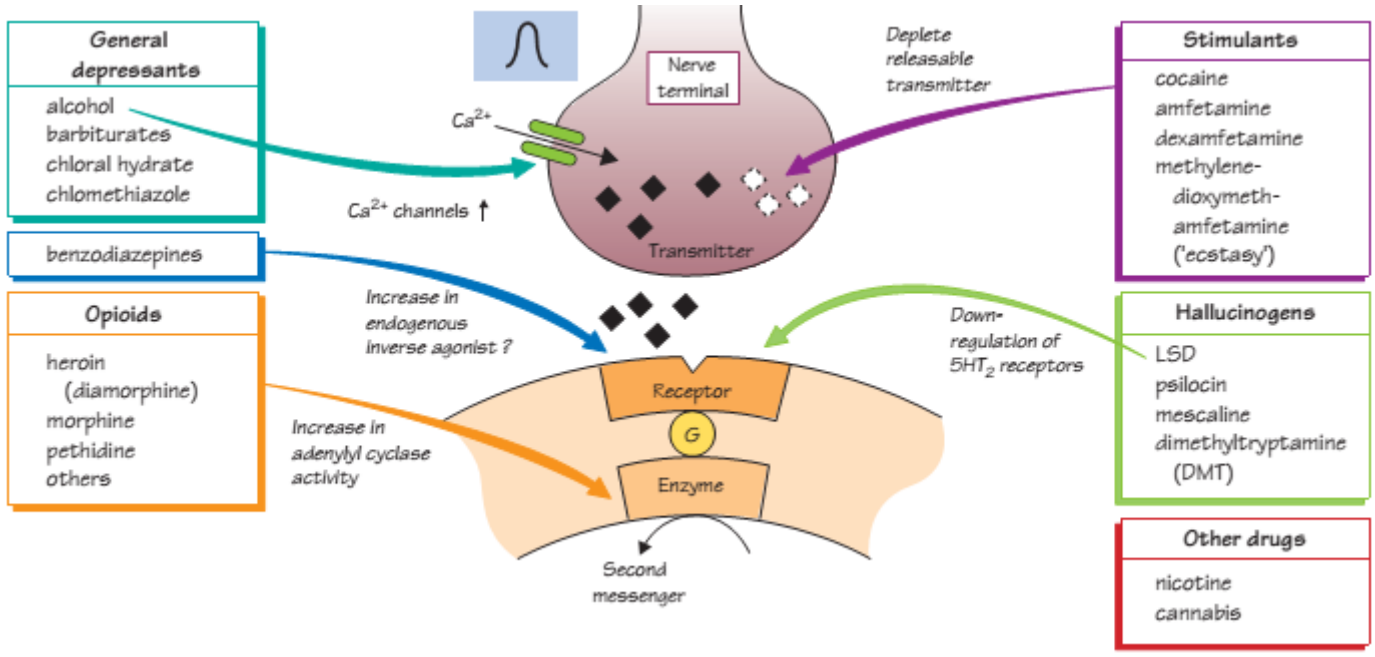
(MORPHINE)

1. **M**iosis
2. **O**ut of it i.e Sedation
3. **R**espiratory depression
4. **P**neumonia (aspiration)
5. **H**ypotension
6. **I**nfrequent urination
7. **N**ausea
8. **E**mesis

DRUGS OF ABUSE

- Drugs of Abuse
  - Sedative-Hypnotics
    - Benzodiazepine
    - Barbiturates
    - Ethanol
  - Opioid Analgesics
    - Fentanyl
    - Morphine
    - Meperidine
    - Heroin
    - Codeine
    - Oxy-codone
  - CNS Stimulants
    - Caffeine
    - Nicotine
    - Cocaine
    - Amphetamines
  - Hallucinogens
    - Phencyclidine
    - LSD
    - Mescaline
    - Psilocybin
  - Marijuana
    - Tetrahydro-cannabinol
    - Cannabidiol
    - Cannabinol
  - Inhalants
    - Anesthetics
    - Industrial Solvents
    - Organic Nitrates
  - Steroids

MECHANISMS OF ACTION OF DRUGS OF ABUSE



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DRUGS OF CHOICE

AUTONOMIC NERVOUS SYSTEM PHARMACOLOGY

CONDITION	DRUG OF CHOICE
Mushroom poisoning	
– Early (Inocybe sp.)	Atropine
– Delayed (Amanita sp.)	Thioctic acid
Glaucoma	
– Open angle	Latanoprost
– Angle closure	Acetazolamide
Myasthenia gravis	
– Diagnosis	Edrophonium
– Treatment	Neostigmine/pyridostigmine
Belladona poisoning	Physostigmine
Atropine poisoning	Physostigmine
Dhatura poisoning	Physostigmine
Alzhiemer's dementia	Donepezil/Rivastigmine/Gallantamine
Cobra bite	Anti-venom
Anticholinesterase poisoning	
– Organophosphate	Atropine
– Carbamate	Atropine
Colicky pain	Anticholinergics like hyoscine/dicyclomine
Bronchial asthma	Salbutamol
Refraction testing	
– In adults	Tropicamide
– In children	Atropine
Fundoscopy	Phenylephrine
Uveitis	
– Iridocyclitis	Atropine + steroids
– Posterior uveitis	Steroids
– Panuveitis	Steroids
Bradycardia	Atropine
Atrioventricular block	Atropine
Drug induced Parkinsonism	Anticholinergics like benzhexol
Shock	
– Cardiogenic	Nor-adrenaline or dopamine
– with oligourea	Dopamine
– Anaphylactic	Adrenaline
– Distributive	Nor-adrenaline or phenylephrine
– Septic	Broad spectrum antimicrobials
– Shock due to adrenal insufficiency	Corticosteroids
– Hypovolumic	Fluids (crystalloids)
– Secondary	Prazosin (α-blockers)
Postural hypotension	Fludrocortisone
Attention deficit hyperkinetic disorder	Methylphenidate
Narcolepsy	Modafinil or armodafinil
Pheochromocytoma	
– Before surgery	Phenoxybenzamine
– Long term	CCBs like nifedipine or nicardipine extended release
Cheese reaction	Phentolamine or tolazoline
Rebound hypertension due to clonidine withdrawl	Phentolamine or tolazoline
Raynaud's phenomenon	CCBs like nifedipine ER or amlodipine
Essential tremors	Propanolol
Akathisia	Propanolol
Hypertrophic obstructive cardiomyopathy	Propanolol
Beta blocker poisoning	Glucagon
Benign hyperplasia of prostate	
– Without hypertension	Tamsulosin
– With hypertension	Prazosin or doxazosin
Performance anxiety	Propanolol

AUTOCOIDS PHARMACOLOGY

CONDITION	DRUG OF CHOICE
Migraine	
– Acute-mild to modrate	NSAIDs
– Acute-severe	Sumatriptan
– Prophylaxis	Propanolol
Abortion < 7 weeks	Mifepristone + misoprostol
Induction of labour	Oxytocin
Post-partum hemorrhage	Oxytocin
Cervical priming	Misoprostol
NSAID-induced peptic ulcer	Proton pump inhibitors
Open angle glaucoma	Latanoprost
To maintain patency of ductus arteriosus	Alprostadil
Treatment of patent ductus arteriosus (PDA)	Indomethacin
Bartter syndrome	Indomethacin
Pulmonary hypertension	Oral diltiazem or amlodipine or nifedipine
Erectile dysfunction	Sildenafil
Rheumatoid arthritis	
– Pain relief	NSAIDs
– Bridge therapy	Corticosteroids
– DMARD	Methotrexate
Flushing due to nicotinic acid	Aspirin
Prophylaxis of MI and stroke	Aspirin
Acetaminophen (Paracetamol) poisoning	N-Acetyl cysteine
Anaphylactic shock	Adrenaline
Acute mediterranean fever	Colchicine
Cancer chemotherapy induced vomiting	$5HT_3$ antagonists like ondansetron
Cisplatin induced vomiting	
– Early	Ondansetron
– Delayed	Aprepitant
Gout	
– Acute	NSAIDs except aspirin
– Refractory acute	Colchicine
– Chronic	Allopurinol
– Chronic (in patient allergic to allopurinol)	Febuxostat
Hyperuricemia secondary to anticancer drugs	Allopurinol

RESPIRATORY PHARMACOLOGY

CONDITION	DRUG OF CHOICE
Bronchial Asthma	
– Acute attack	Salbutamol
– Acute attack in pregnancy	Salbutamol
– Acute attack during labour	Ipratropium
– Acute attack in patients on beta blocker therapy	Ipratropium
– Prophylaxis	Corticosteroids
Exercise-induced asthma	
– Acute attack	Salbutamol
– Prophylaxis	Corticosteroids
Aspirin-induced asthma	
– Acute attack	Salbutamol
– Prophylaxis	Corticosteroids

GASTROINTESTINAL PHARMACOLOGY

CONDITION	DRUG OF CHOICE
Peptic ulcer	
– Gastric ulcer	Proton pump inhibitors (PPI)
– Duodenal ulcer	PPI
– Stress ulcer	PPI
– NSAID-induced	PPI
– H. pylori associated	Lansoprazole + Amoxycillin + Clarithromycin
– Zollinger Ellison syndrome	PPI
– Gastro Esophageal Reflux Disease	PPI
Vomiting	
– Chemotherapy induced	5-HT_3 antagonists like palonosetron
– Levo-dopa induced	Domperidone
– Migraine associated	Metoclopramide
– Drug or disease associated	Metoclopramide
– Post-operative	Ondansetron
– Radiation induced	Ondansetron
– Cisplatin induced	
* Early	5-HT_3 antagonists
* Delayed	Aprepitant
– Prophylaxis of motion sickness	Hyoscine
– Pregnancy (Morning sickness)	Doxylamine + Pyridoxine
Opioid induced constipation	Methyl naltrexone
Diarrhea in carcinoid syndrome	Octreotide
To prevent dehydration in diarrhea	ORS
Crohn's disease	Corticosteroids
Ulcerative colitis	5-ASA derivatives
Hepatic encephalopathy	Lactulose

CARDIOVASCULAR PHARMACOLOGY

CONDITION	DRUG OF CHOICE
Diabetic nephropathy	ACE inhibitors or ARBs
Scleroderma hypertensive crisis	Captopril
Congestive heart failure	
– Decompensated	Dobutamine
– Compensated	ACEI/ARB
Hypertrophic obstructive cardiomyopathy	Propanolol
Angina pectoris	
– Acute attack	Sublingual nitroglycerine
– Prophylaxis	Oral/transdermal nitrates
Esophageal spasm	Nitroglycerine
Cyanide poisoning	Hydroxocobalamin/amyl nitrite
Raynaud's phenomenon	Nifedipine ER or amlodipine
Myocardial infarction	
– Pain relief	Sublingual nitroglycerine ↓ Morphine
– Prophylaxis	Aspirin
– Thrombolytic for STEMI	Reteplase or alteplase
Hypertension	Thiazides
– With BHP	Prazosin
– With diabetes mellitus	ACE inhibitors
– With ischemic heart disease (angina)	Beta blockers
– With chronic kidney disease	ACE inhibitors
– In pregnancy	Labetalol
Acute severe digitalis toxicity	Digibind
Hypertensive emergencies	Nicardipine + Esmolol
– In cheese reaction	Phentolamine
– in clonidine withdrawl	Phentolamine
– In aortic dissection	Nitroprusside + esmolol
– In Pregnancy	Labetalol
Hyperlipidemia	
– Type IIa and IIb	Statins
– Type III (hypertriglyceridemia)	Fibrates
– Type IV	Statins
– Secondary to diabetes or nephrotic syndrome	Statins
Supraventricular tachycardia	
– Narrow QRS complex	Verapamil or beta blockers
– Wide complex	Flecainide
– WPW syndrome	Flecainide
Paroxysmal supraventricular tachycardia (PSVT)	
– Acute treatment	Adenosine
– Prophylaxis	Verapamil
Ventricular tachycardia	Lignocaine
– Digitalis induced	Lignocaine
Long QT syndrome (Torsades' de pointes)	Magnesium

RENAL PHARMACOLOGY

CONDITION	DRUG OF CHOICE
Edema	
– Due to CHF	Furosemide
– Due to renal disease or nephrotic syndrome	Furosemide
– Pulmonary edema	Furosemide
– Cerebral edema	Mannitol
– Edema due to cirrhosis	Spironolactone
Diabetes insipidus	
– Central	Desmopressin
– Nephrogenic	Thiazides
– Lithium-induced	Amiloride
Recurrent calcium stones in kidney due to hypercalciurea	Thiazides
Acute congestive glaucoma	Acetazolamide
Acute mountain sickness	Acetazolamide
Nocturnal enuresis	Desmopressin
SIADH	Fluid restriction + Hypertonic saline + Furosemide

BLOOD PHARMACOLOGY

CONDITION	DRUG OF CHOICE
Anemia	
– Iron deficiency anemia	Ferrous sulphate
– Megaloblastic anemia	
* Folate deficiency	Folic acid
* B12 deficiency	Vitamin B12
* Pernicious anemia	Vitamin B12
* Chemotherapy induced anemia	Erythropoietin
– Anemia due to chronic kidney disease	Erythropoietin
Iron poisoning	
– Acute	Desferrioxamine
– Chronic	Deferipirone
Cyanide poisoning	Hydroxocobalamin/Amyl nitrite
Deep vein thrombosis	
– Prophylaxis	Warfarin
– Initiation of therapy	LMW heparin + warfarin
– With severe chronic kidney disease	Unfractionated heparin
Pulmonary embolism	
– Stable patient	LMW heparin
– Unstable patient	Thrombolytics (Reteplase)
Chronic Atrial fibrillation	
– Prophylaxis	Dabigatran or Rivaroxaban or Apixaban
– In mechanical prosthetic valves	Warfarin
– Advanced kidney disease	Warfarin
– Mitral stenosis	Warfarin
Myocardial Infarction	
– Acute STEMI	Thrombolytics (Reteplase)
– Prophylaxis	Aspirin
Heparin overdose	Protamine
Warfarin overdose	Vitamin K
Bleeding due to overdose of anticoagulants (heparins or warfarin)	Fresh frozen plasma
Fibrinolytic overdose	Tranexamic acid or Epsilon Amino Caproic Acid
Chemotherapy induced leukopenia	Sargramostim
Chemotherapy induced thrombocytopenia	Oprelvekin
Immune thrombocytopenic purpura	Corticosteroids
Heparin induced thrombocytopenia	Argatroban

ANTIFUNGAL PHARMACOLOGY

CONDITION	DRUG OF CHOICE
Candida albicans	Fluconazole
Candida glabrata	Caspofungin
Candida krusei	Caspofungin
Candida endocarditis	Amphotericin B (AMB)
Histoplasmosis	
– Meningeal	AMB
– Non-meningeal	Itraconazole
Coccidioidomycosis	AMB
Para-coccidioidomycosis	Itraconazole (For severe cases: AMB)
Sporotrichosis	Itraconazole
Blastomycosis	
– Mild and Non-CNS	Itraconazole
– Severe or CNS	AMB
Penicillium marneffei	Itraconazole (For severe cases: AMB)
Chromoblastomycosis	Itraconazole
Mycetoma	
– Eumycetoma	Itraconazole
– Actinomycetoma	Itraconazole
Cryptococcal meningitis	
– Induction	AMB (for 2 weeks)
– Maintenance	Fluconazole (for further 8 weeks)
Aspergillosis	
– Invasive	Voriconazole
– Allergic broncho-pulmonary (AMBA)	Prednisolone + Itraconazole/Voriconazole
Mucormycosis	AMB (Posaconazole should be given after disease has stabilized)
Pseudoallescheria boydii	Voriconazole
Fusarium	Voriconazole
Exserohilum	AMB
Febrile neutropenia	
– Treatment	Voriconazole
– Prophylaxis	Fluconazole

ANTIVIRAL PHARMACOLOGY

CONDITION	DRUG OF CHOICE
Herpes simplex	
– Keratitis	Topical vidarabine/Trifluridine
– Neonatal	Acyclovir
– Encephalitis	Acyclovir
– Dissemnated	Acyclovir
– Esophagitis	Acyclovir
– Genital	Acyclovir
– Bell's Palsy	Prednisolone
Varicella	Acyclovir
Herpes zoster	
– Acute	Valacyclovir
– Post herpetic neuralgia	Gabapentin
Epstein Barr virus	Symptomatic (no antiviral)
Cytomegalo virus	
– Retinitis	Ganciclovir
– Post-transplant	
* Mild	Valganciclovir
* Severe	Ganciclovir
Measels	Ribavirin (Indication: Severe pneumonitis)
Prion disease	Flupirtine (↓cognitive decline but does not stop mortality)
Viral hemorrhagic fever	
– Lassa virus	Ribavirin
– Rift Valley fever	Ribavirin
– Congo crimean hemorrhage fever	Ribavirin
– Hantaan virus	Ribavirin
Respiratory syncytial virus	
– High risk patient, acute	Ribavirin (aerosolized)
– Prophylaxis (infants)	Palivizumab
Influenza virus	
– Seasonal influenza	Oseltamivir
– Avian influenza (including bird flu)	Oseltamivir
– Oseltamivir-resistant influenza	Zanamivir
Human immunodeficiency virus (HIV)	
– Treatment	Zidovudine + Lamivudine + Nevirapine
– Post-exposure prophylaxis	Zidovudine + Lamivudine ± Atazanavir

ANTIMYCOBACTERIAL PHARMACOLOGY

CONDITION	DRUG OF CHOICE
Tuberculosis	
– Latent TB Infection (Chemoprophylaxis)	Daily INH for 9 months
– Category 1 (New or previously untreated cases)	2HRZE + 4HR
– Category 2 (Previously treated cases; relapses and treatment defaults)	2HRZES + HRZE + 5HRE
– Treatment failure and special cases:	
a. Resistance (or intolerance) to H	6 RZE + Q (for extensive disease)
b. Resistance (or intolerance) to R	12 HZEQ + S (for extensive disease)
c. Intolerance to Z	2 HRE + 7 HR
d. MDR TB (resistance to H + R)	HRZE
e. Extensive drug resistance (XDR)	HRZE
Leprosy	
– Multibacillary (x 12 months)	Rifampicin (600mg) once monthly supervised Clofazimine 300mg once monthly supervised Dapsone 100 mg OD Clofazimine 50mg OD
– Paucibacillary (x 6 months)	Rifampicin 600 mg once monthly supervised Dapsone 100 mg OD
– Type 1 Lepra reaction	Corticosteroids
– Type 2 Lepra reaction	Corticosteroids
M. avium intracellulare	Azithromycin + Ethambutol ± Rifabutin
M. kansasii	Isoniazid + Rifampicin ± Ethambutol
M. fortuitum chelonei	Cefoxitin + clarithromycin

(Q: Fluoroquinolone, H: Isoniazid, R: Rifampicin, Z: Pyrazinamide, E: Ethambutol, S: Streptomycin)

PARASITIC PHARMACOLOGY

CONDITION	DRUG OF CHOICE
ANTI-PROTOZOAN	
Ameobiasis	
– Asymptomatic intestinal	Diloxanide furoate
– Mild, moderate and severe intestinal	Metronidazole + diloxanide
– Extra-intestinal (hepatic abcess)	Metronidazole + diloxanide
– Primary ameobic meningo-encephalitis (Naegleria fowleri)	AMB
– Acanthameoba keratitis	Topical propamidine isethionate
Coccidiosis	Nitazoxanide/Paromomycin
– Cryptosporidiosis	
– Isoporiasis	Cotrimoxazole
– Cyclosporiasis	Cotrimoxazole
– Microsporidiosis	Albendazole
– Sacrocytosis	No treatment
– Trypanosomiasis	
– East African sleeping sickness	
* Early haemo lymphatic stage	Suramin
* Late CNS stage	Melarsoprol
– South-American (Chagas disease)	Benznidazole (alternative is nifurtimox)
ANTI-HEMINTHICS	
Flukes	
– Fasciola	Triclabendazole
– Schistosoma	Praziquantal
– Clonorchis	Praziquantal
– Opisthorchis	Praziquantal
– Paragonimus	Praziquantal
– Fasciolopsis	Praziquantal
Tapeworms	
– Taenia solium	Praziquantal
– T. saginata	Praziquantal
– D. latum	Praziquantal
– H. nana	Praziquantal
– Echinococcus	Albendazole
– Neurocysticercosis	Albendazole
Nematodes	
– Ascaris	Albendazole
– Trichuris	Albendazole
– Ancylostoma	Albendazole
– Necator	Albendazole
– Enterobius	Albendazole
– Trichinella	Albendazole
– Cutaneous larva migrans	Albendazole
– Visceral lara migrans	Albendazole
– Dracunculus (Guinea worm)	Metronidazole
Filarial worm	
– W. bancrofti	Di Ethyl Carbamezine (DEC)
– B. malayi	Di Ethyl Carbamezine (DEC)
– B. timori	Di Ethyl Carbamezine (DEC)
– Loa loa	Di Ethyl Carbamezine (DEC)
– Onchocerca volvolus	Ivermectin
Strongyloides stercoralis	Ivermectin

ANTIBACTERIAL PHARMACOLOGY

CONDITION	DRUG OF CHOICE
GRAM-POSITIVE COCCI	
Streptococcus	
• S. pneumoniae	Penicillin G[1]
• Hemolytic, groups A, B, C, G	Penicillin G[1]
• S. viridans	Penicillin G[1, 2]
Staphylococcus	
• Non penicillinase producing	Penicillin G[1]
• Penicillinase producing	Penicillinase resistant penicillin (cloxa, oxa, naf or dicloxacillin)
• Methicillin resistant (MRSA)	Vancomycin
• Coagulase negative	Vancomycin
ENTEROCOCCUS	
• faecalis	Ampiillin[3]
• faecium	Vancomycin[3]
GRAM-POSITIVE BACILLI	
• Actinomyces	Penicillin G
• Bacillus	
– Anthracis	Ciprofloxacin or Doxycycline
– Cereus and others	Penicillin G
• Clostridium	Pencillin G
• Corynebacterium	Erythromycin[4]
• Listeria	Ampicillin[5]
GRAM-NEGATIVE COCCI	
• Neisseria	
– meningitides	Penicillin G
– gonorrhea	Ceftriaxone + Azithromycin/Doxycycline
• Moraxella	Fluoroquinolones
GRAM-NEGATIVE BACILLI	
• Campylobacter	Macrolides
• Legionella	Macrolides
• Bordetella	Macrolides
• Brucella	Doxycyline + Rifampicin
• Acinetobacter	Carbapenems
• Hemophilus	
– Serious infections like meningitis	Ceftriaxone
– Respiratory infections, otitis	Cotrimoxazole
– Ducreyi (chancroid)	Azithromycin
• Prevotella	Clindamycin
• Bacteroides	Metronidazole
• Pseudomonas	Anti-Pseudomonal β-lactam (piperacillin or ceftazidime or cefepime or imipenem) + Gentamicin
• Burkholderia	
– mallei (glanders)	Streptomycin + Tetracycline
– pseudomallei (melioidosis)	Ceftazidime
• Helicobacter pylori	Clarithromycin + Amoxycillin + Proton pump inhibitor
• Enterobactericiae	
– Salmonella	Ceftriaxone
– E. coli sepsis	Ceftriaxone[6]
– Klebsiella	Ceftriaxone[7]
– Proteus vulgaris	Ceftriaxone[8]
– Enterobacter	Carbapenems
– Serratia	Carbapenems
– Shigella	Fluoroquinolones
– Yersinia	Streptomycin + tetracycline
SPIROCHETES	
• Treponema	
– pallidum (syphilis)	Penicillin G
– pertenue (yaws)	Penicillin G

• Leptospira	Penicillin G
• Borrelia	
– burgdorferi (Lyme's)	Doxycycline
– recurrentis (Relapsing fever)	Doxycycline
CHLAMYDIAE	
• C. psittaci	Doxycycline
• C. trachomatis	Doxycycline
• C. pneumoniae	Doxycycline
RICKETTSIAE	
• R. prowazekii (Epidemic typhus)	Doxycycline
• R. typhi (Endemic typhus)	Doxycycline
• Orientia tsutsugamushi (scrub typhus)	Doxycycline
• R. rickettssi (Rocky mounted spotted fever)	Doxycycline
• R. akari (Rickettsial pox)	Doxycycline
• Rickettsia fever	Doxycycline
• Ehrlichia	Doxycycline
• Coxiella burnetii (Q fever)	Doxycycline
MYCOPLASMA	Azithromycin
NOCARDIA	Cotrimoxazole

1. *Oral penicillin V can be used for mild cases*
2. *Addition of gentamicin decreases the duration of treatment*
3. *Gentamicin is added for meningitis or endocarditis*
4. *For C. jeikium, vancomycin is drug of choice*
5. *Gentamicin is added for first few days*
6. *For UTI by E.coli, nitrofurantion or fosfomycin are used*
7. *For ESBL producing strains, carbapenems are drug of choice*
8. *For P. mirabilis, ampicillin is drug of choice*

ENDOCRINE PHARMACOLOGY

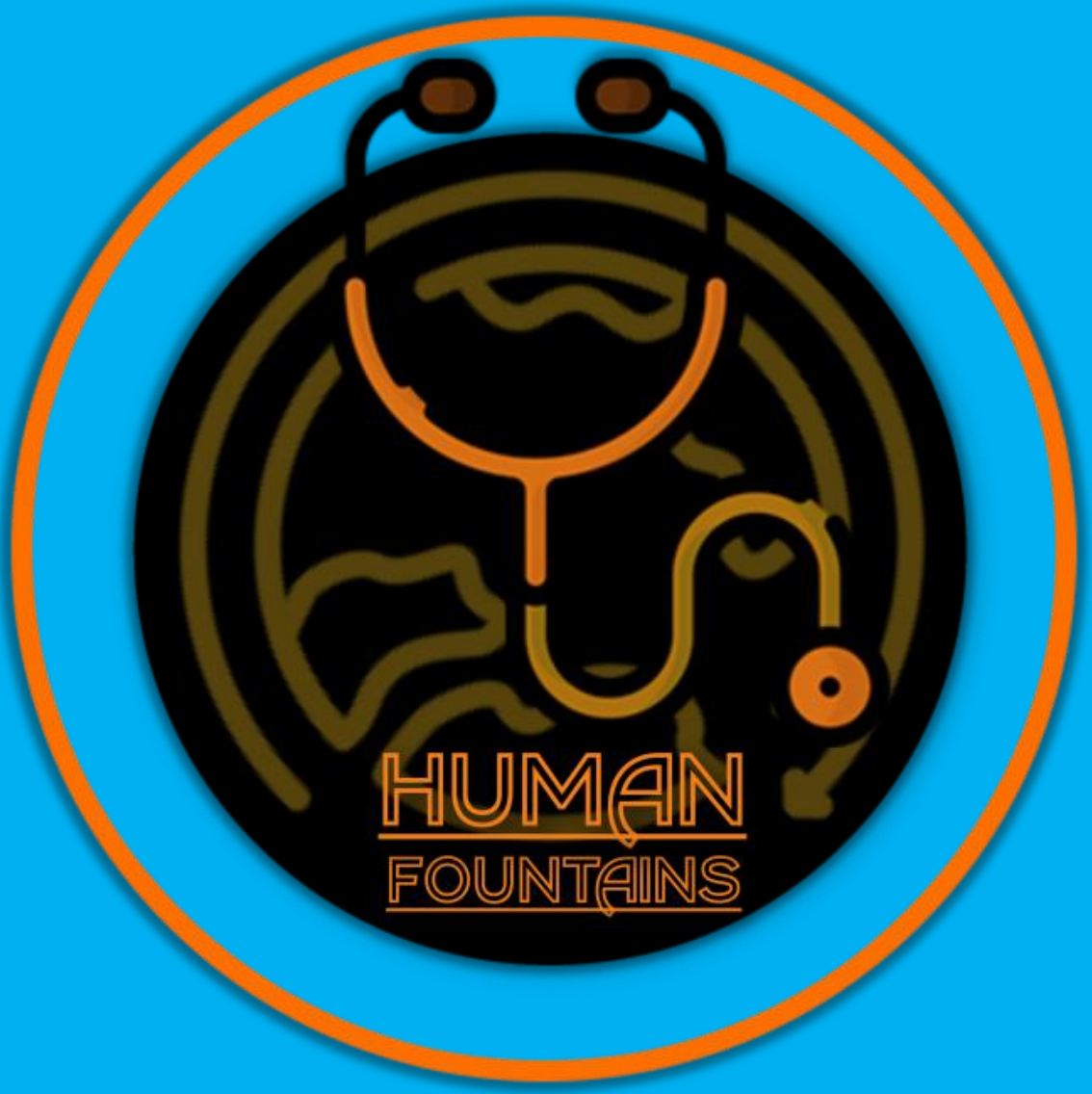
CONDITION	DRUG OF CHOICE
Infantile spasms	ACTH
Hypothyroidism	Levo-thyroxine
Myxedema coma	Levo-thyroxine
Hyperthyroidism	Carbimazole or methimazole
– In lactation	Propylthiouracil
– In 1st trimester of pregnancy	Prophylthiouracil
– In 2nd and 3rd trimester of pregnancy	Carbimazole or methimazole
– Graves' opthalmopathy	Methylprednisolone
Thyroid storm	Propanolol (life saving)+ Iodides
Diabetes mellitus	
Type 1 (IDDM)	Insulin
Type 2 (NIDDM)	Metformin
– In obese	Metformin
– Uncontrolled	Insulin
– Pregnancy	Insulin
– To tide over stress	Insulin
Diabetic ketoacidosis	Insulin (Regular)
Post prandial hyperglycemia	Nateglinide
Acute hyperkalemia	Calcium gluconate
Beta blocker poisoning	Glucagon
Hypoglycemia	Glucose (oral or i.v.)
Adrenal insufficiency	
– Acute	Hydrocortisone
– Chronic (Addison's disease)	Hydrocortisone
Erectile dysfunction	Sildenafil
Contraceptive	
– Newly married	Combined oral contraceptives
– In lactation	Mini pills
– Emergency contraceptive	Levonorgestrel
Anovulatory infertility	Clomiphene
Osteoporosis	
– Post menopausal	Alendronate
– Steroid-induced	Alendronate
– In women with risk factors for breast cancer	Raloxifene
Hypercalcemia of malignancy	Bisphosphonates
Paget's disease of bone	Bisphosphonates
Tetany	Calcium
Induction of labour	Oxytocin
Post partum hemorrhage	Oxytocin
Acromegaly	Cabergoline
Esophageal varices	Terlipressin (if not available, octreotide)
Hyperprolactinemia	Cabergoline
Androgenital alopecia	Finasteride
Dysfunctional uterine bleeding	
– Light bleeding	Medroxyprogesterone acetate
– Heavy bleeding	Combined oral contraceptives
– Intractable bleeding	Leuprolide
Endometriosis	Combined oral contraceptives
Ectopic pregnancy	Methotrexate

CENTRAL NERVOUS SYSTEM PHARMACOLOGY

CONDITION	DRUG OF CHOICE
Alcohol dependence	
– Withdrawl symptoms (including seizures)	Benzodiazepines like chlordiazepoxide or diazepam
– Maintenance therapy	Chlordiazepoxide
– To prevent craving	Naltrexone
Methanol poisoning	Fomepizole
Ethylene glycol poisoning	Fomepizole
Anxiety disorders	
– Performance anxiety	Propanolol
– Generalized anxiety disorder (GAD)	
* Acute attacks	Benzodiazepines
* Sustained treatment	Antidepressants (venlafaxine/duloxetine)
– Panic disorder	
* Acute panic attacks	Benzodiazepines
* Sustained treatment	SSRI (Sertraline)
Insomnia	Zolpidem
Benzodiazepine poisoning	Flumazenil
Epilepsy/seizure disorders	
– Grand mal (GTCS)	Valproate
– Petit mal (Absence)	Valproate
– Focal	Carbamazepine/Oxcarbazepine
– Myoclonic	Valproate
– Atonic	Valproate
– Infantile spasms	
* Without tuberous sclerosis (TS)	ACTH
* With TS	Vigabatrin
– Febrile seizures	Diazepam
– Status epilepticus	Lorazepam
– Eclamptic seizures	Magnesium sulphate
– Epilepsy in pregnancy	Lamotrigine/Topiramate/levetiracetam
– Lennox-Gastaut syndrome	Valproate/Rufinamide/Clonazepam
Neuropathic pain	
– Trigeminal neuralgia	Carbamazepine
– Post-herpetic neuralgia	Pregabalin or gabapentin
– Diabetic neuropathic pain	Pregabalin or gabapentin
Parkinsonism	
– Early	Pramipexole/Ropinirole
– Late	Pramipexole/Ropinirole
– Drug induced	Anticholinergics (Benzhexol)
Levo-dopa induced	
– Vomiting	Domperidone
– Psychosis	Atypical antipsychotics (olanzapine)
Schizophrenia	Olanzapine
– In non-compliant patients	Risperidone LAI (long acting injection)
– Refractory	Clozapine
Manic disorder	
– Acute mania	Benzodiazepines/Antipsychotics (olanzapine) + lithium
– Prophylaxis of mania	Lithium
– Bipolar disorder	Lithium
– Rapid cyclers	Valproate
Gille de la Tourette syndrome	1. Haloperidol (FDA-approved) 2. Clonidine/Guanafacine (off label)
Relapsing remitting multiple sclerosis	Beta-interferon
Huntington's disease	Tetrabenazine
Wilson disease	Zinc
Depression	SSRI
– Mild to moderate	SSRI (Fluoxetine)
– Severe	SNRI (Venlafaxine)
Neurotic disorders	
– Obsessive compulsive disorder	SSRI (Fluoxetine)
– Post-traumatic stress disorder	SSRI (Sertraline)

– Bulimia	SSRI (Fluoxetine)
– Phobia	SSRI (Sertraline)
– Impulse-control disorders	SSRI (Fluoxetine)
Attention deficit hyperkinetic disorder	Methylphenidate
Nocturnal enuresis	Desmopressin
Severe (cancer) pain	Opioids (morpine)
Opioid poisoning	
– Acute	Naloxone
– Maintenance	Naltrexone
Opioid de-addiction	
– Maintenance therapy	Methadone
– To prevent relapse	Naltrexone
– To treat withdrawl symptoms	Beta blockers/clonidine
Alzhiemer's dementia	Donepezil
Amyotrophic lateral sclerosis	Riluzole
Extrapyramidal symptoms	
– Acute muscular dystonias	Benzhexol
– Parkinsonism	Benzhexol
– Akathisia	Propanolol
– Neurolept malignant syndrome	Dantrolene
– Tardive dyskinesia	No treatment (benzodiazepines may help)
Restless leg syndrome	Pramipexole
Neurolept analgesia	Droperidol + Fentanyl
Neurolept anaesthesia	Droperidol + Fentanyl + Nitrous Oxide
GA for internal version	Halothane
GA for asthma	
– Inducing agent	Ketamine
– Inhalational	Halothane
GA to produce controlled hypotension	Isoflurane
GA for cardiac surgery	
– Inducing agent	Etomidate
– Inhalational	Isoflurane
GA for neurosurgery	Isoflurane
Day care surgery	Propofol
Total Intravenous Anaesthesia	Propofol
GA for malignant hyperthermia	Propofol
GA in patients with shock	Ketamine
LA in patients with malignant hyperthermia	Procaine
Intravenous Regional Anaesthesia (IVRA; Bier's block)	Prilocaine
Malignant hyperthermia	Dantrolene
Malignant Neuroleptic Syndrome	Danrolene
MR in patients with asthma	Vecuronium
MR in liver and kidney disease	Atracurium or Cis-atracurium
MR for endotracheal intubation	Succinylcholine

- *GA : General Anaesthetic*
- *LA : Local Anaesthetic*
- *MR : Muscle Relexant*


HUMAN
FOUNTAINS