

PHARMACOLOGY AND TOXICOLOGY

NOTES

FOURTH EDITION

**PRE-SUMMARIZED
READY-TO-STUDY
HIGH-YIELD NOTES**

**FOR THE TIME-POOR
MEDICAL, PRE-MED,
USMLE OR PA STUDENT**



PDF



224 PAGES

A Message From Our Team

Studying medicine or any health-related degree can be stressful; believe us, we know from experience! The human body is an incredibly complex organism, and finding a way to streamline your learning is crucial to succeeding in your exams and future profession. Our goal from the outset has been to create the greatest educational resource for the next generation of medical students, and to make them as affordable as possible.

In this fourth edition of our notes we have made a number of text corrections, formatting updates, and figure updates which we feel will enhance your study experience. We have also endeavoured to use only open-source images and/or provide attribution where possible.

If you are new to us, here are a few things to help get the most out of your notes:

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What's included: Ready-to-study summaries on a broad range of pharmacological concepts and drug-classes, presented in succinct, intuitive and richly illustrated downloadable PDF documents. Once downloaded, you may choose to either print and bind them, or make annotations digitally on your ipad or tablet PC.

Please Note: This subject is intended to give a summarized overview of a wide variety of theoretical pharmacological concepts and clinical therapeutic indications. It is not intended to be an exhaustive list of all known drugs, or a guideline for management of actual patients. Please always refer to your local therapeutic guidelines prior to making treatment decisions.

Pharmacology Notes:

- INTRODUCTION TO CLINICAL PHARMACOLOGY
- PHARMACOKINETICS
- PHARMACODYNAMICS
- ANTIMICROBIAL THERAPY & SELECTIVE TOXICITY
- ANTI-ARRHYTHMIC DRUGS
- COMMON DRUGS USED IN ISCHAEMIC HEART DISEASE
- COMMON DRUGS USED IN MANAGING CHOLESTEROL & LIPIDAEMIA
- COMMON DRUGS USED IN MANAGING HEART FAILURE
- TREATING DIABETES
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- TREATING HYPERINFLAMMATORY DISORDERS
- MODIFYING SEX-HORMONE PROFILES
- GASTROINTESTINAL DRUGS
- GENERAL NERVOUS-SYSTEM DRUGS
- EPILEPSY & ANTI-EPILEPTIC DRUGS
- ANESTHESIA & ANALGESIA
- PSYCHOSIS & ANTI-PSYCHOTICS
- AFFECTIVE DISORDERS, ANTI-DEPRESSANTS AND MOOD-STABILISING DRUGS
- DRUGS FOR HEMOSTASIS
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- DRUGS USED IN HYPERTENSION
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- INTRO TO TOXICOLOGY

INTRODUCTION TO CLINICAL PHARMACOLOGY:

INTRODUCTION TO CLINICAL PHARMACOLOGY:

General Advice For Studying Drugs as a Medical Student – (Compartmentalize Everything):

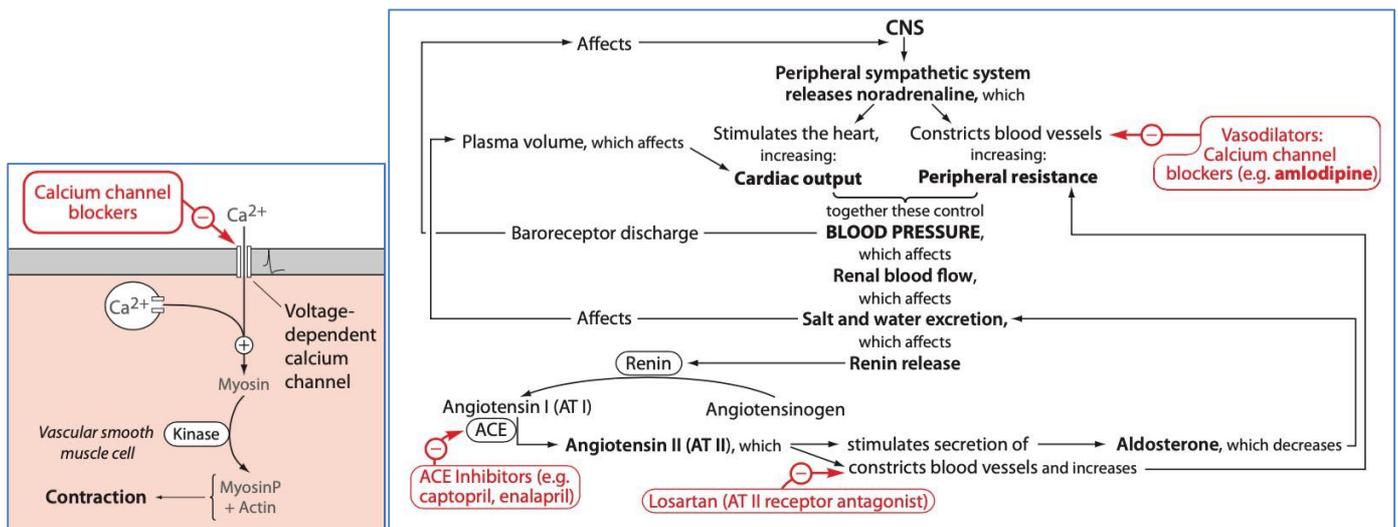
- **1: Focus on Drug Groups/Families first (not individual drugs); (Exception: Generic names for ‘stand-alone’ drugs that don’t have a group – eg: Anti-epileptics/Adenosine/Digoxin/Phenytoin/etc):**
 - o **Learn The Common Suffixes** – (Eg: “-olol”, “-statin”, “-opril”, “-epam”, etc)

Drug Suffix	Example	Action
-azepam	Diazepam	Benzodiazepine
-azine	Chlorpromazine	Phenothiazine
-azole	Ketoconazole	Anti-fungal
-barbital	Secobarbital	Barbiturate
-cillin	Methicillin	Penicillin
-cycline	Tetracycline	Antibiotic
-ipramine	Amitriptyline	Tricyclic Anti-depressant
-navir	Saquinavir	Protease Inhibitor
-olol	Timolol	Beta Antagonist
-oxin	Digoxin	Cardiac glycoside
-phylline	Theophylline	Methylxanthine
-pril	Enalapril	ACE Inhibitor
-terol	Albuterol	Beta 2 Agonist
-tidine	Ranitidine	H ₂ Antagonist
-trophin	Somatotrophin	Pituitary Hormone
-zosin	Doxazosin	Alpha 1 Antagonist

- o **Learn The Primary Uses** – Selected Clinical Applications & Implications
- o **Learn Key Side-Effects** – (Most side-effects are due to mechanism of action, so you shouldn’t have to memorise them – Except idiosyncratic side-effects)

2: Learn the Mechanism of Action of each drug Group/Family:

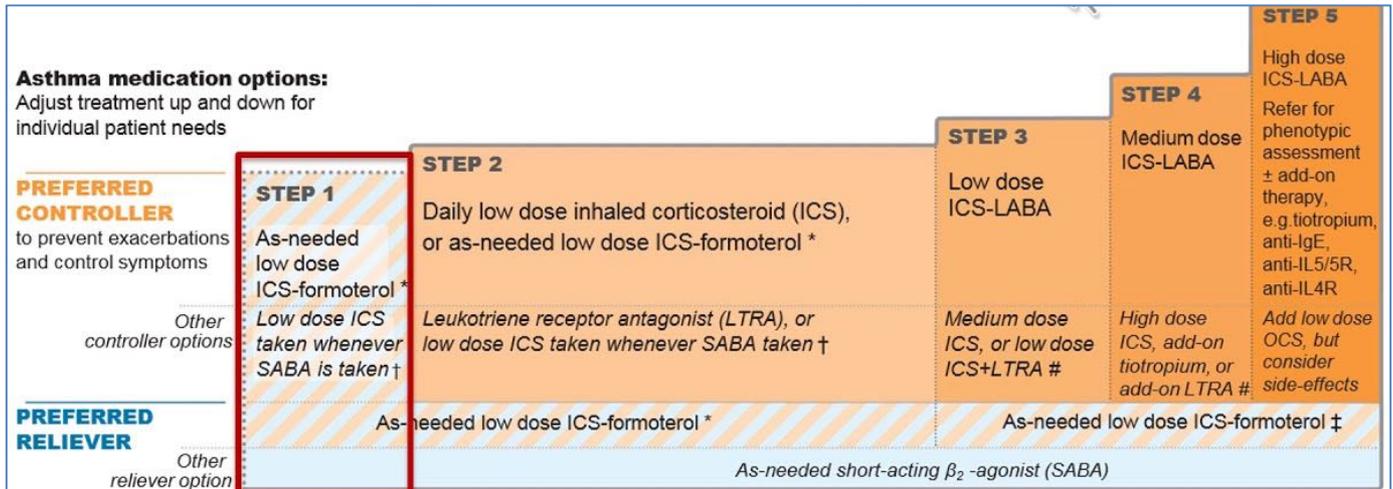
- o **@ The Cellular Level** – Ie: *Target* on the cell & *Effects* on the cell
- o **@ The Physiology Level** – Ie: How the Cellular Effects change the Body’s Physiology



Eg: Amlodipine = Calcium Channel Blocker (@ Cellular Level); Antihypertensive (@ Physiological Level)

Image credit: Rang, Dale, et al. Pharmacology; available from: <https://amzn.to/3Hr51dO>

- **3: Then you can assimilate individual drug names into each Drug Group:**
 - o Eg: **Benzodiazepine Family** includes: Diazepam, Lorazepam, Clonazepam, Midazolam, etc
 - o Eg: **Opioid Family** includes: Codeine, Morphine, Buprenorphine, Oxycodone, Methadone, etc
- **4: Focus on General Therapeutic Principles for treating certain diseases (Rather than specific drugs):**
 - o Eg: Heart Failure is treated with ACE-Inhibitors, Beta-Blockers, and Diuretics
 - o Eg: Asthma is treated with Bronchodilators (Adrenergic & Anti-cholinergic), Corticosteroids (inhaled) & other Novel drugs (eg: Montelukast, etc)



(Example of the general therapeutic algorithm for asthma). Source: <https://ginasthma.org/>

- **Save learning specific Clinical Therapeutic Guidelines for the workplace**
 - o **Why?**
 - Therapeutic Guidelines are specific to your location/workplace/hospital/health-system
 - Therapeutic Guidelines change regularly and without warning
 - Likely, by the time you graduate, the specific drug/dose/guideline will have changed
 - When treating your patient, you'll want to check the most up-to-date guidelines first anyway, regardless of what convention you learned in medical school
 - o **Instead, if you insist on learning the current Therapeutic Guidelines now, then do it more to aid your own understanding of the treatment rationales, than for use in future clinical practice; Eg:**

Mild to moderate community-acquired pneumonia

For children aged 2 weeks to 3 months with mild disease, afebrile, often with conjunctivitis, use

erythromycin 10mg/kg orally, 6-hourly.

For adults and older children (>3 months), use

amoxicillin (child: 15mg/kg up to) 1g orally, 8-hourly

OR

doxycycline (child >8 years: 4mg/kg up to) 200mg orally, initially, then (child >8 years: 2mg/kg up to) 100mg 12-hourly.

OR

roxithromycin 300mg orally, daily (child: 4mg/kg up to 150mg orally, 12-hourly).

If parenteral therapy is required, use

benzylpenicillin (child: 30 to 60mg/kg up to) 1.2g intravenously, 6-hourly

OR

procaine penicillin (child: 50mg/kg up to) 1.5g intramuscularly, daily.

For patients hypersensitive to penicillin, use

cephalothin (child: 25mg/kg up to) 1g intravenously, 6-hourly OR cephazolin (child: 25mg/kg up to) 1g intravenously, 8-hourly.

Once the patient is stable, therapy may be given in an established outpatient intravenous antibiotic therapy program, or orally, see p.144. If response is slow, consider reasons for treatment failure, see Table 8.

Definitions for Keywords:

- **Drug:**
 - A Chemical substance of known structure, other than a nutrient or an essential dietary ingredient, which, when administered to a living organism, produces a biological effect
- **Chemical Name:**
 - Describes the chemical structure (Eg: N-(4-hydroxyphenyl)acetamide = Acetaminophen Aka: Paracetamol)
- **Generic Name:**
 - The generally-agreed upon official name for a drug (Eg: Acetaminophen / Paracetamol)
- **Trade/Brand Name:**
 - The brand name/registered trademark (Eg: Tylenol / Panadol)
- **Pharmacodynamics:**
 - Describes the drug's effect on the body at the receptor level, including efficacy, potency, agonism and antagonism
- **Pharmacokinetics:**
 - The relationship between drug administration, time-course/rate of absorption & distribution, concentration changes in the body, and the drug's removal from the body
- **Selective Toxicity:**
 - A useful feature of Chemotherapy & Antibiotic drugs – I.e: Drugs that are 'Selectively Toxic' to Microbes/Tumours, while having minimal effects on the host
 - Selective Toxicity depends on the ability to exploit Biochemical differences between Microbes/Tumours & the Host
- **Agonist:**
 - A drug capable of binding and activating a receptor, leading to a pharmacological response that may mimic that of a naturally occurring substance. Can be classified as full, partial or inverse
- **Antagonist:**
 - Does not produce a biological response on binding to a receptor but instead blocks or reduces the effect of an agonist. It may be competitive or non-competitive.
- **Allosteric modulator:**
 - A drug that binds to a receptor at a site distinct from the active site. A conformational change is induced in the receptor, altering the affinity of the receptor for the endogenous ligand.
- **Desensitization**
 - A loss of responsiveness which may be due to the continued presence of an agonist at a receptor or repeated presentation of the agonist
- **Efficacy**
 - Used to describe agonist responses in relation to receptor occupation. High efficacy agonists can produce a maximal response whilst occupying a relatively low proportion of receptors.
- **Half-life ($t_{1/2}$)**
 - The metabolic half-life of a drug in vivo is the time taken for its concentration in plasma to decline to half its original level
 - Clearance and distribution of a drug from the plasma are important parameters for half-life determination
- **Potency:**
 - Measure of the effective concentration of a drug. It is a vague term and it is advisable to further categorise the measurement
- **Occupancy**
 - The proportion of receptors to which a drug is bound

Quality Use of Medicines – Ie: Choosing Between Drug Therapies:

- **Beneficial Effects:**

- Where does the drug sit on the wide spectrum of benefits?:

← Low-level relief, but ↑Quality of Life → Prevent/Control Serious Symptoms → Prevent Death →

- **Harmful Effects:**

- Where does the drug sit on the wide spectrum of drawbacks?:

← Low-level harm, but tolerable → Serious/Severe Effects → Potentially Fatal→

- **Cost-Benefit Analysis – Important Considerations for Therapeutics:**

- Risk of Treatment Vs Risks associated with Non-Treatment
- Financial cost of treatment vs Opportunity cost of that money elsewhere (eg: Public health)
- Personal toll of side effects Vs Personal benefit of treatment

- **Reducing Risk – How?:**

- Get a better Understanding of the Disease:
 - Gives insight into potential Drug Targets
 - Helps explain to patient Why Drug is Useful/Necessary → ↑Patient Compliance
 - Understand How the Drugs Work (Major Effects/Side-Effects)
- Improve the Pharmacokinetics – Eg: Deliver drug Specifically to the Site of Action
- Improve the Pharmacodynamics – Eg: Use drugs that are more Selective (to receptor subtypes)
- Ensure Informed, Careful & Responsible Prescription

- **Evidence-Based Medicine:**

- Ie: Not Playing the Odds (Eg: Test to eliminate all other possibilities)
- All western medicines undergo multiple phases of drug testing prior to mass adoption
- “The Integration of Clinical Expertise with the Best Evidence from Systematic Research”

4 Qualities of A Good Prescription:

- **1: Judicious use of Medicines:**

- Consideration of non-medical alternatives (Eg: Exercise to ↓BP rather than Anti-hypertensives)

- **2: Appropriate Use:**

- Is the medicine chosen *The Most* Appropriate, given all clinical factors? (Eg: A K⁺ wasting diuretic in someone with an existing arrhythmia)

- **3: Safe Use:**

- Minimise Misuse – Ie: Make sure the patient knows how/when to use the drug (Eg: Diabetic taking too much insulin → DKA)

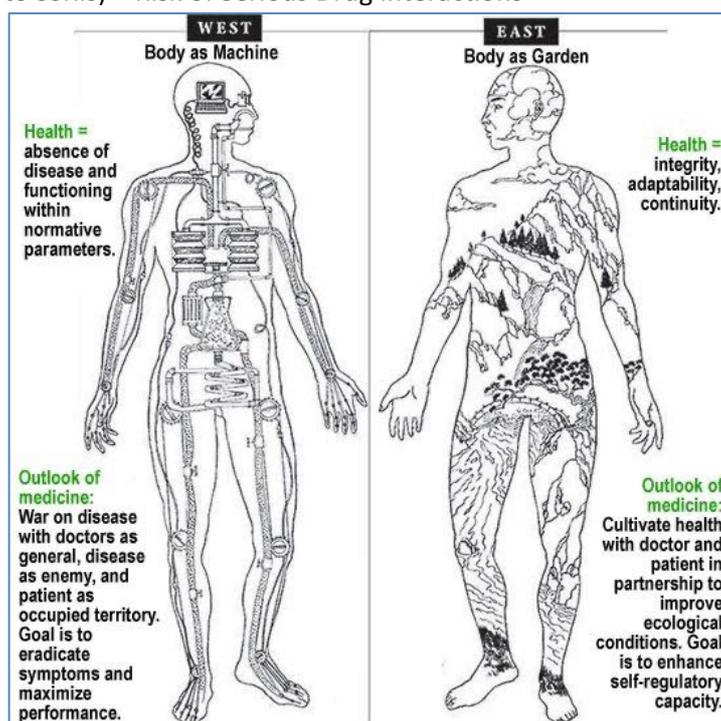
- **4: Efficacious Use:**

- Drug MUST deliver beneficial outcomes that are GREATER than adverse outcomes



“Traditional” Medicine Vs Western Medicine:

- **Generally, Western Medicine is objectively more effective because:**
 - Purity of the active compound
 - Accurate Dosage & Concentration
 - Knowledge of Toxicity
 - **Note: Many existing drugs are purified from natural sources:**
 - **Atropine:**
 - Source – ‘Deadly Nightshade’ plant;
 - Competitive Antagonist for the Muscarinic ACh-Receptor (Ie: An Anticholinergic);
 - Prevents the Inhibitory action of the Vagus Nerve on the Heart → ↑Firing of SA-Node & ↑AV-Node Conduction
 - **Digitalis:**
 - Source – ‘Foxglove’ Plant;
 - Decreases Na/K-ATPase function in cardiac myocytes → Na⁺ Accumulation → ↓Rate of Na/Ca-Exchanger → ↑Intracellular Ca⁺ → ↑Refractory Period → ↓HR
 - Useful in treating Atrial Fibrillation & Sometimes Heart Failure
 - **Botox (Botulinum Toxin):**
 - Source – Bacterium *Clostridium Botulinum*
 - Blocks ACh-Release from Pre-Synaptic Neurons
 - Used to treat muscle spasms
 - **Warfarin:**
 - Source – Woodruff plant
 - Anticoagulant → Used as Primary & Secondary Prophylaxis for Thrombosis
 - **Penicillin:**
 - Source – Penicillium Fungi
 - Inhibits formation of Peptidoglycan Cross-Links in bacteria cell wall → Weakens Bacterial Wall → Kills Bacteria → Antibiotic
- **Why some people prefer Traditional Medicine:**
 - Some people believe that “Natural” = “Safer” = Good for you ... (Although not necessarily the case; all of the most potent toxins and venoms are ‘natural’)
 - May be ‘cheaper’ than prescription medicines ... (Although not necessarily the case when taking into account the **Cost:Efficacy ratio**)
 - May be easier to purchase OTC (Over the counter)
 - **Common Eg: St John’s Wort** – a crude OTC ‘antidepressant’ (Weak NA/5HT Uptake Inhibitor – similar mechanism to SSRIs) – Risk of Serious Drug Interactions



Drug Administration

- **Goals:**
 - **1: Get it into the Circulation** – So it can access its target tissue
 - **2: Make sure it is a “Free-Drug” by the time it reaches its target** – So it can exert its effect
- **Routes of Administration:**
 - There are numerous routes of Administration (eg: IV/Oral/Suppository/Mucosal-Absorption)
 - Choice depends on drug properties, desired onset, duration of action, pH of entry environment, & bioactivation requirements (eg: Prodrugs)

Table 1. Routes of Drug Administration

Route	Advantage	Disadvantage
Oral (PO)	Convenient, easy to administer Large surface area for absorption Inexpensive relative to parenteral administration	Incomplete absorption Hepatic first-pass effect Potential GI irritation
Buccal/Sublingual (SL)	Rapid onset of action No hepatic first-pass effect	Must be lipid-soluble, non-irritating Short duration of action
Rectal (PR)	Almost no hepatic first-pass effect Use when NPO, vomiting, or unconscious	Inconvenient, irritation at site of application Erratic absorption
Intravenous (IV)	No hepatic first-pass effect Slow infusion or rapid onset of action Easy to titrate dose	Hard to remove once administered Risk of infection, bleeding, vascular injury extravasation Expensive
Intramuscular (IM)	Depot storage if oil-based = slow release of drug Aqueous solution = rapid onset of action	Pain/hematoma at site of injection
Subcutaneous (SC)	Non-irritating drugs, small volumes Constant, even absorption Alternative to IV	Pain at site of injection Smaller volumes than IM May have tissue damage from multiple injections
Intrathecal	Direct into CSF Bypass BBB and blood-CSF barrier	Risk of infection
Inhalation	Immediate action in lungs Rapid delivery to blood No hepatic first-pass effect	Must be gas, vapour, or aerosol
Topical	Easy to administer Localized (limited systemic absorption)	Effects are mainly limited to site of application
Transdermal	Drug absorption through intact skin No hepatic first-pass effect	Irritation at site of application Delayed onset of action Hydrophilic drugs not easily absorbed
Others (intraperitoneal, intra-articular)	Local effect	Risk of infection

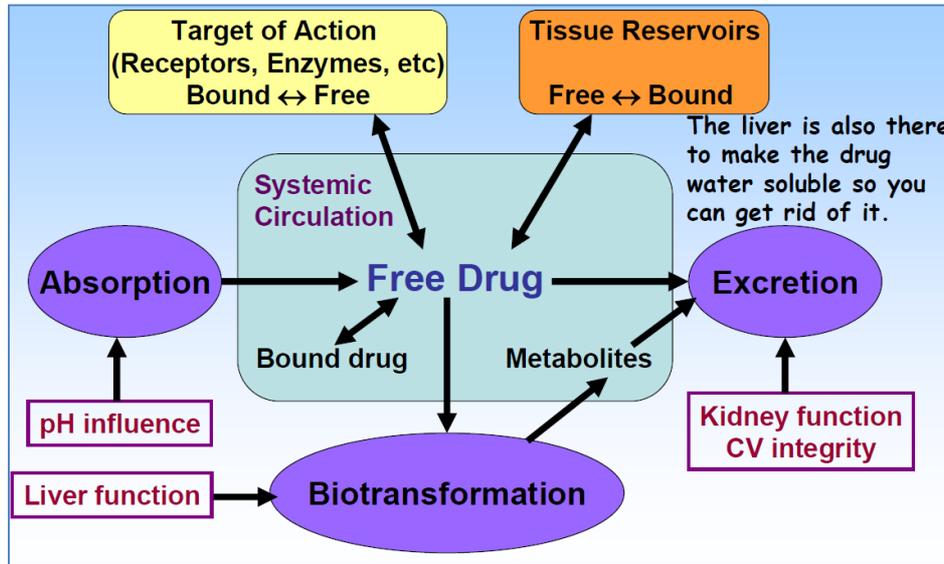
- **Tissue Reservoirs:**
 - After absorption, some of the Free-Drug is lost to Tissue Reservoirs/Blood Proteins
 - Often bound drugs are released from tissues/proteins as the Concentration Of Free Drug dwindles (Bound Drug ↔ Free Drug → Used/Metabolised)
- **Target of Action:**
 - Where are the target Receptors/Enzymes/Cells/Tissues?
 - Will Free-Drug in the blood be able to access its target?

Biotransformation:

- The Liver plays an important role in:
 - **Bio-Activation:** Drug Precursor → Active Drug Metabolites
 - **Bio-Inactivation:** Active Drug → Water-Soluble, Inactive Drug Metabolites
 - **Detox:** Toxic Substance → Water-Soluble, Non-toxic Metabolites
 - **Conjugating:** Ie: Making H₂O-Soluble → Aids Renal Excretion
- **Q:** Does the drug pass through the liver before its target? (Eg: Yes- if oral; No- if IV)

Excretion:

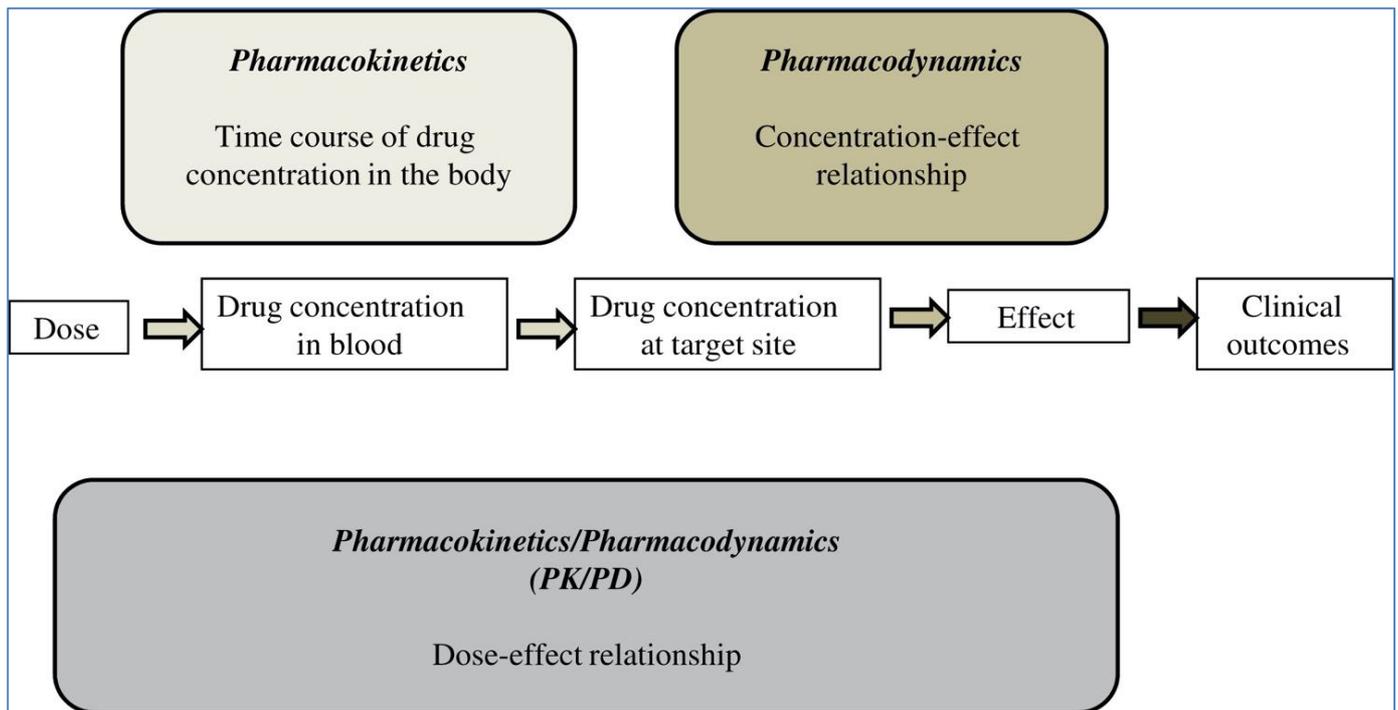
- Typically via the Kidney
- Substance must be H₂O-Soluble



Pharmacokinetics Vs Pharmacodynamics:

The TWO Influences on Drug's Ability to Interact with its Target:

- **1: Pharmacokinetics:** Access of the drug to its target, & subsequent **Elimination** from the body
- **2: Pharmacodynamics:** Ability of the drug to **Bind & Exert an Effect** on the Target



PHARMACOKINETICS:

PHARMACOKINETICS

What is Pharmacokinetics? – “What the Body Does to the Drug”:

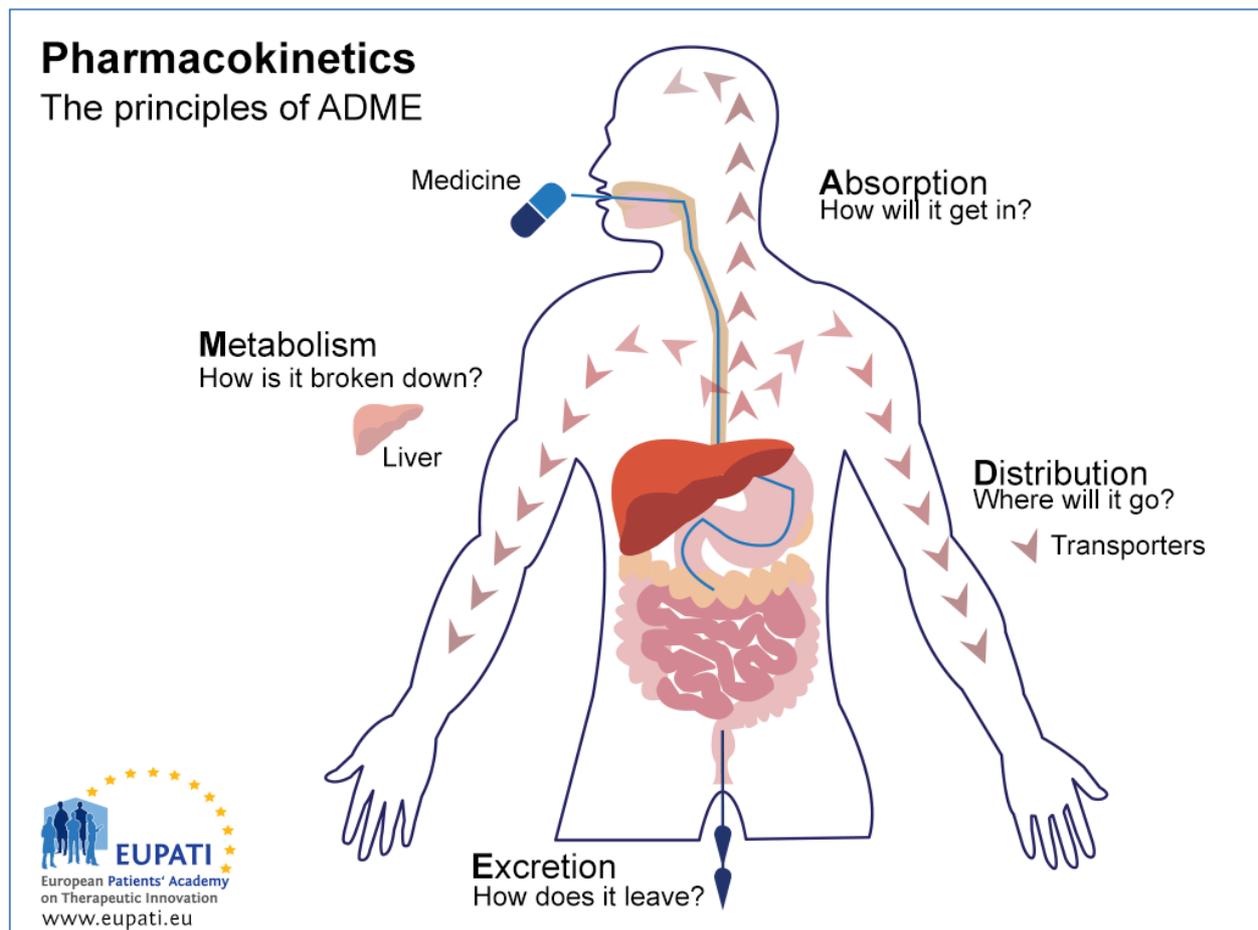
- The relationship between drug administration, time-course/rate of absorption & distribution, concentration changes in the body, and the drug's removal from the body

What Determines a Drug's Pharmacokinetics?:

- **Characteristics of Biological Membranes (across which ALL drugs must pass):**
 - o Bi-phospholipid layer
 - o Hydrophilic Exterior
 - o Lipophilic Interior
 - o Selectively Permeable – allows passage of some, but not all drugs
- **Properties of the Drug (Physical/Chemical):**
 - o *** Lipid Solubility (High Solubility = High Permeability)
 - o Degree of Ionisation (Ionised/Charged molecules = Impermeable)
 - Determined by pKa (The pH where the drug is 50% Ionised)
 - o Molecular Size (Smaller = More Permeable)
- **Concentration Gradient (Simple Diffusion):**
 - o Most drugs cross membranes via Simple Diffusion
 - o 'Diffusion-Controlled Distribution' = Drugs will move down Concentration Gradients until Concentrations of the drugs are equal in all parts of the body

Why Pharmacokinetics is Important:

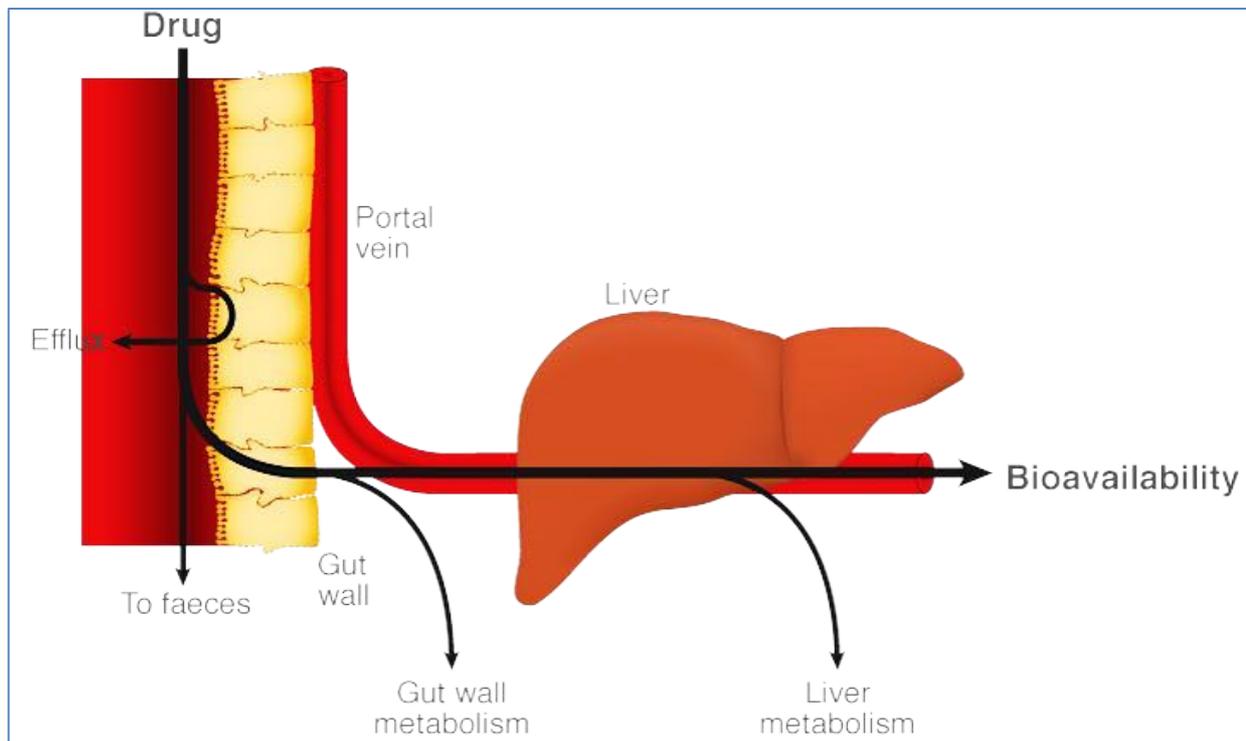
- A Drug must reach its site of action to exert its pharmacological effect
- **4 Things that determine the Concentration Of the drug at its site of action:**
 - o 1: Absorption
 - o 2: Distribution
 - o 3: Metabolism
 - o 4: Elimination



Source: <https://toolbox.eupati.eu/glossary/pharmacokinetics/>

1: Absorption:

- **Definition:**
 - The movement of the drug from site of administration into the plasma
 - The *Rate of Absorption* determines the *Intensity* and *Duration* of drug action
 - Eg: IV drugs bypass the problem of absorption because they're instantly available in plasma
- **Mechanisms of Drug Absorption:**
 - Most drugs are absorbed by Simple Diffusion → Therefore the Rate depends on:
 - Solubility (Influenced by pH & drug's pKa)
 - Tissue Permeability
 - Surface Area
 - Blood Supply
 - Other mechanisms include **active transport, facilitated diffusion, etc**
- **(F) - Bioavailability:**
 - The amount of active drug that reaches the systemic circulation
 - Is expressed as a percentage of the dose (Eg: IV dose has 100% bioavailability)
 - **Low 'F'-values** for Bioavailability occur with:
 - 1: Poorly Absorbed drugs
 - 2: Drugs that undergo extensive '*First Pass Metabolism*' in the liver
 - **High 'F'-Values** for Bioavailability occur with IV dosing
- **The 'First-Pass' Effect:**
 - Where a drug is metabolised by the liver before it reaches systemic circulation
 - Results in reduced Bioavailability (F)
 - Eg: An Orally-administered drug is:
 - 1: Absorbed in the GIT
 - 2: Transported via the Portal Vein → Liver
 - 3: Liver metabolises drug (first pass metabolism)
 - 4: Then releases metabolites into the systemic circulation
 - Eg: Lignocaine – local anaesthetic & treat arrhythmias
 - If administered Subcutaneously, it is instantly at the site of action
 - If orally administered, all is absorbed, but none is available because it passes through the liver before reaching the site of action



<https://www.cyprotex.com/useruploads/ADME-Guide/Fig3-1-Metabolism-Schematic.png>

2: Distribution:

- **Definition:**
 - Movement of drugs between different body compartments and to the site of action
 - (I.e: Once the drug is in the circulation, How Well & How Much gets to the site of action)
- **Major Body Fluid Compartments:**
 - Plasma
 - Interstitial Fluid
 - Intracellular Fluid
 - Transcellular Fluid (eg: CSF, Peritoneal Fluid, Pleural Fluid)
 - Fat
 - Brain
- **Depends on Drug's Ability to Cross Membranes:**
 - **Lipid Solubility:**
 - Lipophilic drugs readily cross membranes
 - Hydrophilic drugs don't cross membranes
 - **Blood pH & Drug pKa:**
 - Charged drugs don't cross membranes
 - **Protein Binding:**
 - Limits amount of drug that is free to cross membranes
 - Note: Generally, only unbound drug can be distributed across membranes
 - Most acidic drugs (Including All antibiotics) bind to albumin
 - **Regional Blood Flow:**
 - Determines the amount of drug that is 'available' to that tissue in a given time period
- **V_d - (Volume of Distribution):**
 - The volume that an Amount/dose (A) of a drug *Appears* to be dispersed in, given the *Blood-Concentration* (C)
$$V_d = A/C$$
 - This concept exists due to the fact that certain drugs disperse into different tissues more readily than other tissues
 - Eg: For a drug confined to plasma, V_d = Blood Volume
 - Eg: For a drug distributed equally through the body, V_d = Total Body Volume
 - Eg: For a drug concentrated in the tissues, V_d = More than Total Body Volume
 - It is useful for calculating initial loading dose (D_L) to achieve a target (Steady-state) concentration (C_{ss}):
$$D_L = V_d \times C_{ss}$$
- **Multicompartment model:**
 - Drug can move from Blood → Other Tissues (eg: Nitrogen saturation in scuba divers doesn't distribute evenly between bodily tissues – eg: Prefers adipose tissue) – This is the same for many drugs
 - Drugs can move from Other Tissues → Blood (As blood Concentration decreases)
 - **Note:** Redistribution of an administered drug out of the blood to another compartment reduces blood levels – Hence the need for the **V_d - (Volume of Distribution)**
- **Plasma Protein Binding:**
 - Drug molecules in the blood exist as EITHER:
 - **'Bound' Drugs:** Bound to plasma proteins (eg: Albumin & α₁-acid Glycoprotein)
 - **or 'Unbound/Free' Drugs:** Readily leave the circulation to distribute into tissues
- **Depots:**
 - Certain body compartments with higher drug affinity than other compartments may act as a 'drug depot', which will effectively store the drug and release it slowly over a longer period of time
 - Eg: Fat is a depot for lipid soluble drugs (eg: Diazepam)
- **Barriers:**
 - Certain specialised body structures limit/prevent diffusion of drugs
 - Eg: Placenta, blood brain barrier

3: Metabolism / 'Biotransformation':

- **Definition:**
 - Chemical transformation of a drug within the body as a result of 'Biotransformation'
- **Sites of Biotransformation:**
 - Mainly Liver
 - GI Tract
 - Lung
 - Plasma
 - Kidney
- **Biotransformation may result in:**
 - **Pro-Drug Activation:**
 - Pro-drug → Active (for some drugs the active form of the drug is unsuitable for absorption/distribution, and hence has to be administered in an inactive form that gets metabolised by the liver into an active form)
 - **Drug may be Changed to another Active Metabolite**
 - Eg: Diazepam to Oxazepam
 - Eg: Codeine to Norcodeine & Morphine
 - **Drug may be Changed to a Toxic Metabolite**
 - Eg: Meperidine to Normeperidine
 - **Drug may be Inactivated:**
 - Active Drug → Inactive form
- **Factors Influencing Biotransformation:**
 - **Interactions Between Drugs:**
 - Drug-induced alterations of liver-enzymes: (includes herbal medicines & natural remedies)
 - Competition for metabolic pathways
 - **Enzyme Inhibition:**
 - Enzyme inhibition may lead to increased concentration/bioavailability of another drug
 - Eg: Erythromycin (a CYP3A4 inhibitor) can increase risk of simvastatin toxicity (which is metabolised by CYP3A4)
 - **Enzyme Induction:**
 - Some drugs can enhance gene transcription, increasing the activity of a metabolizing enzyme
 - Eg: Phenobarbital can induce the metabolism of oral contraceptives via the CYP system
 - **Genetics:**
 - Some people vary in their expression of the Cytochrome-P450-Enzymes
 - May alter the effectiveness of a drug (may have no effect/may overdose)
 - Eg: CYP2D6 is absent in 7% of Caucasians → no response
 - CYP2D6 is hyperactive in 30% of East Africans → same dose = toxic
 - **Disease Status:**
 - Compromised organs:
 - Liver
 - Kidney
 - Heart
 - Vasculature
 - Viral infections can alter enzyme activity
 - Bacterial infections can produce toxins → alter drug activity/metabolism
 - **Hormone Status:**
 - Oestrogen can affect metabolic enzyme activity
 - **Age/Gender:**
 - Enzyme expression & activity changes with age
 - Gender differences related to hormonal status
 - **Diet:**
 - Enzyme activity is affected by certain foods, vitamins & alcohol

- **Phase I Reactions:**

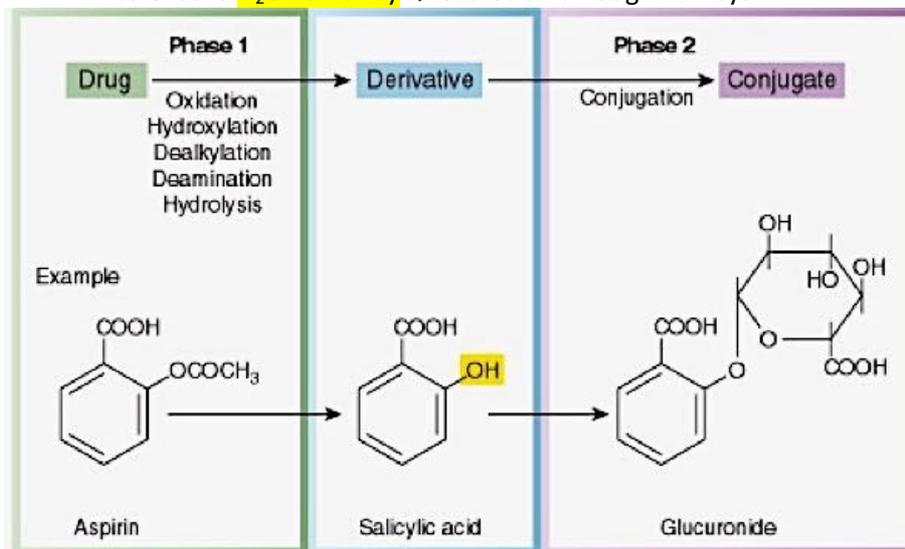
- **Functional Group** of drug is *Exposed or Added to*
 - New functional groups
 - Interchange existing functional groups
 - Expose existing functional groups
- **Types of Phase I Reactions:**

- **oxidation** (hydroxylation) = create new group
» $RH \rightarrow ROH$
- **reduction** = interconvert group
» $C=O \rightarrow CH-OH$
- **hydrolyses** = expose group
» $R-CO_2CH_3 \rightarrow RCOOH + CH_3OH$

- **Note: Oxidation Reactions** are the **most common**
- **Note: Oxidation Enzymes:** part of the **Cytochrome P450 Mono-Oxygenase** family:
 - **Other Roles of Cytochrome P450 Mono-Oxygenases:**
 - **Synthesis:**
 - Conversion of cholesterol \rightarrow bile acid
 - Hydroxylation of steroids & Vit-D
 - Conversion of Alkanes \rightarrow Fatty Acids
 - Conversion of FA's \rightarrow eicosanoids
 - **Catabolism:**
 - -of Fatty Acids
 - -of Steroids
 - -of eicosanoids

- **Phase II Reactions ('Conjugation')**

- **Drug/ Drug Metabolite** is conjugated
 - le: It is **merged with an endogenous polar compound**
 - Aim: to ensure **H₂O solubility** \rightarrow excretion through kidneys



- **Types of Phase II Reactions:**
 - Glucuronide Conjugation – Most Common
 - Glutathione Conjugation
 - Amino Acid Conjugation
 - Sulphate Formation
 - Acetylation
 - Methylation

4: Elimination:

- **Definition:**
 - o The removal of the drug from the body
- **Multiple Possible Routes of Elimination:**
 - o **Urine (Most drugs)** – Must be naturally Water Soluble or Conjugated
 - Glomerular filtration (Passive excretion of Free Drugs only)
 - Tubular Secretion (Active process of Protein-Bound & Free Drugs)
 - o Lungs (Anaesthetic agents / Alcohol)
 - o Bile (Antibiotics)
 - o Faeces
 - o Saliva
 - o Breast Milk
- **Renal Excretion depends on:**
 - o GFR
 - o Water Solubility
 - o Tubular Secretion
 - o Reabsorption
- **$T_{1/2}$ – (Half Life):**
 - o An exponential process
 - o The time taken for the drug concentration in the blood to decrease by 50%
 - o Can be Due to Either:
 - **Redistribution $T_{1/2}$** – decrease in drug concentration due to drug redistribution to the tissues
 - **Or Metabolism $T_{1/2}$** – decrease in blood concentration due to drug elimination
 - o For a given dose rate, 5xHalf-lives are required for 97% completion of steady state
 - o Similarly, it takes 5xHalf-lives to clear 97% of drug from the body
- **Steady State:**
 - o Where drug concentration remains constant
 - o Amount of drug entering the system = Amount of drug being eliminated
- **Cl - (Clearance):**
 - o The volume of blood *Completely* cleared of drug per unit time (Measured in L/min)
 - o Can be calculated for specific organs or for the whole body
- **1st Order & Zero-Order Elimination Kinetics:**
 - o Rate of elimination is usually proportional to the amount of drug:
 - Ie: A **1st-Order Process** (Constant % is eliminated per unit time)
 - (Exponential wash-out curve)
 - o However, when the Drug-Concentration is high (overdose), metabolic pathways become saturated:
 - Ie: A **Zero-Order Process** (Drug is slowly eliminated at a Fixed Rate)
 - (Linear)

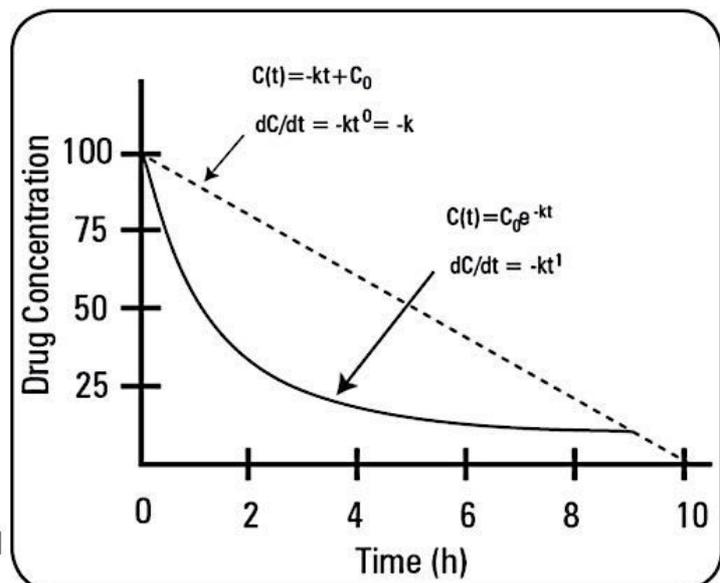
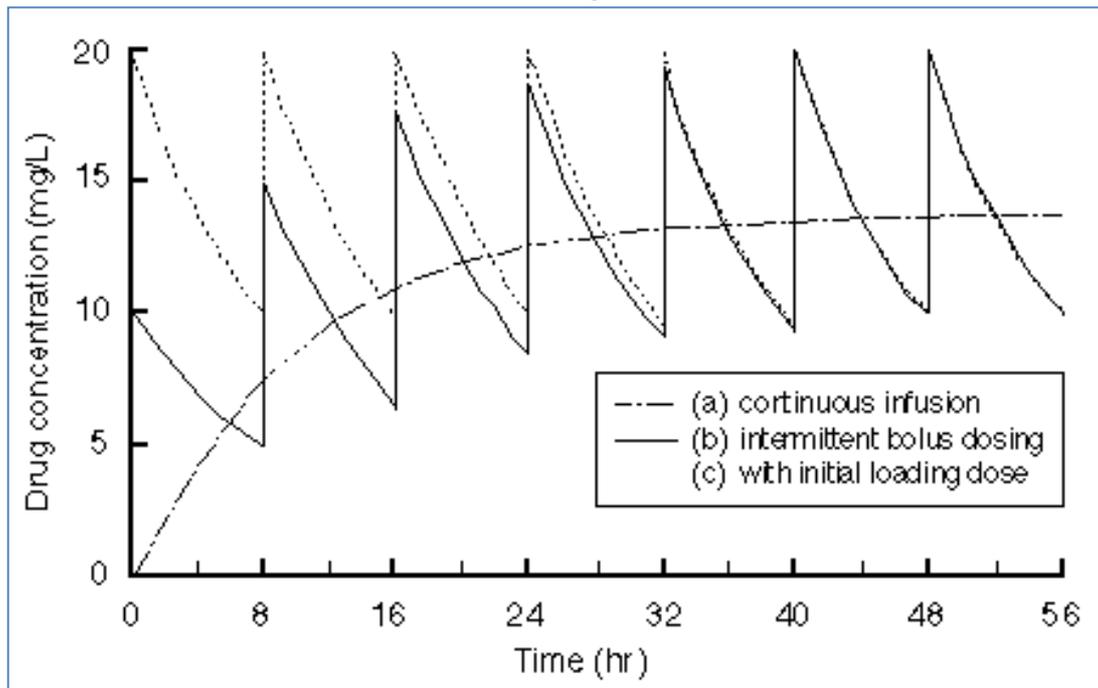


Figure 4. First and zero order kinetics

In first order kinetics (solid line), a constant fraction of the drug is eliminated per unit time; in zero order kinetics (dashed line), a constant amount of the drug is eliminated per unit time

Practical Applications of Pharmacokinetics:

- **Loading Dose:**
 - o A big 'Bolus' dose given initially to *Quickly* get Plasma Concentration of Drug to a Therapeutic Level
 - o This dose is based on the Volume of Distribution (V_d)
- **Maintenance Dose:**
 - o Doses given which aim to maintain a Therapeutic Concentration of the Drug
 - o This dose is based on Clearance Rate and Drug Half-Lives



- **Dosage Schedules in the Sick, Elderly, Paediatrics**
- **Renal Function is important in drug dosing**
- **Altered Physiological States (Eg: Lean/Ideal/Fat) affect Pharmacokinetics**

Applying Pharmacokinetics to Clinical Cases:

Station A – Renal Function and its importance in drug dosing

A patient has a creatinine level of 160 $\mu\text{mol/L}$. Yesterday the level was 120 $\mu\text{mol/L}$ and the day before it was 80 $\mu\text{mol/L}$

(Normal Creatinine = 70-120 $\mu\text{mol/L}$)

(Normal GFR = 125mL/min)

1. **What additional information is needed before an assessment of the Glomerular Filtration rate (GFR) can be made?**
 - a. Age
 - b. Weight
 - c. Gender
2. **Estimate this patient's GFR using the additional information you requested above**
 - a. Using Cockcroft-Gault Equation, you determine GFR=48mL/min
3. **How would this deteriorating GFR influence the clearance of Vancomycin from the body?**
 - a. 90% of Vancomycin is excreted unchanged in the urine – Hence, a \downarrow GFR \rightarrow \uparrow Longevity of Drug
 - b. Note: Vancomycin is given IV (Can't be absorbed orally)
4. **How would this reduced clearance influence Vancomycin dosing?**
 - a. Same Dose, Less Often
 - b. Or, Smaller Dose @ Same Frequency
5. **What could be causing the deterioration in the patient's renal function over the past few days?**
 - a. Sepsis (Most likely) \rightarrow \downarrow Renal Function
 - b. Note: Vancomycin can be Nephrotoxic

Station B – Pharmacokinetic models

You are working as an intern in the Emergency Department when a patient is brought in after taking an over-dose of Paracetamol (forty X 500 mg tablets). The patient states that she took the tablets 8 hours ago and now does not want to die. On arrival in the ED the serum paracetamol level was found to be 163 mg/L. Drug screen also revealed a blood alcohol level of 27 mmol/L.

Data:

- Weight = 63kg
- $V_d = 1 \text{ L/kg}$
- Bioavailability 90%
- Elimination half-life = 2 hours
- $CL = 5 \text{ ml/min/kg}$
- Metabolism:
 - o 80% to glucuronide
 - o 10% via Cytochrome P450 to highly reactive intermediary that is inactivated by conjugation to glutathione

1. How much paracetamol did she ingest?

- a. $40 \times 500 \text{ mg} = 20000 \text{ mg}$

2. What is the bioavailability of the paracetamol?

- a. $80\% \times 20000 \text{ mg} = 18000 \text{ mg}$

3. What is her Volume of Distribution?

- a. $1 \text{ L} \times 63 \text{ kg} = 63 \text{ L}$

4. What would have been her initial serum concentration?

- a. $18000 \text{ mg} \div 63 \text{ L} = 285 \text{ mg/L}$
b. Note: $>350 \text{ mg/L}$ is lethal

5. How long will it theoretically take to clear the paracetamol?

- a. 5 Half Lives = 97% cleared
b. Therefore: $5 \times 2 \text{ hrs} = 10 \text{ hrs}$

6. What effect does the highly reactive intermediary have on the body?

- a. NAPQI (A highly-reactive free radical) is produced by P450 Enzymes of the Phase-1 Reactions once the Normal Phase-2 (Conjugation) Reactions are saturated

7. Given that the body's stores of glutathione are minimal, how can continued metabolism of the highly reactive intermediary be assured?

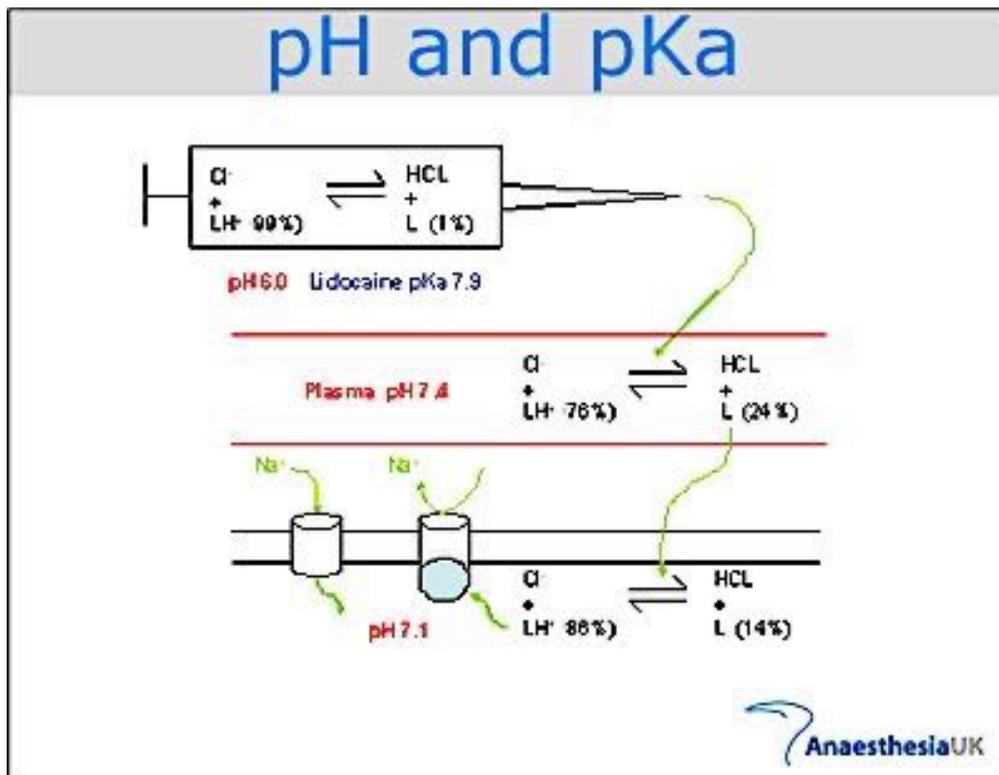
- a. Glutathione is required by Phase-2 enzymes. Hence, once it is used up, the Phase-1 reactions take over, and produce NAPQI as a by-product
b. Hence, by supplementing Glutathione with Acetylcysteine (a Glutathione precursor), you can prevent the body resorting to Phase-1 Reactions

Station C – Pharmacokinetics in altered physiological states

Lignocaine is the most frequently utilised local anaesthetic in the western world. It is frequently used to 'numb' the skin prior to the suturing of a minor cut. It is also often used to provide local anaesthesia to an area to assist with minor surgery such as the removal of skin lesions, tattoo's etc.

Lignocaine is an amide local anaesthetic and is a poorly soluble weak base with a $pK_a = 7.9$. It comes in a variety of strengths and compositions, the most frequently used being 1% plain Lignocaine vials for injection. The lignocaine is provided as the hydrochloride salt (Lignocaine HCl) which renders the compound highly water soluble, with the pH of 1% plain Lignocaine HCl being about 4.0

1. Detail the kinetics involved in a dose of lignocaine HCl spreading from the point of injection to its site of action?
 - a. See Diagram
2. What clinical factors can modify these kinetics?
 - a. Doesn't work in infected tissues because they are typically acidic
 - b. Adrenaline \rightarrow Vasoconstriction \rightarrow \downarrow Bleeding & Prolonged Action
3. With the above knowledge, explain the following clinical scenario:
 - a. A young patient presents with an abscess on the forearm. It is a raised inflammation of some 1.5cm diameter. You decide to lance this in your rooms, and prior to this you infiltrate around the abscess with 1% plain lignocaine. You wait 5 minutes and when you insert the scalpel, the patient jumps and complains bitterly of pain. Why?
 - i. Because Abscesses are due to infection, and Local Anaesthetic doesn't work in areas of infection due to the Acidic Environment



PHARMACODYNAMICS:

PHARMACODYNAMICS:

What is Pharmacodynamics? – “What the drug does to the body”:

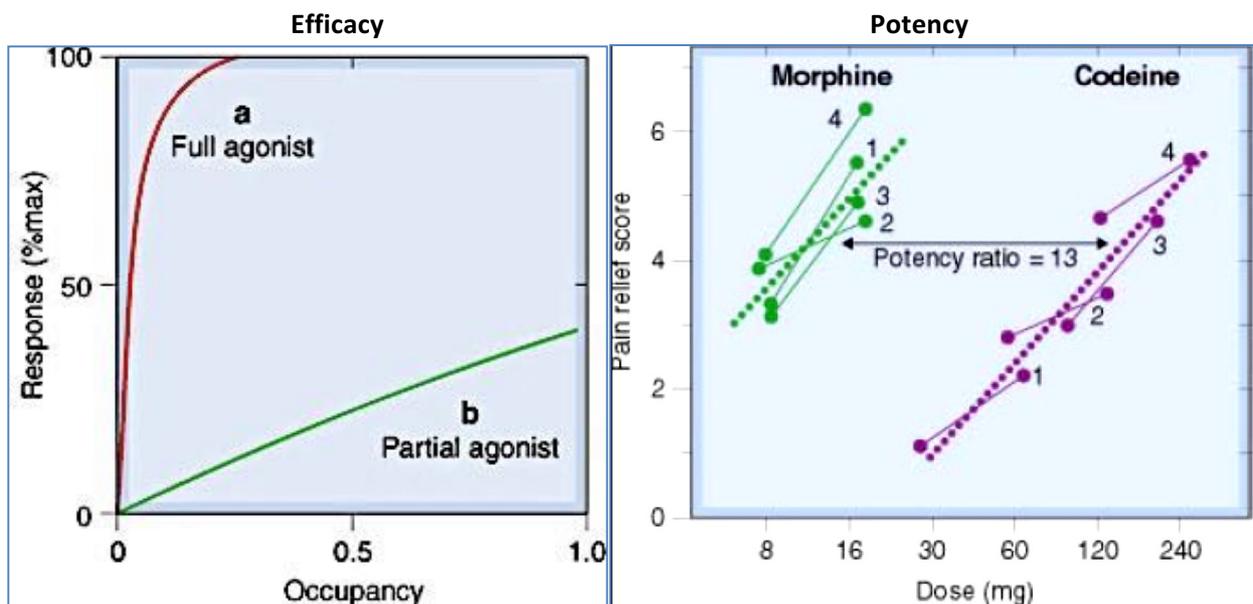
- Study of Drug Interactions with Targets within the Body
- “Interactions (dynamics) between Drugs (Pharmaco) & their Targets”

Principals Behind Pharmaceutical Treatments:

1. **Chemical-Receptor Signaling Controls body functioning;** Hence, Cell Action doesn't change if Message Isn't Received
2. **In Disease, Chemical Signalling is altered, affecting body functioning;** Hence, by compensating for the Altered Signal, we can treat the disease

Things that Influence the Drug:Target Interaction:

- **Affinity:**
 - o The tendency of the drug to **Bind to** the target receptor (High/Low)
 - o Does it require Co-Factors / Mediators?
- **Efficacy:**
 - o The tendency for the drug (once bound), to **Activate** the target receptor (Fully/Partially)
 - o Ie: **Relationship between Occupation of the Receptor & Effect Elicited (See Dose-Response curve)**
 - **Partial Agonists:**
 - Drugs with intermediate levels of Efficacy
 - Ie: Even if 100% of receptors were occupied, the tissue-response is sub-maximal
 - **Full Agonists:**
 - Drugs with high Efficacy
 - Ie: Elicit a Maximal Tissue Response at or before 100% occupancy
 - o Note: Antagonists have Zero Efficacy
- **Potency:**
 - o Drugs with High Potency, generally have:
 - **A high Affinity** → Occupy a significant proportion of receptors even at low concentrations
 - **AND A high Efficacy** → Elicit a stronger response per receptor occupied
 - o The lower the potency, the higher the dose needed
 - o If Highly Potent – you only need a small amount of the drug for maximal effect
 - o Eg: Morphine Vs Codeine – For a given response, less Morphine is required than Codeine; Hence Morphine is more potent



4 Most Common Drug Targets:

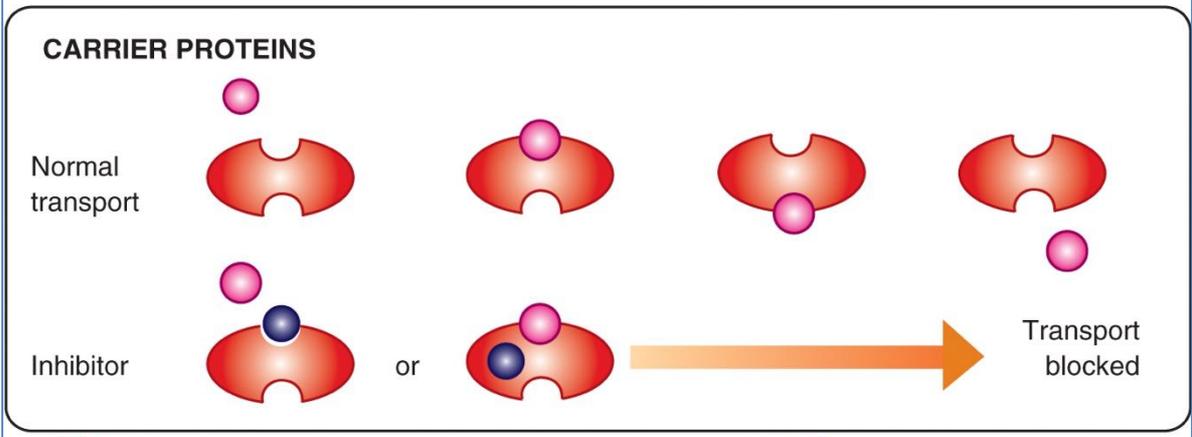
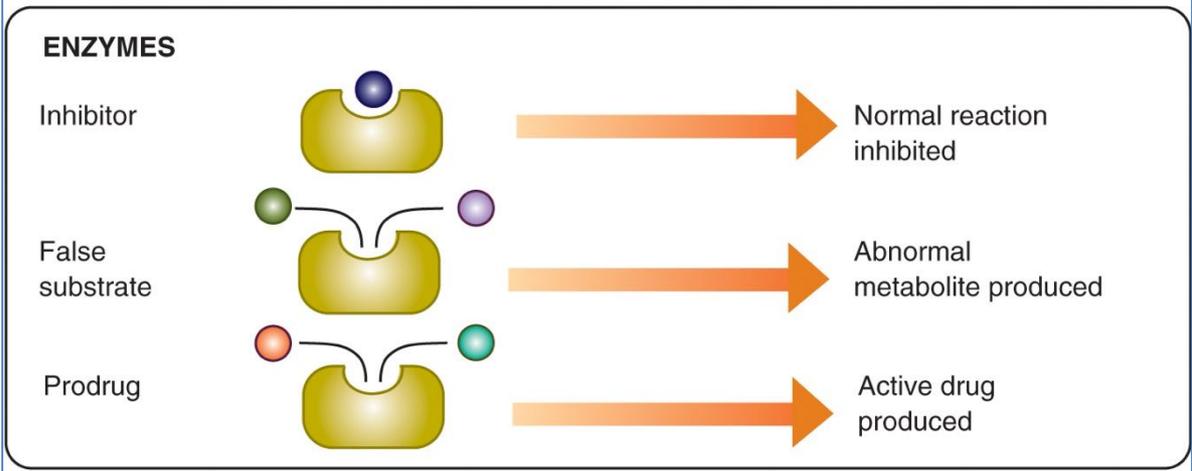
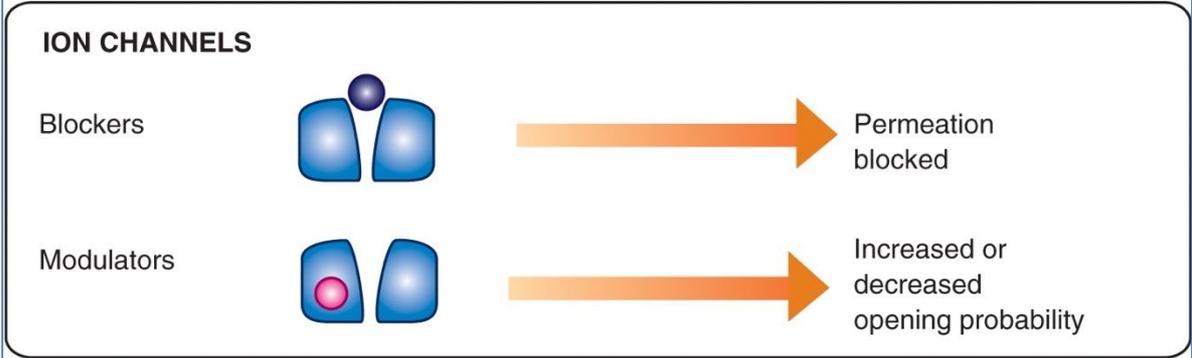
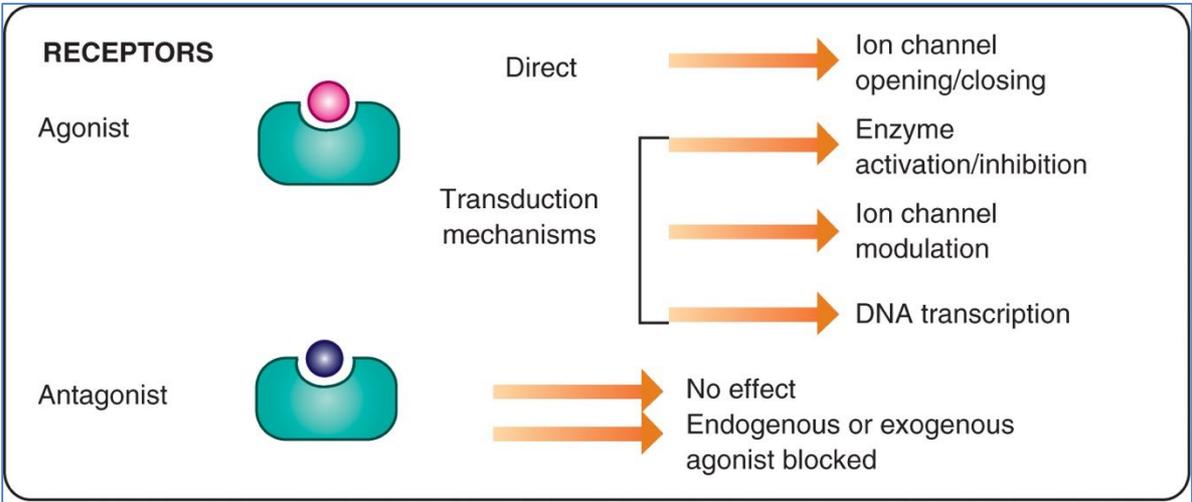
- **1: **Receptors:**
 - “Protein molecules whose function is to recognise & respond to **Soluble** physiological mediators (hormones/NTs/cytokines/etc)” Note: Other Macromolecules that drugs interact with are known as Drug Targets
 - **Drugs act as either:**
 - **Agonists** → Range of Effects
 - **Antagonists** → No Effect
 - Eg: β -Adrenergic Receptors in the Heart → \uparrow HR & Contractility

- **2: Ligand-Gated Ion Channels:**
 - Ion Channels with a ligand-receptor which, when activated, causes the channel to open
 - **Drugs act as either:**
 - **Antagonists** → Channel remains Closed
 - **Modulators** → Increased/Decreased opening Probability
 - **Indirect Agonists** → in the case of G-Protein-Linked Ion Channels
 - Eg: Local Anaesthetics Block Na^+ Channels in Nerve Cells → Inhibit Na^+ Influx → Inhibit Action Potential
 - **Side Note: Ion-Channelopathies:**
 - Abnormalities in various Ion-Channels contribute to some Cardiac & Neurological Diseases
 - Eg: Mutated Cardiac K^+ -Channel → Long QT-Syndrome
 - Eg: Other Mutated K^+ -Channels → Familial Deafness; & Epilepsy

- **3: Enzyme Targets:**
 - Endogenous bodily enzymes are often targeted by drugs for multiple reasons
 - **Drugs act as either:**
 - **Inhibitors** → Normal reaction is Inhibited
 - Eg: Captopril – an ACE-Inhibitor;
 - Eg: Acetylcholinesterase Inhibitors → Prolongs ACh in Synapse
 - **False Substrates** → Drug molecules that occupy enzymes by wasting their time
 - **Pro-Drugs** → The Enzyme converts them into their Active Forms

- **4: Transport/Carrier Proteins (Remember - Symporters & Antiporters):**
 - Membrane-Bound proteins that aid in transporting molecules that are Too-Big/Polar across the PM. They exhibit *Recognition Sites* that make them specific to their ‘cargo’, which can be targets for drugs.
 - **Drugs act as either:**
 - **Inhibitors** → Block Transport
 - **False Substrates** (that fits in the Recognition Sites) → Accumulation of Drug inside cell
 - Eg: Glucose Transporters/Amino Acid Transporters/LDL Receptors/Transferrin Receptors
 - Eg: Amphetamines – Compete with NA for uptake into Presynaptic Cell, & also competes for packaging into vesicles → Accumulation of NA in Synapse & Cytoplasm → NA ‘leaks’ out of presynaptic cell inappropriately

- **Note: Exceptions Include:** Some Antimicrobial & Antitumour drugs, as well as Mutagenic & Carcinogenic Agents, interact directly with DNA rather than cell proteins

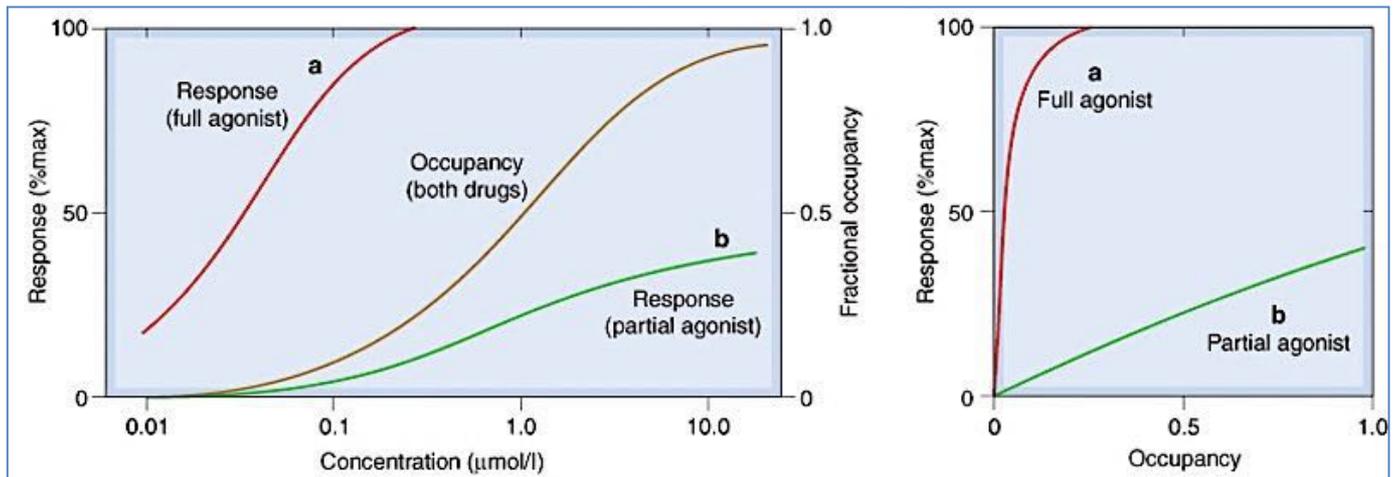


-  Agonist/normal substrate
-  Antagonist/inhibitor
-  False substrate
-  Abnormal product
-  Prodrug
-  Active drug

Drug-Receptor Interactions:

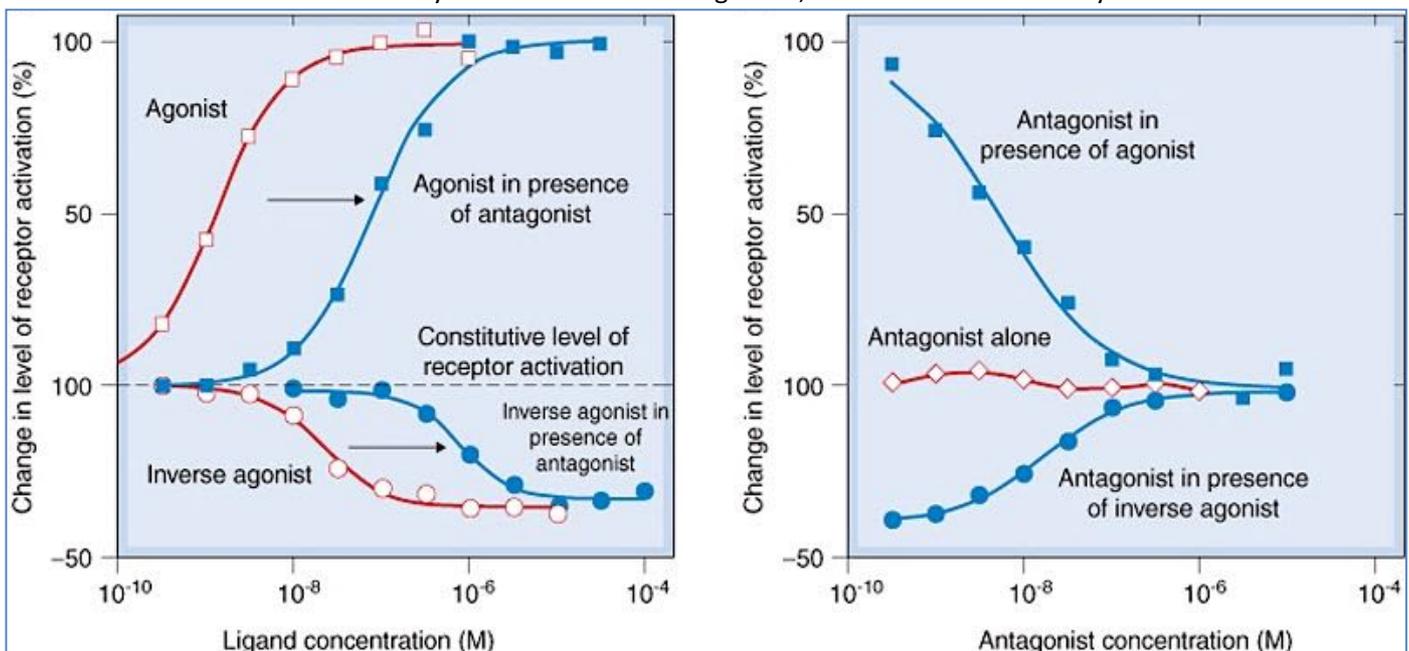
- Agonists – Keys that Open the Lock:

- Drug binds to, and Activates, the Receptor (*Change the Physical Shape of the Receptor*)
 - Ie: Has **Affinity, Efficacy & Potency**
 - Note: These characteristics will vary among Different Agonists
- **Partial Agonists:**
 - Drugs with intermediate levels of Efficacy
 - Ie: Even if 100% of receptors were occupied, the tissue-response is sub-maximal
 - Note: Partial Agonists are often used as ‘Antagonists’ because they compete with the Endogenous Ligands for receptors, and elicit a Reduced Response
- **Full Agonists:**
 - Drugs with high Efficacy
 - Ie: Elicit a Maximal Tissue Response



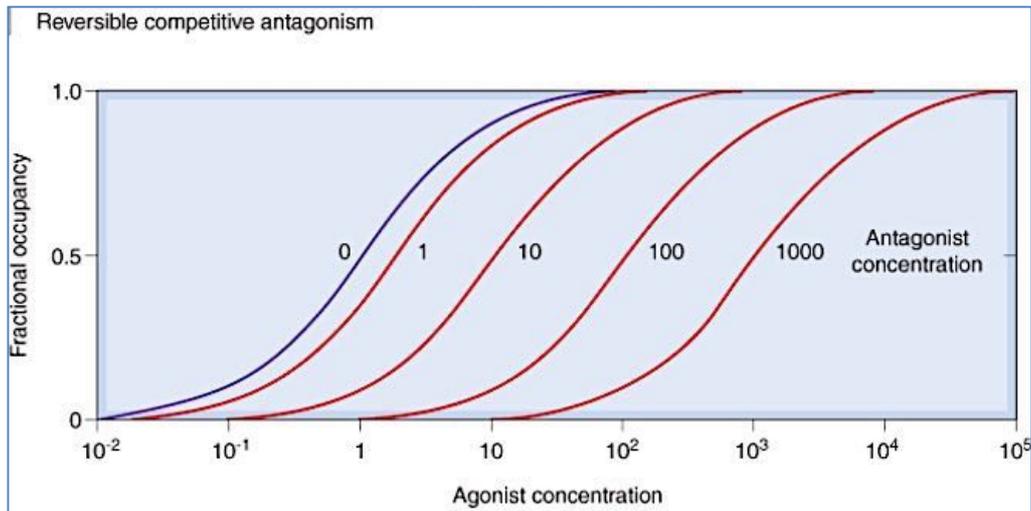
○ Inverse Agonists (Double-Antagonists):

- Note: Some receptors (eg: For Benzodiazepines, Cannabinoids, Serotonin) exhibit baseline spontaneous activation, even in the absence of any ligand. This is called “**Constitutive Activation**”. It is often too low to have any effect under normal conditions, but it becomes evident if receptors are overexpressed → Pathophysiological Implications.
- Ligands that **Reduce** the level of **Constitutive Activation**
 - Ie: Drugs with **NEGATIVE EFFICACY** → Produce a conformational change in the Opposite Direction to the Active Conformation, making it harder for an Agonist to activate it again
 - They are distinct from Antagonists, which have Zero Efficacy



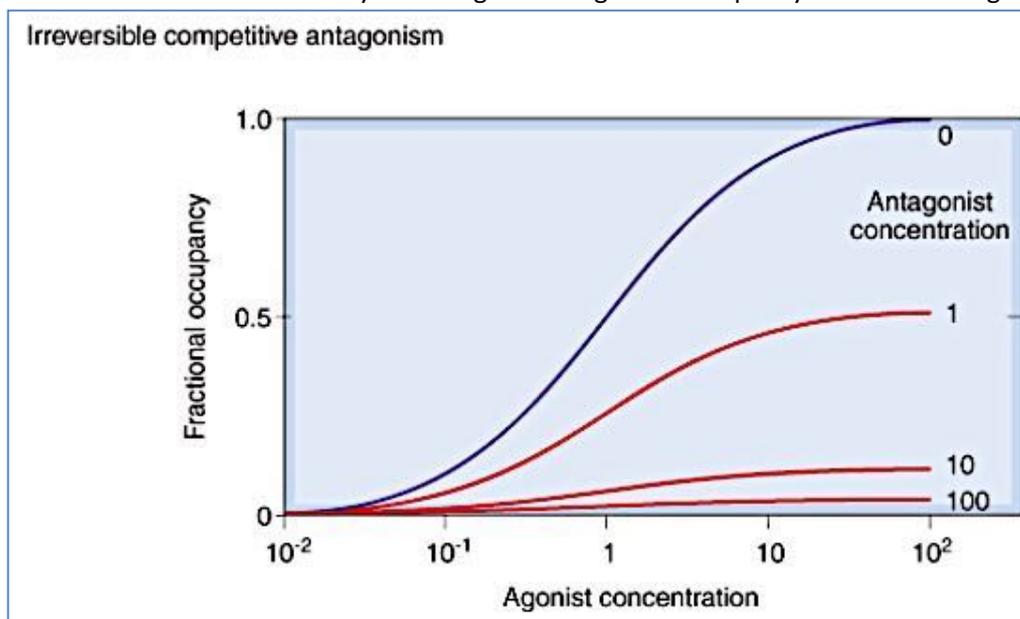
- **Antagonists – Keys that fit, BUT DON'T Open the Lock:**

- Drug binds to Receptor, but Doesn't Activate it (*Do NOT Change the Shape of the Receptor*)
 - I.e: Has **Affinity & Potency, but NO Efficacy**
- Note: Antagonists occupying binding sites block binding of Agonists. I.e:
- **Types of Receptor-Mediated Antagonists:**
 - **Competitive Antagonists:**
 - Have the same Binding Sites as Agonists, & therefore **Compete for Occupancy**
 - Competitive Antagonists can be overcome with a high enough dose of Agonist. I.e: Agonist can act as an Antidote
 - Eg: Beta-Blockers → Reduces effects of NA & Adrenaline by blocking β -Adrenergic Receptors in the Heart/Brain/Kidneys/etc



▪ **Irreversible (Non-Equilibrium) Competitive Antagonists:**

- Similar to Competitive Antagonism, however, Irreversible Antagonists dissociate very slowly, if at all, from the receptors
- I.e: → Virtually no change in Antagonist Occupancy occurs when Agonist is added



▪ **Non-Competitive Antagonists:**

- Blocks the effect of the Agonist by either:
 - 1: Binding to a different part of the Receptor
 - 2: Binding to a different component in the Agonist's chain of effects
- Non-Competitive Antagonists CANNOT be overcome by Agonist; I.e: Agonist Can't be used as Antidote
- Graph is very similar to Irreversible Competitive Antagonism

- **Types of Non-Receptor-Mediated Antagonists:**
 - **Chemical Antagonism:**
 - Antagonist binds to the Free-Agonist, making it incapable of activating its target
 - Ie: Chemical Antagonism → ↓ Bioavailability of the Agonist
 - Eg: Chelation – Chelating agents bind heavy metals to ↓ their Bioavailability
 - **Pharmacokinetic Antagonism:**
 - 'Antagonism' by way of:
 - Competition for uptake into bloodstream (Hinders Absorption)
 - Promoting Ligand Metabolism/Elimination
 - Altering its Distribution throughout the body
 - Eg: Alcohol Vs Warfarin – Alcohol → ↑ Liver Metabolism → ↑ Clearance of Warfarin
 - **Note: Cytochrome P450 Mono-Oxygenases:** are Liver Enzymes that Detoxify/Bioactivate drugs in the bloodstream. Varied expression of these enzymes across a population leads to significant variability in drug effectiveness
 - **Physiological Antagonism:**
 - When 2 drugs that have opposing actions in the body cancel each other out
 - Eg: Histamine (↑ Gastric HCl) + Proton-Pump Inhibitor (↓ Gastric HCl) → No Change

Biological Specificity of a Drug:

- Does the drug prefer ONE target (Highly Specific), or is it Promiscuous (Low Specificity)?
- For a drug to be useful, it must act selectively on particular cells & tissues (Ie: High **Binding-Site Specificity**)
- Conversely, proteins that function as Drug Targets generally have High **Ligand Specificity**

Receptor Families: Receptors are named for their natural chemical interactions:

- **Adrenergic:**
 - Receptors for Catecholamines (eg: Noradrenaline, adrenaline)
 - Targets for Drugs (eg: B-Blockers, A-Agonists, etc)
- **Cholinergic:**
 - Receptors for AcetylCholine
 - Targets for Drugs (eg: Nicotine)
- **Dopaminergic:**
 - Receptors for Dopamine
 - Targets for Drugs (eg: Levodopa, Pramipexole etc)
- **Serotonergic:**
 - Receptors for Serotonin
 - Targets for Drugs (eg: Metoclopramide, Sumatriptan, Dihydroergotamine, LSD, etc)
- **GABA-ergic:**
 - Receptors for GABA
 - Targets for Drugs (Eg: Gabapentin, Gabamide, Topiramate, Zolpidem)
- **Glutamatergic**
 - Receptors for Glutamate
 - Targets for Drugs (eg: Ketamine, Memantine, Amantadine)
- **Opioidergic**
 - Receptors for Opioids
 - Targets for Drugs (eg: Fentanyl, Codeine, Morphine, etc)

Receptor Subtypes:

- Groups of different receptors within a single Receptor Family (Ie: Respond the same Ligand) that are expressed on Different Tissues, and cause widely different (often opposing) Cellular Effects
- Clinical Relevance: by targeting receptor subtypes, you can Target Specific Organs & decrease Side-Effects
- **Eg: Adrenergic Receptors**
 - **α₁-Adrenergic Receptors** → Smooth Muscle Constriction
 - (Vasoconstriction – Useful in Nasal Decongestants & Eye Exams)
 - **β₂-Adrenergic Receptors** → Smooth Muscle Relaxation
 - (Useful in treating Asthma → Bronchodilation)

Desensitization: - The Mechanisms by which the following physiological states occur:

- **Different States of Desensitization:**
 - **Tachyphylaxis:**
 - A rapid decrease in the response to a drug after repeated doses over a short period of time
 - **Tolerance:**
 - Similar to Desensitisation/Tachyphylaxis Describes a more gradual decrease in responsiveness to a drug, developing over a few days/weeks
 - **Refractoriness:**
 - A term also used to describe a loss of Therapeutic Efficacy for a period of time
 - **Drug-Resistance:**
 - Loss of Effectiveness of Antimicrobial/Antitumour Drugs

- **How Desensitization Occurs:**
 - **Change in Receptors:**
 - **Conformational Change:**
 - Change in receptor shape, resulting in the inability to 'activate', despite binding of the agonist
 - Eg: Ion Channels in the NMJ, change shape, resulting in tight binding of the agonist, without the opening of the Ion Channel
 - **Phosphorylation:**
 - Phosphorylation of Intracellular Regions of the receptor protein
 - Eg: Phosphorylation of G-Protein-Linked Receptors interferes with their Intracellular Signalling Cascades, despite binding the Agonist
 - **Downregulation - Loss of Receptors:**
 - Internalisation of receptors via Endocytosis, due to prolonged exposure to Agonists
 - Eg: β -Adrenergic receptors fall to $\approx 10\%$ of normal within 8 hrs of continued stimulation
 - **Exhaustion of Mediators:**
 - Depletion of an essential intermediate substance
 - Eg: Amphetamine, which acts by releasing amines from nerve terminal, shows tachyphylaxis due to depletion of amine stores
 - **Increased Metabolic Degradation of the Drug:**
 - Repeated administration of the same dose produces a progressively lower plasma concentration, because of increased metabolic degradation
 - Eg: Alcohol consumption Tolerance
 - **Physiological Adaptation:**
 - Decrease of a drug's effect due to Homeostatic Response
 - Eg: The BP-lowering effect of Thiazide Diuretics is limited because of a gradual activation of the Renin-Angiotensin System
 - **Active Extrusion of Drug from Cells:**
 - Mainly relevant in Cancer Chemotherapy

Adverse Reactions to Drugs:

- **2 Major Mechanisms:**
 - **Dose-Related Reactions:**
 - Eg: Anticholinergic Side Effects
 - Eg: Tricyclic Antidepressants
 - **Dose-Independent Reactions:**
 - Eg: Allergic Reactions (Type-I Hypersensitivity)
 - (Eg: Myositis)
 - Or Altered cellular antigens → Antibody-Mediated attack (Type-II Hypersensitivity)
 - (Eg: Drug-Induced Haemolytic Anaemia)
- **Other Types of Adverse Drug Reactions:**
 - **Carcinogenesis:**
 - Seen with Chronic Hormone Treatment → Promotion of Hormone-mediated Carcinogenesis
 - Also seen with Cytotoxic Agents → DNA Damage
 - Immunosuppressants → Allows unchecked viral-mediated carcinogenesis
 - **Reproductive Alterations:**
 - **Infertility:**
 - (Eg: Cytotoxic Drugs such as Alkylating Agents)
 - **Teratogens → Foetal Malformations:**
 - (Eg: Anti-Epileptics, Thalidomide & Cytotoxics)

Table 3. Characteristics of Type A-E Adverse Drug Reactions

Classification	Definition	Characteristics
A (Augmented)	Dose related	<ul style="list-style-type: none">• Predictable extension of drug's pharmacologic effect (e.g. β-blockers causing bradycardia)• >80% of all ADRs
B (Bizarre)	Non-dose related	<ul style="list-style-type: none">• Reactions unrelated to the known pharmacological actions of the drug• Examples include: drug hypersensitivity syndromes, immunologic reactions (penicillin hypersensitivity), and idiosyncratic reactions (malignant hyperthermia)
C (Chronic)	Dose and time related	<ul style="list-style-type: none">• Related to cumulative doses• Effects are well-known and can be anticipated (e.g. atypical femoral fracture from bisphosphonates)
D (Delayed)	Time related	<ul style="list-style-type: none">• Occurs some time after use of drug (e.g. carcinogen)• May also be dose-related
E (End of use)	Withdrawal	<ul style="list-style-type: none">• Occurs after cessation of drug use (e.g. opiate withdrawal)

Hepatic & Renal Toxicity – Why is it so Common?

- **Liver:**
 - Huge role in Drug Metabolism – Sometimes Detox & Sometimes Toxication
 - *During Drug *Toxication*, Hepatocytes are exposed to high concentrations of toxic metabolites (Much higher than other bodily cells) → Hence are susceptible to damage
- **Kidneys:**
 - Huge role in Drug Excretion - *But *Also* in fluid balance
 - *Water soluble drugs filtered by the kidneys, and are concentrated in the filtrate as water is reabsorbed → Renal Tubules are exposed to *Higher* (Often Toxic) Concentrations of Drugs

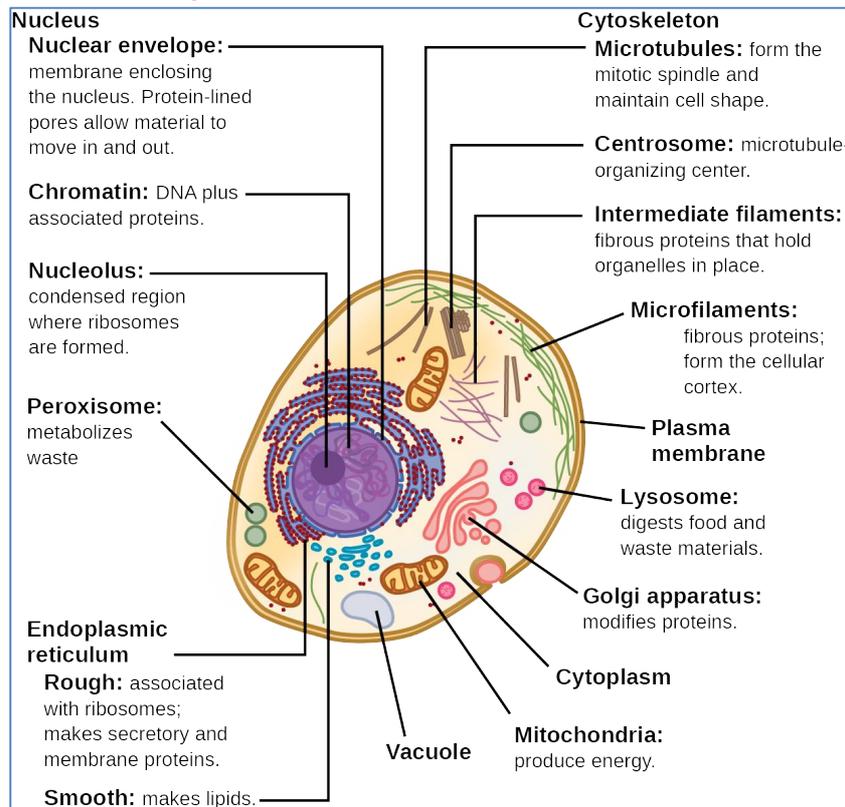
ANTIMICROBIAL THERAPY & SELECTIVE TOXICITY

ANTIMICROBIAL THERAPY & SELECTIVE TOXICITY

Review of Microbial Cell Biology:

- **Host (Humans):**

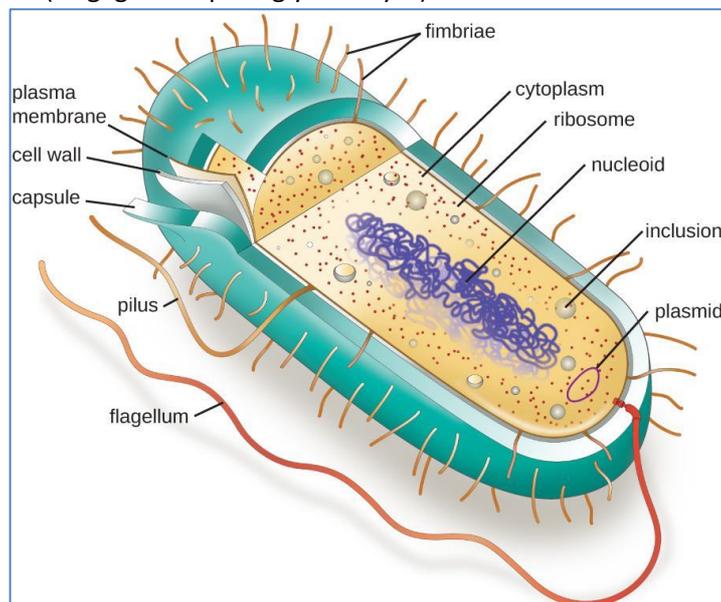
- Human cells are **Eukaryotes**



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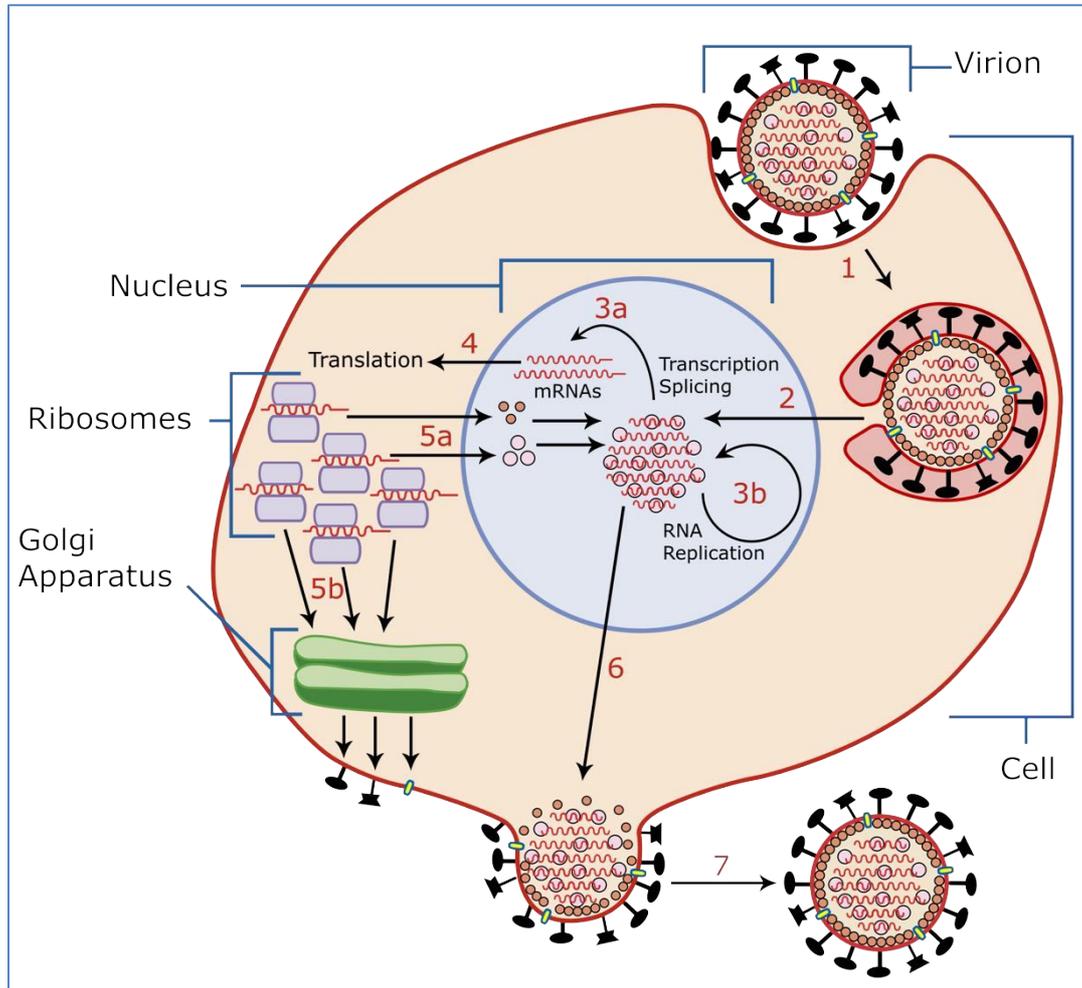
- **Bacteria:**

- **Prokaryotes** – (Very different from Eukaryotic Host Cells – Therefore **Selective Toxicity** is possible)
 - (Antibacterials have less side effects than Antifungals because fungi are Eukaryotic)
- **Gram Positive & Gram Negative Bacteria also Differ by their Cell Wall Structures:**
 - **Gram Positive:**
 - Thick Peptidoglycan Layer
 - **Gram Negative:**
 - Primarily Lipid-Based (Including Lipopolysaccharide – LPS)
 - (Negligible Peptidoglycan Layer)



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- **Fungi/Parasites:**
 - o **Eukaryotes** – (Very similar to Eukaryotic Host-Cells – Therefore Selective Toxicity is Difficult)
 - (Hence why Antifungals have significant side effect profiles)
- **Viruses:**
 - o **Encapsulated DNA/RNA** – (Very different from Eukaryotic Host Cells)
 - o They are also “*Obligate Intracellular Pathogens*” – I.e: Hijack Host-Cell Machinery to Replicate
 - → Antiviral treatments often have to inhibit Host-Cell machinery in order to stop the virus

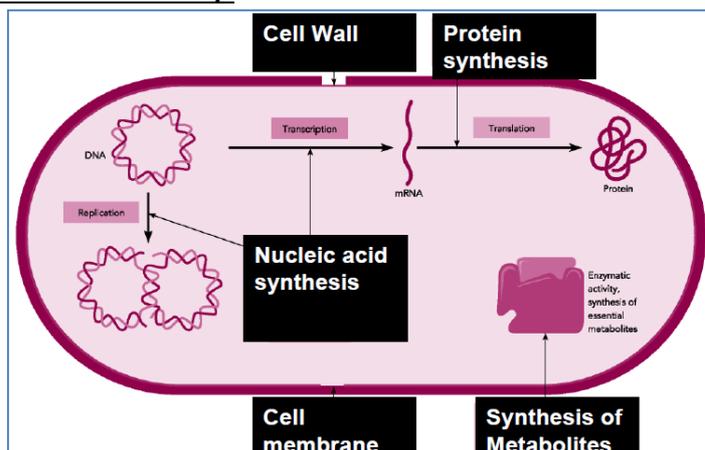


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Principle of Antimicrobial Therapy:

- **Origins of Antimicrobial Therapy:**
 - o Note: Most Anti-Microbials are derived from other Organisms
 - o Eg: Penicillin's Anti-Bacterial property was discovered by Alexander Fleming as it was killing his Bacterial Cultures
- **Selective Toxicity:**
 - o **Critical to Efficacy & Safety of Anti-Microbials**
 - o **Exploits Differences in Cell Biology between *Host* & *Pathogen* Cells**
 - o **Aim → Kill only the Pathogen Cells**
- **Scope of Activity:**
 - o **Specific to Class of Microbe:**
 - Ie: Antibacterials aren't effective against Viruses
 - o **The Effect on the Microbes:**
 - Eg: Bacterio-*Cidal* → Kills Bacteria (Eg: Penicillin)
 - Eg: Bacterio-*Static* → Slows Bacterial Growth (Eg: Tetracycline)
 - (FYI: Bacteriostatic drugs are more useful than Bactericidal drugs for Sepsis – Because bactericidal drugs will liberate the bacteria's *Endotoxins* → Further Inflammation)
 - o **Synergy:**
 - Some antibacterial agents can amplify each-other's mechanism of action
 - **Eg: Aminoglycosides + β -Lactams:**
 - Aminoglycosides Inhibit Protein Synthesis, but need to gain access into cell
 - β -Lactams inhibit Cell Wall Synthesis → ↓Cell wall Integrity → ↑Access into cell
 - o **Broad Spectrum Antibiotics – (“Empirical Therapy”):**
 - Compounds active against a wide range of bacteria
 - Eg: Gram + & Gram – Bacteria
 - o **Narrow Spectrum – (“Directed Therapy”):**
 - Compounds active against a specific class/type of bacteria
 - Eg: Gram + only
- **Antimicrobial Therapy Should be EVIDENCE BASED:**
 - o Ie: **KNOW** what organism you are dealing with before treatment – (Unless Emergency):
 - Allows treatment to be “Directed” rather than “Empirical”
 - → Maximises Efficacy
 - → Minimises Antibiotic Resistance
- **Antimicrobial Resistance:**
 - o **Note: Bacteria employ ‘Antibiosis’ of their own to potentiate their Own Survival**
 - They also develop *Resistance* to Antibiosis from other bacteria to potentiate survival
 - - **THIS CAN WORK AGAINST US** – As Bacteria develop *Resistance* to *Our* Drugs!
 - o **Note: Also, Bacterial “Resistance Genes” exist, and Mutation Potential is HIGH!**
 - (Due to huge numbers of rapidly proliferating bacteria)
 - o **Antibiotic Usage Preferentially Selects these resistant strains, giving them a Competitive Advantage over the rest → Transmission of “Resistance Genes” to offspring**
 - o **THEREFORE – “Restraint of antimicrobial use is the best way to ensure their efficacy”**

Sites for Selective Toxicity:



ANTIBACTERIAL DRUG CLASSES:

- 1: Anti Cell-Wall Synthesis Antibiotics – (Bactericidal):

- Target Peptidoglycan Synthesis on Gram-Positive Bacteria

Classical Agents:	Common Uses:	Mechanism of Action:	Side Effects:
β-Lactam Antibiotics:			
Penicillins: Penicillins 'G' & 'V' Amoxicillin & Ampicillin Flucloxacillin Methicillin Ticarcillin (Suffix = "-Cillin")	Gram Positive Bacteria (Note: Bacteria Producing β-Lactamase are resistant) (Note: Flucloxacillin – for β-Lactamase Resistant) (Note: Cephalosporins – for Non-β-Lactamase Resistant)	Block "Penicillin-Binding Proteins" (Enzymes) → Inhibit Synthesis of the Peptidoglycan Layer of the Bacterial Cell Wall.	GI Upset & Diarrhoea Allergic Rash Anaphylaxis (Need Adrenaline Handy)
Cephalosporins: (Ceftriaxone)			(As above) + Mild Renal Toxicity
β-Lactamase Inhibitors: Augmentin	(In Combination with Penicillins) for Penicillin-Resistant Gram Positive Bacterial Infections	Inhibits β-Lactamase → Allows β-Lactams to work on Penicillin-Resistant Bacteria.	Nausea/Vom/Diarr Allergy
Glycopeptide Antibiotics:			
Vancomycin Teicoplanin Telavancin	Gram Positive Bacteria <i>(As a LAST RESORT for MRSA)</i> (Also if Pt. is allergic to β-Lactams)	Prevents incorporation of specific Peptide Subunits into the Peptidoglycan Layer of the Bacterial Cell Wall.	Local Pain Phlebitis (Vein Inflammation) Kidney Damage Hearing Loss

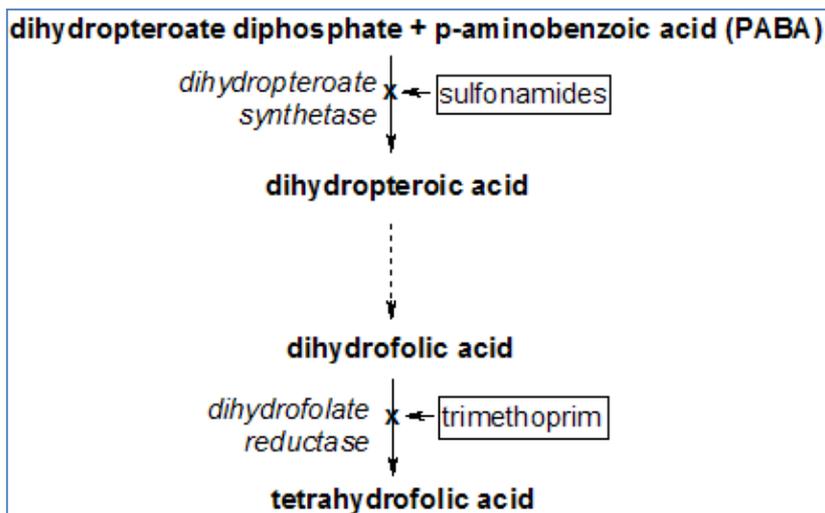
- 2: Anti Protein-Synthesis Antibiotics – (Bacteriostatic):

- Exploits differences between Eukaryotic (Human) Ribosomes & Prokaryotic Ribosomes
- **Selective Toxicity** – Due to specific binding to Prokaryotic Ribosomes
- **Note: Aminoglycosides are Solely eliminated by the Kidneys & Are Nephrotoxic** (Need to assess renal function first, then Dose Accordingly)

Classical Agents:	Common Uses:	Mechanism of Action:	Side Effects:
Aminoglycoside Antibiotics:			
Gentamicin Streptomycin Tobramycin	Gram Negative Bacteria (Used Synergistically with β-Lactams to ↑ drug entry into Bacteria)	Bind Specifically to <i>Prokaryotic Ribosomal</i> Subunits → Causes Misreading of mRNA → Inhibits Synthesis of Proteins vital to Bacteria.	Ototoxic (Hearing Loss & Vertigo) Nephrotoxic (Kidney Damage)
Tetracycline Antibiotics:			
Doxycycline Tetracycline (Suffix = 'Cycline')	Gram Negative Bacteria Syphilis (G ⁻), Chlamydia (G ⁻), Lyme Disease (G ⁻) (And Malaria -Protozoa)	Bind Specifically to <i>Prokaryotic Ribosomal</i> Subunits → Inhibits Binding of tRNA to mRNA → Inhibits Synthesis of Proteins vital to Bacteria.	Nausea/Vom/Diarr. Photosensitivity Staining of Teeth Renal/Liver Toxicity.
Macrolides:			
Erythromycin, Azithromycin	Gram Negative Bacteria Syphilis, Lyme Disease.	Bind Specifically to <i>Prokaryotic Ribosomal</i> Subunits → Inhibits release of tRNA → Inhibits Synthesis of Proteins vital to Bacteria.	Nausea/Vom/Diarr. Jaundice

3: Anti Nucleic-Acid Synthesis Antibiotics – (Bacteriostatic):

- Exploits differences in the Metabolic Pathways of DNA Synthesis – (Humans rely solely on *Dietary Folate*, while Bacteria have to make their own):
 - Eg: Competitive Inhibition of *Dihydropteroate-Synthase*, a key Enzyme involved in Folate Synthesis in Bacteria
 - Eg: Competitive Inhibition of *Dihydrofolate-Reductase*, a key Enzyme involved in Folate Synthesis in Bacteria (Note: Humans share this pathway, but bacteria require it 100x more than humans)
 - Eg: Inhibition of Bacterial DNA Gyrase/Topoisomerase → Stops DNA Replication/Transcription



<u>Classical Agents:</u>	<u>Common Uses:</u>	<u>Mechanism of Action:</u>	<u>Side Effects:</u>
Sulphonamides:			
Sulfasalazine (Prefix = "Sulfa")	Urinary Tract Infections	Competitive inhibition of <i>Dihydropteroate-Synthase</i> , a key Enzyme involved in Folate Synthesis. (Folate is necessary for Nucleic Acid Synthesis → & Hence DNA Synthesis.	Nausea/Vom/Diarr Allergy Precipitation in Urine –Kidney Failure Leukopenia Photosensitivity
Trimethoprim:			
Trimethoprim	Urinary Tract Infections	Competitive inhibition of <i>Dihydrofolate-Reductase</i> , a key Enzyme involved in Folate Synthesis. (Folate is necessary for Nucleic Acid Synthesis → & Hence DNA Synthesis.	Nausea/Vom/Diarr Allergy Precipitation in Urine –Kidney Failure Leukopenia Photosensitivity (BIRTH DEFECTS)
Quinolones:			
Ciprofloxacin Norfloxacin (Suffix = "Floxacin")	Urinary Tract Infections Community Acquired Pneumonia Bacterial Diarrhoea Gonorrhoea	Inhibits bacterial DNA Gyrase or Topoisomerase → Inhibits DNA Replication & Transcription.	Nausea/Vom/Diarr Allergy

- **4: Antimycobacterial Drugs:**

- **2 Main Types of Mycobacterial Diseases:**
 - Tuberculosis
 - Leprosy
- **Why are they a Problem?**
 - Because Mycobacteria can live inside Macrophages following Phagocytosis
 - Also, Multi-Drug-Resistant strains are on the rise
- **Compound Drug Therapy:**
 - A frequent strategy to decrease the probability of the emergence of resistant organisms
 - Also requires Long-Term Therapy

Classical Agents:	Common Uses:	Mechanism of Action:	Side Effects:
Isoniazid:			
Isoniazid	Combination Treatment of M. Tuberculosis	MOA unknown. (Bacteriostatic & Bactericidal)	Allergic Skin Eruptions Fever Hepatotoxicity Haemolysis (in G6PD Deficiency)
Rifampicin:			
Rifampicin	Combination Treatment of M. Tuberculosis	Binds to & Inhibits DNA-Dependent <i>Prokaryotic RNA-Polymerase</i> → Inhibits DNA Transcription & therefore Inhibits Protein Synthesis. (Bacteriostatic & Bactericidal)	Allergic Skin Eruptions Fever Hepatotoxicity
Ethambutol:			
Ethambutol	Combination Treatment of M. Tuberculosis	MOA Unknown. (Bacteriostatic)	Optic Neuritis Visual Disturbances Colour Blindness.
Pyrazinamide:			
Pyrazinamide	Combination Treatment of M. Tuberculosis	Active in Low pH--(In Phagolysosomes) (Bacteriostatic)	Gout GI Upset Hepatotoxicity

ANTIFUNGAL DRUGS:

- **Note: Fungi are Eukaryotic:**
 - o Therefore Selective Toxicity is Difficult
- **Drug Targets:**
 - o **1: Difference in Lipid Composition of Cell Membrane:**
 - Fungi – Ergosterol
 - Humans – Cholesterol
 - o **2: Inhibition of Ergosterol Synthesis:**
 - Fungal Cell Cytochrome Enzymes
 - o **3: Inhibition of DNA & RNA Synthesis:**
 - Intracellular Conversion to Inhibition Substances
- **Routes of Administration:**
 - o **Systemic (Oral/Parenteral)** – For Systemic Fungal Infections
 - o **Oral** – For Mucocutaneous Infections
 - o **Topical** – For Mucocutaneous Infections (Selective Toxicity is less important)

Class	Mode of action	Side effects
Polyene (amphotericin B, nystatin, natamycin, etc.)	Cell membrane permeability (directly binds to ergosterol, leading to losing of membrane integrity)	Nephrotoxicity, hepatic toxicity, etc.
Azoles (fluconazole, itraconazole, posaconazole, voriconazole, ketoconazole, clotrimazole, miconazole, etc.)	Cell membrane permeability (ergosterol biosynthesis pathway by targeting 14 α —lanosterol demethylase)	Anaphylaxis, nausea, gastrointestinal disturbance, phototoxicity, cardiomyopathy, etc.
Echinocandin (caspofungin, micafungin, anidulafungin, etc.)	Inhibit cell wall components (inhibitors of glucan synthase)	Hepatic toxicity, etc.
Nucleoside analogs (flucytosine, griseofulvin, etc.)	Inhibit nucleic acid synthesis, disrupt microtubule functions	Gastrointestinal disturbance, anemia associated with decreased erythropoietin production, etc.
Allylamines (naftifine, terbinafine, tolnaftate, etc.)	Inhibit the <i>ERG1</i> gene of ergosterol biosynthesis	Rash, photosensitivity, etc.
Others (aurones, ciclopirox, haloprogin, miltefosine, orotomide, etc.)	Inhibitors of cell membrane respiration processes, morphogenesis, ergosterol, etc.	Hepatic toxicity, rash, etc.

List of antifungal drugs, mode of action, and their side effects in human.

ANTIVIRAL DRUGS:

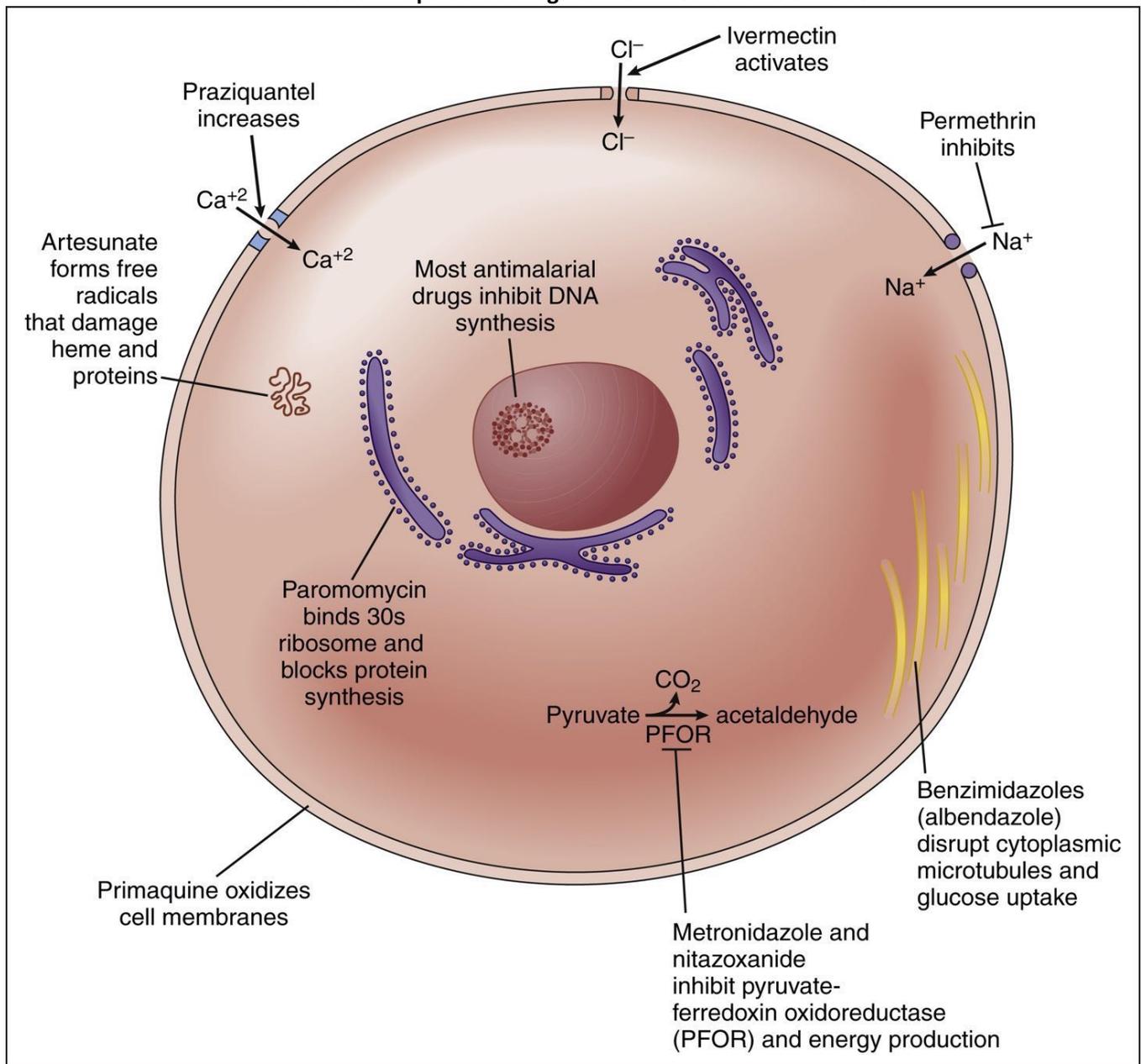
- **Viruses are “Obligate Intracellular Pathogens” – Ie: Hijack Host-Cell Machinery to Replicate:**
 - o Therefore, Selective Toxicity is Difficult, because you have to inhibit Host-Cell machinery in order to stop the virus
- **Mechanisms of Antiviral Selective Toxicity:**
 - o **Nucleoside Reverse Transcriptase Inhibitors**
 - o **Non- Nucleoside Reverse Transcriptase Inhibitors**
 - o **Protease Inhibitors**
 - o **Viral DNA Polymerase Inhibitors**
 - o **Inhibitors of Fusion with Host Cells**
 - o **Inhibitors of Viral Coat Disassembly**
 - o **Biologics & Immunomodulators (Eg: Interferon)**

Drugs	Therapy Strategy Categories	Mechanisms of Therapy
Chloroquine phosphate/ hydroxychloroquine	Anti-malaria anti-viral anti-inflammatory	Increasing endosomal pH, interfering with the glycosylation of cellular receptors of SARS-CoV-2, immunomodulator
Remdesivir	Antiviral drug (Nucleoside analogue)	Interfering with the viral replication
Baricitinib	Rheumatoid arthritis (RA) drug, AP2-associated protein kinase 1 (AAK1) inhibitor	Interfering with viral entry by inhibiting one of the endocytosis regulators
lopinavir/ritonavir	HIV protease inhibitor	Could act by inhibiting SARS-CoV-2 protease for proteins cleavage, interfering with virus replication
Darunavir	HIV protease inhibitor	Could act by inhibiting SARS-CoV-2 protease for proteins cleavage, interfering with virus replication
Camostat Mesylate	Transmembrane protease, serine 2 (TMPRSS2) inhibitor	Interfering with viral entry
Favipiravir	Nucleoside analog	Binds to the viral RdRp and reduce its reproduction
Cepharanthie, Selamectin, and mefloquine hydrochloride	Anti-viral Anti-inflammatory activities	Significantly reduced cytopathic effects of SARS-CoV-2, and decrease the viral load
Ivermectin	Anti-parasite	Inhibits SARS-CoV-2 replication in vitro

ANTIPARASITIC DRUGS:

- **Note: Parasites are Eukaryotic:**
 - o Therefore Selective Toxicity is Difficult
- **Drug Targets:**
 - o **1: Unique Enzymes**
 - o **2: Shared Enzymes – but those Indispensable for Parasite**
 - o **3: Common Pathways with Different Properties**
- **Note: Antimalarial Drugs & G6P-Dehydrogenase Deficiency:**
 - o **Eg: Chloroquine/Primaquine/Pamaquine:**
 - Must NOT be given to Pts with Glucose-6-Phosphate Dehydrogenase Deficiency, as they can cause Fatal Haemolysis
 - (Note: G6PD is an essential enzyme in RBC Metabolism)

The Various Antiparasitic Drugs & Their Mechanisms of Actions:



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