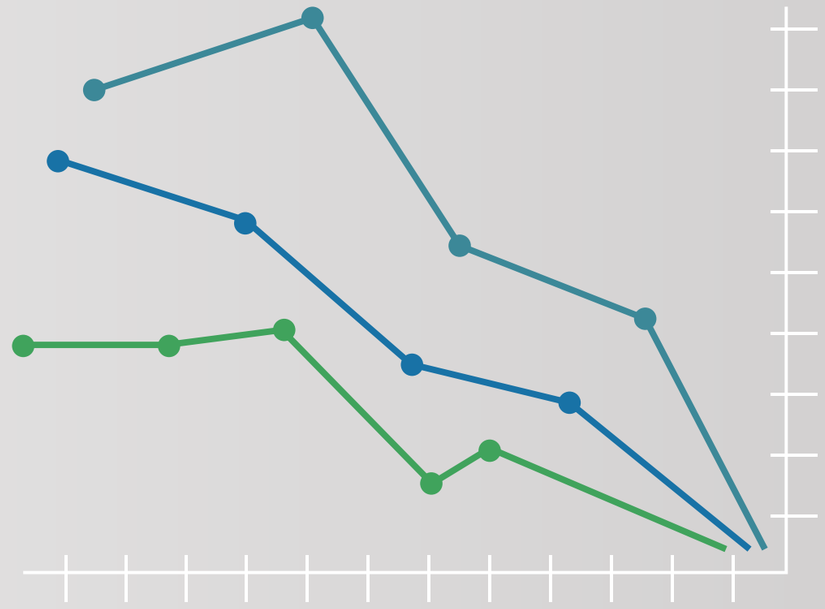
MED iQ presents

PHARMACOLOGY
DRUG PRINCIPLES
- MOD 108 -

SCAN OR CLICK!

Team MED iQ
Dr Nour Abuzeid
Dr Moataz Alshrarkawy



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Dr Nour Abuzeid & Moataz Alshrarkawy

Introduction

Henderson Hasselbalch

Weak acids: $pK_a = pH + \log \frac{unionized}{ionized}$

Weak bases: $pK_a = pH + \log \frac{ionized}{unionized}$

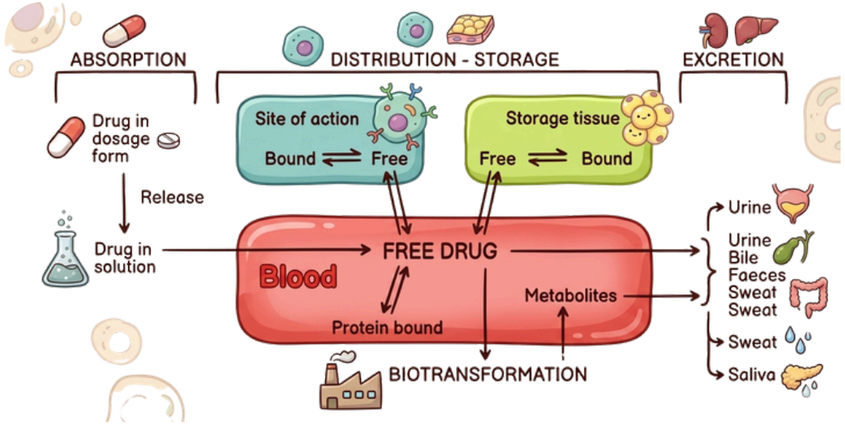
"Medical pharmacology" is often defined as the science of substances used to prevent, diagnose, and treat disease.

- **Drugs: chemical substances stimulate or inhibit** an existing cell function.
  - Used for **treatment, prevention and diagnosis** of diseases or **modify a physiological process**.

1. Pharmacokinetics: It describes what the **body does to the drug** includes:
- **Absorption, Distribution, Metabolism & Excretion [ADME]**.

2. Pharmacodynamics: describes what drug does to the body, includes:
- Study of the pharmacological **actions of drugs.**
- Their possible **mechanisms of action.**

3. Pharmacotherapeutics: Study of **selection and use of drugs**
- For **diagnosis**, **prevention** and **treatment** of disease.



N.B The **main goal of a physician is to prescribe the most appropriate drug** for each individual patient **in adequate doses**, so that **therapeutic levels are obtained**, to **produce the desired response** with the **minimal adverse effects**.

N.B: Lipid/water partition coefficient: ratio of drug conc in lipid medium to its conc in water medium when it is put in lipid water system.

Passage of drugs across cell membranes

- The cell membrane is lipid sheet interrupted by protein in form of:
  - **Ion channels, carriers and receptors, and contains water filled channels.**
- **Passage** of drugs across cell membranes occurs mainly by:

1. Simple diffusion
2. Carrier mediated transport

chief process involved in absorption & distribution — 1) Simple diffusion — **Depends on:**

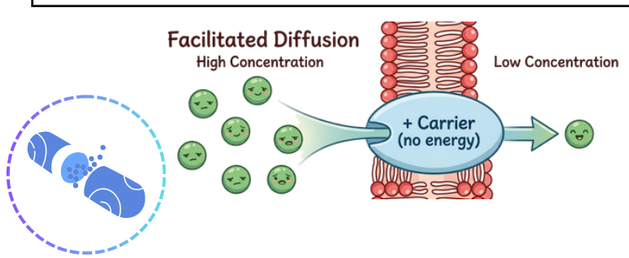
1) Concentration gradient:
- From one side of cell membrane **to the other along conc gradient**

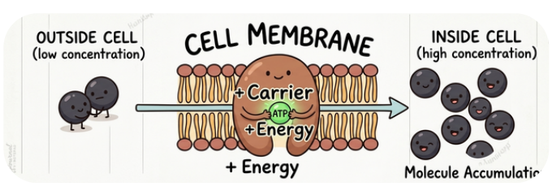
2) Molecular size: The **smaller** the molecular size **the better absorption**.
3) ↑ Lipid solubility & lipid/water partition coefficient, the **better absorption**.
4) Ionization degree:
- **↑ Ionization, the ↓ lipid solubility.**
- Degree of ionization **depends on: pKa of the drug & pH of the medium**.

5) No energy & no carriers are needed.

2) Carrier mediated transport:

a) Facilitated diffusion	b) Active transport:
Drugs are transferred across cell membranes: - **Along their concentration gradient.** - **Carrier** for substances which are **too large or lipid insoluble** to diffuse passively - **No energy** is required. **e.g. glucose uptake by cells.**	Drugs are transferred across cell membranes: - **Against their concentration gradient** - Transport **requires a carrier** - Transport **requires energy** **e.g. secretion of penicillin by renal tubules.**





- pKa (ionization constant of a drug).
- pH at which **½ of the drug is ionized and ½ non-ionized**

e.g. pKa of aspirin 3.5, So in pH 3.5 aspirin will be 50% ionized and 50% non-ionized.

- pH of the medium.

1. Most drugs are either weak acids or weak bases.
2. **Weak acids: absorbed in acidity** as it's **↓ionized so ↑ lipid soluble.**
3. **Weak bases: absorbed in alkalinity** as it's **↓ionized so ↑ lipid soluble**.

- Acidic drugs as aspirin ↓ ionized in stomach acidity → ↑ absorption in stomach.
- When filtered by the glomeruli, **big aspirin %** can be **reabsorbed** from the renal tubules **since urine is usually acidic.**
  - So **making urine less acidic** (more alkaline) would **↑ excretion of aspirin** because **less aspirin will be reabsorbed**.

- Weak base drugs as amphetamine will be **better absorbed from the intestine & acidic urine will ↑ excretion.**

Team MED iQ
Dr Nour Abuzeid
Dr Moataz Alshrakawy

Pharmacokinetics

ADME

Absorption

Transfer from site of administration → systemic blood

Drug related

Patient related

Nature

- **Inorganic > Organic**


small


Big

Solubility

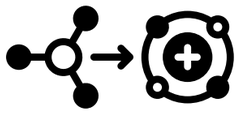
- Drug MUST be **Water & lipid soluble.**
- Must be completely dissolved in H2O to be absorbed.
- **↑ lipid solubility**
- **↑ Lipid/Water partition coefficient**
- **↑ absorption.**

Valency

- **Ferrous > Ferric**

Ionization

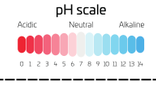
- **Non-ionized**
- **More lipid soluble**
- **Better absorption**



Pharmaceutical Preparation

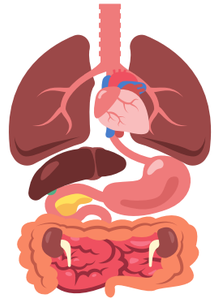
- **Solution > Suspension > Tablet.**

Gut pH



- Weak **acids better absorbed in acidic** media.
  - **(aspirin) (stomach)**
- Weak **bases better absorbed in basic** media.
  - **(amphetamine, ephedrine) (intestine)**

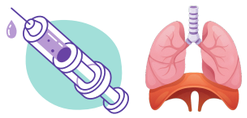
Distribution



Metabolism

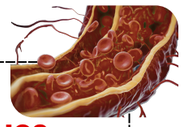
Excretion

Route of Admninistration



- **I.V. & inhalation > I.M > S.C > Oral > Skin**

Absorbing Surface



- Vascularity:
  - **Alveoli > Skeletal muscle > SC tissues.**
- Surface area:
  - **Alveoli > Intestine > Stomach**

(Intestine has 10^3 times the area of stomach) ; due to microvilli & rich blood.

Absorbing surface State of health

- Oral **absorption is DECREASED**:
  - Gastritis
  - malabsorption
  - Diarrhea

Gut contents

Other drugs & food presence

- **Adrenaline S.C → V.C :**
  ↓ Absorption of Local anesthetics
  ↑ duration of action of local anesthetics.
- **Milk (Calcium): ↓ Oral abs Tetracyclines** (Abs)
- **Grape fruit juice: ↑ absorption of drugs**
  - by **inhibiting P. glycoprotein** (cause **reversed transport** from gut wall to lumen).
- **Tea: ↓ iron absorption** ; due to **tannic acid.**
- **Food** presence:
  - **Bad** → **dilutes** Drugs & **compete** for absorption.
  - **Good** → with **IRRITANT** drugs e.g. aspirin & iron.

Specific factors

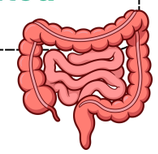
- **Intrinsic factor** for Vit B12.

Gut motility & rate of dissolution

- **Prokinetic drugs increase motility.**
  - e.g. **Metoclopramide**
- **Atropine inhibits motility.**

↑ motility ↑ gastric emptying
↑ abs rapid disintegrated
- **paracetamol**

↓ abs slow disintegrated
- **digoxin**



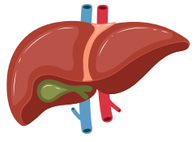
Systemic circulation

- **Absorption is DECREASED**:
  - Shock
  - Heart failure

First pass effect

drug metabolism before reaching systemic circulation.

- Gut first pass effect:
- **Gastric acidity:** destroys **benzyl penicillin**.
- **Digestive enzymes:** destroy **insulin**
- **Mucosal enzymes:** destroy **chlorpromazine**.



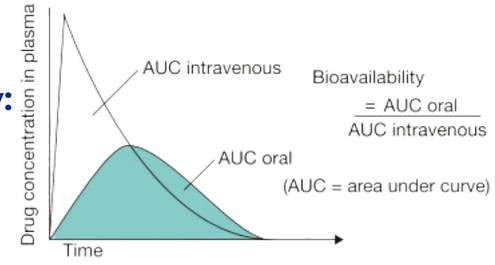
- Hepatic first pass effect:
- Drugs **extensively metabolized: Nitroglycerine**
  - **To avoid:** change the route of administration.
  - Nitroglycerine is **administered sublingually.**
- Drugs **metabolized to large extent: propranolol & nitroglycerine.**
  - **To compensate: INCREASE the oral dose.**

Bioavailability

% unchanged drug reaches systemic circulation after administration.

- **100 % after IV administration.**
- Variable after oral administration.

- Factors affecting oral bioavailability:
1. Amount of drug absorbed
   = Factors affecting GIT absorption.
2. First pass metabolism.



Pharmacokinetics

Team MED iQ
Dr Nour Abuzeid & Moataz Alsharkawy

ADME

Physicochemical properties

Molecular weight & degree of ionization & lipid solubility.

Plasma proteins binding

drugs may **bound to plasma proteins (chiefly albumin)**.
Salicylates are strongly bound to plasma proteins.
So, drugs are carried in blood in 2 forms:

Free form	Bound form
active diffusible	**Inactive** non-diffusible
metabolized	**not** metabolized
excreted	**not** excreted (act as **reservoir**)

Amount of drug bound change according to:

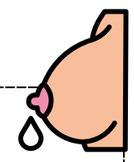
- Affinity for binding sites:
Competition between drugs , may displace other.
- e.g. **Salicylates** can **displace warfarin** → **hemorrhage**.

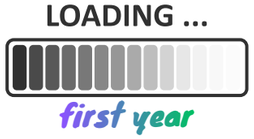
- Hypoalbuminemia → ↑ free drug:
- e.g. in **starvation**, **malnutrition**.
- **Therapeutic dose changes to toxic dose** e.g. **Phenytoin**.
- **The ↑ binding , the ↑ duration** e.g. **sulphonamides**.

Passage across barriers

Through breast milk:

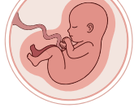
· Most drugs for lactating women detectable in milk.
·**milk pH** is **more acidic (7.0)** than that of plasma (7.4),
so **basic drugs ionize & accumulate in milk (ion trapping)**
· Milk contains more fat than plasma which favors retention of lipid soluble drugs.





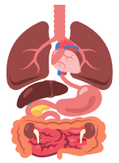
Passage to fetus across placental barrier:

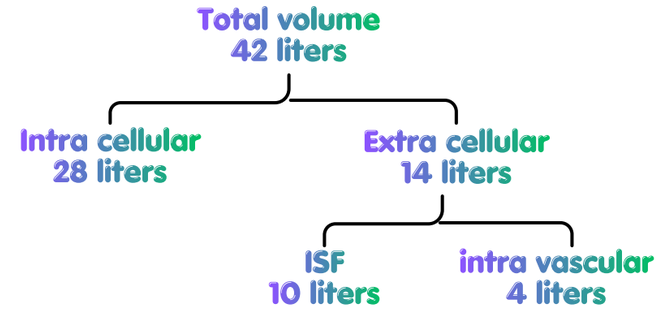
placental barrier acts like a cell membrane.
So **non-ionized**, **lipid soluble** drugs **pass** from the mother **to fetus more easily**
Drugs passing may cause: **During pregnancy** → **Teratogenicity (Tetracyclines)**.
During Labor → **Neonatal asphyxia (Morphine)**.



Distribution

drug distributed among body compartments after absorption





One compartment model (IV)

Drugs having **↑ MWT are trapped in IV compartment** distributed in 4 L which's = 6% of a 70kg BW.
- e.g. **heparin** or drugs highly bound to proteins **(warfarin)**.

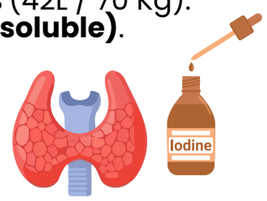
Two compartments model (extracellular)

The **IV space and ISF** space.
↓ MWT , not lipid soluble are distributed to 14 L= 20% BW
- e.g. **quaternary ammonium** & **aminoglycoside** antibiotics.

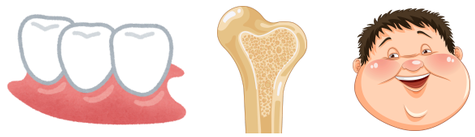
Multicompartment model (Extra & intracellular)

Drugs are distributed **to total body fluids** (42L / 70 Kg).
They are of **↓ MWT & hydrophobic (Lipid soluble)**.

Special affinity for certain tissue



1. **Iodine in thyroid.**
2. **Thiopentone in fat.**
3. **Tetracycline and Ca in bone & teeth.**



- Apparent volume of distribution (Vd):
Assuming that body consists of 1 big fluid compartment and that total amount of drug (A) would be uniformly distributed in that compartment such that it would have the same concentration as in plasma (C).

$$Vd = \frac{\text{dose (mg)}}{\text{plasma conc (mg/L)}}$$

Significance:

1. Rough estimation of drug distribution:
↓ Vd drugs retained in vascular compartment
↑ molecular weight & ↑ plasma proteins binding
↑ Vd drugs occupy multicompartment or concentrated in tissues
- e.g. **digoxin** in **heart**.

- It is **called apparent Vd** because Vd of some drugs as **digoxin (500L/70kg) can extremely exceed any physical volume in the body**.

2. Determine loading dose & total drug amount in body:

3. In cases of drug toxicity
- Dialysis can be done **only** with **↓ Vd** which means that most of **drug present in circulation.**
- e.g. **Aspirin**.

CNS across Blood Brain Barrier (BBB)

- BBB composed of basement membrane & 3 cellular elements: endothelium , pericytes, astrocyte end feet
- Aim: shield brain from harmful substances.
- **Non-ionized,lipid soluble** drugs **can pass the BBB.**
  - e.g. **Physostigmine stimulate** the CNS, **neostigmine** can**not**.
- **Inflammation** (Meningitis) **↑ permeability of B.B.B.**
  - **Penicillin** can **pass inflamed meninges but NOT normal one.**

Team MED iQ
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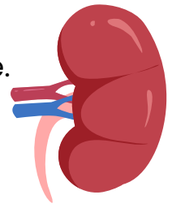
Pharmacokinetics

ADME

Excretion

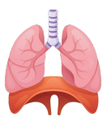
- Removal of a drug from the body
- **Most important route via kidney** into urine.
- Other routes: GIT, skin glands, and lungs.



Renal

1. **Non**volatile drugs and **metabolites**.
2. Renal excretion is the **result of glomerular filtration and active tubular secretion & reabsorption**.
3. **Passive Glomerular filtration** for:
   - **Water soluble**
   - **Nonbounded drugs with M.W. < 500 daltons.**
4. **Active Tubular Excretion:**
   - **Saturable & Site for competition & Drug Interaction**.
5. **Changes in urinary pH:**
   - **Alkalinization:**
- By giving **Na or K Acetate, Bicarbonate or Citrate**.
- Renal **excretion of weak acids:**
  - **e.g. aspirin (Ion Trapping)**.
   - **Acidification**:
- By giving **NH4Cl or ascorbic acid (Vit C)**.
- Renal **excretion of weak Base drugs:**
  - **e.g. Ephedrine (Ion Trapping).**
6. The **clearance of some drugs depends mainly on renal excretion (Little or no metabolism)**
   - **BE CAUTIOS in Renal patients.**

The Lungs



- **Gases (CO_2).**
- **Volatile Liquids.**

- **Halothane** that is used in **anesthesia**.

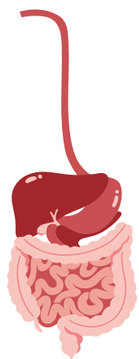
Skin Glands

1. **Sweat**:
Vit B-1, Hg, As, rifampicin
2. **Milk**: affect suckling baby
e.g. **purgatives**

The Alimentary Tract

1. **Saliva (pH=8): Iodide.**
2. **Stomach: Morphine.**
3. **Bile:** some may be secreted in bile by mechanism similar to renal tubular secretion. Such drugs reach the intestines in the bile & have one or more of the following fates:
- Be excreted in large intestine.
- Be absorbed again from the small intestines **and undergo enterohepatic circulation.**
   - e.g. **Rifampicin**.
4. **Large Intestine:**
via the bile or unabsorbed oral drugs.

N.B Rifampicin which causes sweat red discoloration.



Site of Metabolism (Organs):

- **Liver is the main site** for biotransformation
- The **Lungs** have enzymes that can metabolize:
  - **angiotensin I, prostaglandins & nicotine.**
- In the **presence of UV light:**
  - **Skin** converts **provitamin D to pre-vitamin D**.
- The **kidneys** convert **vitamin D to a more active** form.
- **Plasma choline esterases inactivate acetylcholine** & other similar compounds.
- **G.I.T. & Gut flora** metabolize **Tyramine & Histamine**

Phase-I (Non-Synthetic) Oxidation, Reduction & Hydrolysis

1. Oxidation:
- **Alcohol** → Acetaldehyde → Acetic acid → CO_2+H_2O+E
2. Reduction:
- **Chloral hydrate** (**Active**) → Trichloroethanol (More **active**)
3. Hydrolysis:
- **Acetylcholine** (**Active**) → Acetic acid + Choline (Inactive)

Phase-II (Synthetic) Conjugation

- Usually leads to inactivation
- **Glucuronidation of paracetamol** → inactivation
- **Acetylation of isoniazid** → inactivation
- **Glycine conjugation of aspirin** → inactivation
- **May lead to activation**
  - **Methylation of adrenaline** → **active noradrenaline** .
  - **Morphine** → **Morphine-6-glucuronide** (More **active**)

Metabolism

active lipid soluble → **inactive water soluble**

to be easily excreted.

- Results of Phase-I Metabolism:

1. Inactivation (commonest fate):

Adrenaline & Noradrenaline ⟶ **Vanil Mandilic Acid (VMA)**

2. Activation:
Inactive (Prodrug) → Active metabolite

CortisONNEE ⟶ **Hydrocortisone (CortisOOLL)**

3. Maintain Activation:
Active Drug → Active Metabolite

Diazepam ⟶ **Nor-diazepam**

4. Toxification:
- Methyl alc → Formaldehyde → Blindness

N.B Most drugs undergo phase I then Phase II.
- **Some have reverse order e.g. Isoniazid**

Acetylation (Phase II) then → Hydrolysis (Phase I).

	HME	Non-Microsomal enzymes
Site	**Smooth endoplasmic reticulum**	**Cytoplasm, Mitochondria, etc.**
Organs	**Mainly Hepatic**	**All organs**
Phase-I	**Oxidation / Reduction (CYT P-450)**	**Oxidation/Reduction & Hydrolysis**
Phase-II	**Glucuronidation ONLY**	**All *Except* Glucuronic acid**
Induction	**Inducible**	**not Inducible**
Substrate	**Usually lipophilic**	**Lipophilic & hydrophilic**

MediQ Academic Team
Dr. Moataz Alsharkawy
Dr. Nour Abuzeid

Pharmacodynamics

Possible Mechanism of Drug Action:

Drugs may act through one or more of the following

A | Physical

- **Absorption:** eg;
  - Kaolin in Diarrhea
- **Osmotic:** eg;
  - MgSO4 as saline purgative
  - Mannitol as osmotic Diuretic

B | Chemical

- **Neutralization:** eg;
  - $NaHCO_3$ (Antacid) + HCl in treatment of Hyperacidity
- **Chelation:** organic compound + Heavy metal → produce nontoxic easily excreted complex. eg;
  - Desferrioxamine for Fe^{3+}

C | Interference with Cell Division

- **eg;** Anti Cancer Drugs

D | Interference with a Metabolic Pathway

- **eg;** Sulfonamides compete with PABA in bacteria → inhibition of formation of Folic Acid

E | Inhibition of important Enzymes

- **Physostigmine** & Cholinesterase
- **Aminophylline** inhibits Phosphodiesterase (PDE)
- **Aspirin** & Cyclooxygenase (COX)

F | Action on Membrane Ionic Channels

- **Local Anesthetics** as procaine block Na^+ Channels → Stabilize nerve cell membrane

G | Inhibiting Membrane Carriers

- **Thiazide** Diuretics block NaCl Symport in distal tubules of kidney → ↑ Na & water excretion

H | Action on a Specific Receptor

- **Most common mechanism**

Definition of a Receptor:

A receptor is a **chemo-sensitive & selective** protein that interacts with a **ligand** (drug, transmitter or hormone) to produce a **response**. The receptor may be located in the membrane, cytoplasm or nucleus.

$$Drug + Receptor \underset{K_d}{\overset{K^a}{\rightleftharpoons}} Drug/Receptor\ Complex \rightarrow Response$$

Ka = Association constant with the receptor

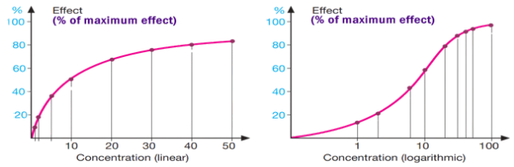
Kd = Dissociation constant for the receptor

Affinity: ability of the drug to fit onto receptor to form Drug-Receptor (D/R) Receptor

Efficacy / Intrinsic Activity (IA) = Ability of D/R Complex to evoke a response

Relationship between drug concentration and response:

Represented by **Concentration-Response curves**, usually **hyperbolic** but becomes **sigmoid** when **log** concentration is plotted against response.



Concentration-Response Curve of Drugs:

Relation between Log Conc. and Response (effect) of drug.

Useful to know **Effects**:

- Minimal Effect (E_{min})
- Maximal Effect (E_{max})
- Submaximal Effect (E_{50} = 50% effect)

Useful to know **Doses**:

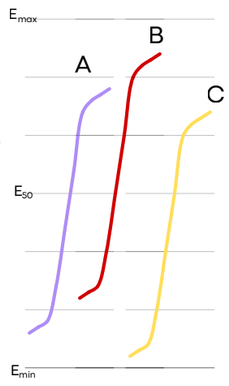
- Produce Minimal Effect (ED_{min})
- Produce Maximal Effect (ED_{max})
- Submaximal Effect (ED_{50} → E_{50})

Useful to **Compare** drugs:

- **Efficacy** → Compare Emax (B>A>C)
- **Potency** → Compare doses that produce same submaximal effect (A>B>C)

Useful to determine **type of blocker** if:

- **Competitive** → Parallel shift to right (↓ Potency) with same E_{max} (Efficacy)
- **Non-competitive** → Non-parallel shift to right (↓ Potency) with ↓ E_{max} (Efficacy)



Types of Inhibitors:

A | Competitive Antagonists

- Antagonists bind **Reversibly** with the receptors
- Antagonists can be **Displaced** by excess agonist → **(Surmountable Block)**
- **Parallel** shift of the Conc-Reponse curve of the agonist to **RIGHT → ↓ Potency**
- **No** effect on maximum response (E_{max}) **= Same Efficacy**

Examples:
→ Propranolol → Atropine → Naloxone

B | Noncompetitive Antagonists

- Antagonists **NOT Displaced** by agonist **→ (Nonsurmountable Block)**
- **Non-Parallel** shift of the Conc-Reponse curve of agonist to **RIGHT → ↓ Potency**
- **Decrease** maximum response (E_{max}) to agonist → **Decreased Efficacy**

Types of Ligands:

Drugs are classified, according to the nature of their interaction with receptors in **Agonists**, **Partial Agonists**, and **Antagonists.**

Drug	Definition	Affinity	Efficacy	K_a & K_d	Effect	Example
Agonist	Drugs that have **affinity**, **efficacy**, and **rapid disassociation**	High	High	Rapid	Full resonse	Acetylcholine Adrenaline
Partial Agonist	Produce **lower** response at full receptor capacity than agonists Act like weak agonist in **absence** of agonist **OR** like antagonist in **presence** of agonist	High	Low	Slow / Moderate	Full response OR Block agonist	Pindolol Sumatriptan
Antagonist	Drugs that block receptors. They have affinity, no efficacy & slow disassociation	High	NONE	Slow	Block Agonist	Atropine

Types of Noncompetitive Block

Reversible	Irreversible
Antagonists bind **REVERSIBLY** to receptor	Antagonists bind **IRREVERSIBLY**
Block ends by: **Metabolism** of Antagnoist	Block ends by: **Resynthesis** of Receptors
Usually **short** duration of action	Usually **long** duration of action
eg; Nicotine LD & Succinylcholine	**eg;** Phenoxybenzamine & Organophosphorus'

N.B: Chronic use of drugs affects the number & Sensitivity of Receptors

Long use of **Agonists** → Decrease in number & Sensitivity of Receptors → **Down Regulation**
Long use of **Antagonists** or **Transmission inhibiting Drugs** → Increase number & Sensitivity of Receptors → **Up Regulations**

MediQ Academic Team
Dr. Moataz Alsharkawy
Dr. Nour Abuzeid

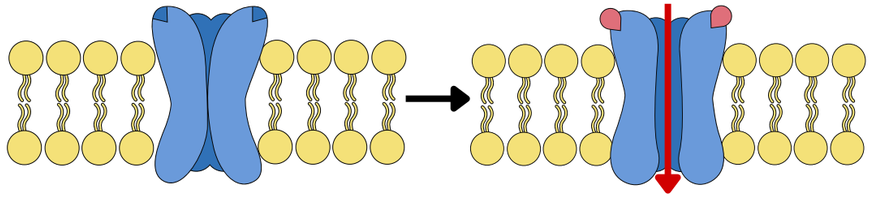
Receptors & Signals

Ligand-Gated Ion Channels:

Ligand binds to the extracellular domain of a ligand-gated ion channels

➡️ **Membrane-bound** receptors located on the **gate** of an ion channel
➡️Binding of **Ligand** to **Receptor** results in conformational change to receptor, resulting in **change** of membrane **permeability** to ions.
➡️**Milliseconds** Between **binding** and **response**
➡️**Examples:**

- **A.Ch** + Nicotinic Receptors ➔ ↑ Na^+ Influx ➔ Depolarization
- **GABA** + GABAA Receptors ➔ ↑ Cl^- Influx ➔ Hyperpolarization



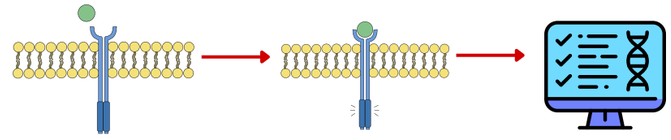
Types of Receptors

- Receptors have 2 main functions:
  - Ligand Binding
  - Generating Effector Response by interacting with closely associated cellular proteins called "Signaling Systems"

Enzyme (Tyrosine Kinase) Linked Receptors

Ligand Binds to ECM Domain of a receptor ➔ activates kinase

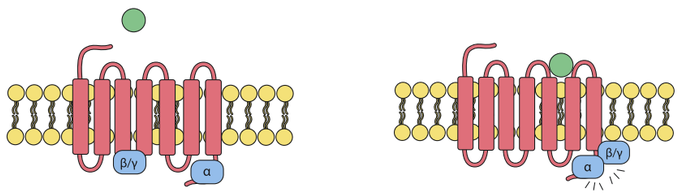
➡️**Polypeptide Receptors** consisting of **Extracellular** domain (Where Insulin / Growth Hormone attach)
➡️Connected to **Cytoplasmic** Enzymatic domain containing **Tyrosine Kinase** Enzyme, which when activated phosphorylates:
1️⃣Signal Transducer ➔ Non-genomic Actions
ℹ️Takes **seconds/minutes**; eg: Hypoglycemia of Insulin
2️⃣Activate transcriptor ➔ Separate from receptor ➔ Cross nuclear membrane ➔ Gene transcription ➔ Genomic Action
ℹ️Takes **Hours**; eg: anabolic effect of insulin & GH



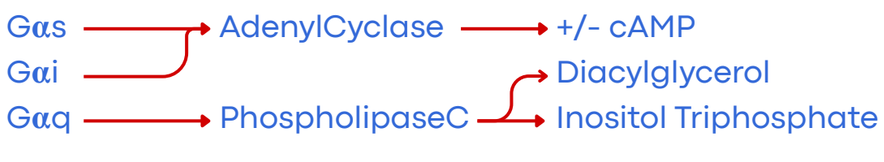
G. Protein Coupled Receptors & 2nd Messengers:

Ligand binds to domain of transmembrane receptor coupled to a G Protein

➡️**Cell surface receptors** which facilitate binding of **GTP** to specific proteins on cytoplasmic surface (**G Protein**)
➡️**G. Protein** regulates activity of membrane **enzymes** & ion **channels**.
➡️**G. Protein** is a membrane protein made up of 3 Subunits (**α**, **β**, **γ**)
➡️**G. Proteins** **EITHER** regulate intracellular 2nd messages (**α**-subunits with GTPase activity)
OR control opening of ion channel (**β**-subunits & **γ**-subunits)
➡️There are different **Gα** subunits (**$G\alpha_s$** - **$G\alpha_i$** - **$G\alpha_q$**)
➡️**Few Seconds/Minutes** between ligand bind & effect.



Mechanism of Action



Examples

- **Adrenaline** + **β** Receptors ➔ **$G\alpha_s$** Protein ➔ stimulate **A.C** ➔ ↑ cAMP
- **Adrenaline** + **α_2** Receptors ➔ **$G\alpha_i$** Protein ➔ inhibit **A.C** ➔ ↓ cAMP
- **A.Ch** + M1&3 Receptors ➔ **$G\alpha_q$** Protein ➔ stimulate **PhospholipaseC** ➔ ↑ IP_3 & DAG ➔ ➔ Ca^{2+} + Calmodulin ➔ Response
- **A.Ch** + M2 Receptors ➔ **$G_\beta\gamma$** ➔ K^+ Efflux ➔ Hyperpolarization

Gene-Active Intracellular Receptors (DNA Linked Receptors)

Lipid soluble ligand diffuse across membrane to modulate gene expression

➡️**Cytosolic** or **Nuclear** Receptors that modulate transcription of **genes** leading to changes in **protein synthesis**

✳️**eg;** Lipid soluble ligand (Steroid hormones, Thyroxine, Vit. D) + Intracellular Receptor ➔ **DNA Transcription** ➔ **mRNA** ➔ change in **Protein Synthesis**

🔁**Delayed Lasting** Effect (**Hours** between ligand binding and cellular response)

⛔Drugs act on **more than one** receptor
eg; Acetylcholine

MediQ Academic Team
Dr. Moataz Alsharkawy
Dr. Nour Abuzeid

Adverse Reactions

Type A: Augmented or Predictable Undesirable Adverse Effects

Predictable undesirable effects related to normal pharmacological actions of the drug.

A | Side Effect

- An **unintended** & **inevitable** expected effect of drug related to its **pharmacological** properties & is produced by the Therapeutic Dose of drug.
- Usually **Unpleasant** or **Hurtful**
- **Examples:**
  - Dry mouth from **atropine** when used as antispasmodic
  - Gastritis induced by **NSAIDs** when used as **antipyretic**

B | Secondary Effect

- **Indirect consequence** of a drug related to its pharmacologic properties (**Pharmacodynamics**) and produced by **Therapeutic dose**. Examples:

Drug	Primary Effect	Secondary Effect
Oral Broad Spectrum antibiotics. Used to treat Resp. Tract infections	Killing pathogenic bacteria in the Respiratory tract	Kills intestinal flora ↓↓ Synthesis Vit B & K Overgrowth of resistant bacteria → Super infection
Inhaled corticosteroids used to treat bronchial asthma	Anti-inflammatory & Anti-allergic effect on bronchi	Suppress cell-mediated immunity → overgrowth of oral bacteria → Oral Candidiasis

C | Overdose

- **Exaggerated** pharmacological action of the drug occurs when drug attains high **toxic** plasma levels.
- **Causes:**
  - **Very large** dose of drug / **larger** than therapeutic dose in drug with **narrow margins**
  - **Drug accumulation:** on repeated administration with impaired elimination (Liver/Kidney Failure)
- **Example:**
  - Insulin Large Dose →Hypoglycemia

D | Supersensitivity

- **Exaggerated** pharmacological action of the drug in response to **small therapeutic dose** in SOME individuals due to tissue **hyper-responsiveness.**
- **Management** → Decrease dose
- **Example:**
  - **Hyperthyroidism** → Sensitive to **sympathomimetics**

E | intolerance

- **A Severe toxic effect in response to therapeutic doses.**
- **Example:**
  - **Statin Intolerance → Severe liver & muscle injury**

F | Interactions

- See **Drug Interactions Mindmap**

G | Direct Effects

- **Drug** or its **metabolites** react with tissues → **damage cells**.
- **Cytotoxicity** ≠ immune mediated

Examples

- **Cardiotoxicity:**
  - Halothane & Doxorubicin
- **Hepatotoxicity:**
  - Halothane & Paracetomol
- **Nephrotoxicity:**
  - NSAIDs & Aminoglycosides
- **Neurotoxicity:**
  - Aminoglycosides → 8th cranial N
- **Bone Marrow Inhibition:**
  - Chloramphenicol

Type B: Bizzare / Unpredictable Adverse Effects

Unpredictable undesirable effects related to pharmacological actions of the drug.

A | Idiosyncrasy

- **Unpredictable abnormal** response due to **genetic abnormality**.
- Occurs at **first exposure**
- **Examples:**
  - **Hemolytic anemia** in patients with **favism** (G6PD Deficiency)
  - Induced by **Primaquine**, **Aspirin**, and **Sulfonamides.**

B | Allergy (Hypersensitivity)

- **Unpredictable Abnormal** response to drugs due to immune reactions.
- **Drug** or its **Metabolites** may act as **antigen** or a **hapten**.
- **Hapten:** molecule that cant cause an allergic reaction by itself but causes an allergic reaction when it binds to **another carrier molecule**.
- **Cross Allergy** can happen between **chemically related** drugs (eg; Penicillins & Cephalosporins)
- Sometimes **Excipient** is the cause of allergy.
- Doesn't happen on **First Exposure** to drug **(IgE Mediated Only)**
- **IgE Mediated Reactions** may lead to drug resistance.
- **Management:** Don't reuse same or related drug again.

Type C: Chronic Effects

Effects of prolonged / continuous use of drug.

A | Tolerance

- **Lack** of drug sensitivity that responds to dose > therapeutic dose
- **2 Types: Congenital** (Inborn / innate) & **Acquired**

Congenital

- **Racial:** Black races tolerate mydriatic effect of ephedrine
- **Species:** Some herbivores tolerate ingestion of large amounts of **Atropine** without toxicity (unlike humans). This **MAY** be due to strong **atropinase**.
- **Inter-individual Variability:** Pharmacogenetics
  - Some humans need higher doses to achieve effect.
  - Possible Explanations:
    - **Kinetics**: ↓ Drug absorption or ↑ Elimination
    - **Dynamics**: ↓ Number of receptors / ↓ post-receptor signaling.
  - Examples:
    - Congenital **CYP2C19*** Deficiency → No activation of **clopidogrel** → **Triple** maintenance dose to **225mg** Daily.
    - Genetic mutation of **vitamin K epoxide reductase** → **Reduced** affinity to **warfarin** → requires doses **5x-20x** higher than average.

Acquired

- **Progressive** decrease of drug sensitivity due to **continued administration**.
- **Types:**
  - Cross-Tolerance: between similar drugs; eg: different types of nitrates.
  - Tachyphylaxis (**Acute Acquired Tolerance**): Rapid tolerance following a **few** doses over a **short** period.
- **Mechanisms of Acquired Tolerances:** Either due to **Kinetics** or **Dynamics**.
  - Kinetic Changes: ↓ Absorbance or **HME Inducers***
  - Dynamic Changes:
    - **Down-regulation** of receptors; eg: β2 or Opioid receptors
    - **Antibody formation**; eg: Insulin

Notes

- **CYP2C19** is a liver enzyme that is responsible for metabolism of 10% of all known drugs. it is an example of an **HME Inducer.**

B | Drug Dependence

- **3 Types: Habitual/Psychic** Dependence, **Physical** Dependence, and **Addictions**.

Habitual / Psychic Dependence

- The **Drive** for continuous administration of the drug to produce **pleasure**, sense of **well-being**, and **enhance cognitive functions** (attention & working memory)
- **Examples: Coffee / Tea**, **Smoking** (Now considered Nicotine Addiction)
- **Symptoms:** Lasting for **Short** period of time.
  - Anxiety & Depression • Dysphoria • Deteriorating Cognitive Function • Craving

Physical Dependence

- A state of body **Adaption** to drug presence → Abrupt stop of administration causes drug-dependent **withdrawal syndrome**.
- **Examples: Opioids** like morphine & **Amphetamines**.
- **Symptoms:** Depends on the drug.
  - Opioids: Muscle pain, anxiety, insomnia, lacrimation (increased tears), rhinorhea, sweating, diarrhea, dilated pupil, and high blood pressure.
  - Amphetamines: Sleepiness, fatigue, increased appetite, depression, cognitive decline, aches and pains.

Addiction / Substance Dependence

- **Neuropsychological** disorder caused by repeated use of a substance and consisting of a strong internal drive to use that substance.
- **Essential Features:**
  - Impaired control over substance use
  - Craving (Strong desire to use substance) often accompanies impaired control.
  - Increased Priority given to substance use over other aspects of life.
  - Tolerance, Physical dependence, and Withdrawal may be expected, however **impaired control** or **increased priority** should be present.

-- C -- Latrogenic Diseases

- **Any** drug induced **disorder** that **mimics** a natural disease.
- **Example:** Drug Induced Cushing Syndrome
  - Long-term use of **cortisol → Latrogenic Cushing Syndrome**
  - **Reversible** after drug discontinuation

Type D: Delayed Effects

Delayed effects appearing after long use, even after stopping drug.

A | Teratogenicity (Dysmorphogenesis)

- **Teratogen** is any agent that results in abnormalities in a fetus, or a child after birth, as result of maternal exposure.
- Highest risk during **First Trimester**.
- **Drug use during pregnancy also cause:**
  - Abortion, growth retardation, and pharmacological effects in neonates that are reversible.
  - Examples:
    - **Thalidomide → phocomelia** (Malformed short limbs)

B | Mutagenicity

- Induction of **gene mutations** in Somatic cells or germ cells.
  - **In Somatic Cells → Carcinogenicity**; eg: Sirolimus & Risk of skin cancer
  - **In Germ Cells → Infertility** or Teratogenicity

Type E: End of Use Effects

Adverse Effects after sudden stopping of drug after long use.

- **Abstinence Syndromes** of addicting drugs as **morphine**, **cocaine**, **barbiturate.**
- **Acute Addisonian Crisis** of chronic **Steroid** Therapy.
- **Worsening of Existing Disease:** • Myocardial infarction after beta blockers • Rebound Hypertension & clonidine • Withdrawal seizures & anti-epiliptics • Rebound Insomnia & hypnotics • Rebound nasal congestion & Decongestants

MediQ Academic Team
Dr. Moataz Alsharkawy
Dr. Nour Abuzeid

Drug Interactions

Overview

Drug Interactions are **altered pharmacological responses** due to **multiple drugs** acting **concurrently**

BENEFICIAL (Desired)

Obtained by combining drugs with different mechanisms or drugs that correct adverse effects of each other

Harmful (Undesired)

Can be predictable effect of one or both drugs (Type A reaction) or an unpredictable toxicity (Type B).

Types of Drug Interactions

1 Pharmaceutical (Outside Body)

Physical or chemical interactions between drugs before administration (in Vitro)

Example: mixing **ceftriaxone** (an antibiotic) to IV containing calcium (eg: Ringer's lactate) forms a precipitate)

2 Pharmacokinetic (Affects ADME)

A D M E

Affects the **Absorption**, **Distribution**, **Metabolism** (Biotransformation), and **Execretion** of drugs

3 Pharmacodynamic (Affects Drug Response)

Drug interactions occur at **sites of action, receptor sites** or **secondary physiological mechanisms**; leading to changes in drug responses.

Results of Drug Interactions

Addition / Summation (1 +1 = 2)	Resultant action **equals** sum of indivisual drug actions; eg: Aspirin + Paracetomol
Synergysm (1 + 1 > 2)	Resultant action **exceeds** sum of indivisual drug actions; eg: Cotrimoxazole (trimethoprim + sulfamethoxazol)
Potentiation (1 + 0 > 1)	One drug has no action but increases effect of another drug (>1) eg: Aspirin + Barbiturates
Reversal of Action	Adrenaline after Phenatolamine (α Blocker) → Hypotension
Antagonism	Occurs when using drugs of opposing actions

Pharmacokinetic Drug Interactions

- **Drugs affecting gut motility**: Motility (↑ by metoclopramide & ↓ by atropine) affects absorption of other drugs.
- **Drugs affecting gut pH**: Gastric acidity ↑ absorption of acidic drugs as aspirin & Intestinal alkalinity ↑ absorption of basic drugs as ephedrine & quinine.
  - Antacids such as calcium carbonate **inhibits** oral absorption of iron preparations.
- **Drug binding, adsorption or chelation**: **Tetracyclines** chelate metals (**Ca, Mg, Al & Fe**) and decrease their absorption.

- Drugs with **high affinity** to plasma proteins (eg; aspirin & sulfa) can displace other drugs bound to plasma proteins (eg; warfarin) leading to ↑ free concentration and toxicity.

- **Enzyme Induction:** HME **Inducers increase** metabolism of the inducer & co-administered drugs; eg: **phenobarbitone**, **phenytoin** & **tobacco smoking**.
- **Enzyme Inhibition**: HME **Inhibitors decrease** metabolism of their own & co-administered drugs; eg: **chloramphenicol** & **estrogen**.

- **Competition for active renal tubular secretion**:
  - **Probenecid** blocks excretion of weak acids; **penicillins**.

Changes in urinary pH:

- **Acidification** of urine by **ammonium chloride** ↑ excretion of basic drugs as **ephedrine**.
- **Alkalinization** of urine by **sodium bicarbonate** ↑ excretion of acidic drugs as **aspirin**.

Pharmacodynamic Drug Interactions

1 Interactions at Specific Receptor Sites:

(Phrmacological Antagonism → 2 Drugs 1 Receptor)

Types of Pharmacological Antagonism

A. Competitive Antagonism
(Antagonism displaced by excess agonist)

Example: Acetylcholine & Atropine (Muscarinic Receptor)

B. Non-Competitive Antagonism
(Antagonism not displaced by excess agonist)

Reversible	Irreversible
Block end by Metabolism of Antagonist	Bind **Covalently**, block end by resynthesis of receptor
eg: Succinylcholine	**eg:** Phenoxybenzamine

2 Interactions on the Same Physiological System:

Caffine antagonizes CNS Depressant effect of barbiturates

3 Interactions Involving Combined Toxicity:

Combined use of 2 or more drugs with toxic effects on the same organ can greatly increase organ damage.
Example: Use of 2 nephrotoxic drugs (eg; Aminoglycosides & Cephaloridine)

Types of Antagonism

1 Chemical Antagonism

One drug reacts chemically with an active drug forming an inactive compound.

Example: Neutralization: HCl + $NaHCO_3$.

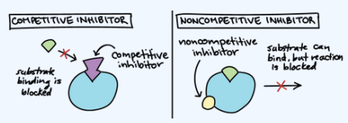
2 Physiological Antagonism

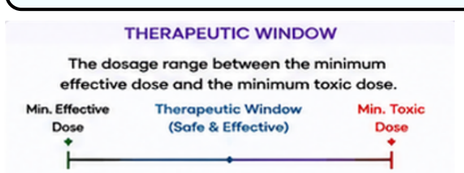
Two agonists acting on 2 different receptors producing opposite actions

Example:
Adrenaline (β2) → bronchodilatation +
Histamine (H1) → bronchospasm

3 Pharmacological Antagonism

Two different drugs acting on 1 receptor
Types: Competitive / Non-Competitive





Therapeutic Index

$TI = LD_{50} / ED_{50}$

LD50 = Dose lethal in 50% Cases
ED50 = Dose effective in 50% Cases
TI is a measure of a drugs safety. Higher TI indicated wide margin between effective and lethal doses → Safer drug

Median Lethal Dose

LD_{50} = Fatal dose in 50% of Cases (Kills 50% of Animals)

Uses of LD_{50}

- Measure of acute Toxicity
  (Smaller LD50 = More Toxic)
- Determine therapeutic index and safety margins
- Clinical trials usually start with 1/10 LD_{50}

Key Formulas

$LD = Vd \times Css$

$MD = Cl \times Css \times Tm$

VD: Volume of Distribution
Css: Desired Plasma Conc.
Cl: Clearance **Tm**: Dosing Interval

Core Drug Doses

- **Therapeutic Dose**: Average dose required to produce therapeutic effect (Adult male: 20-60yrs, 70kgs)
- **Loading Dose (LD)**: Initial large dose to build up therapeutic blood level
- **Maintenance Dose (MD)**: Repeated doses at regular intervals to maintain therapeutic blood level
- **Minimal Effective Dose**: Lowest dose to produce therapeutic effect
- **Maximal Tolerated Dose**: Largest dose without toxic effect.