DENT 3005:Introduction to Pharmacology

Pharmacokinetics

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Acknowledgement: Sheetal Maria Rajan

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Acknowledgement of country

The University of Western Australia acknowledges that its campus is situated on Noongar land, and that Noongar people remain the spiritual and cultural custodians of their land, and continue to practise their values, languages, beliefs and knowledge.

Artist: Dr Richard Barry Walley OAM

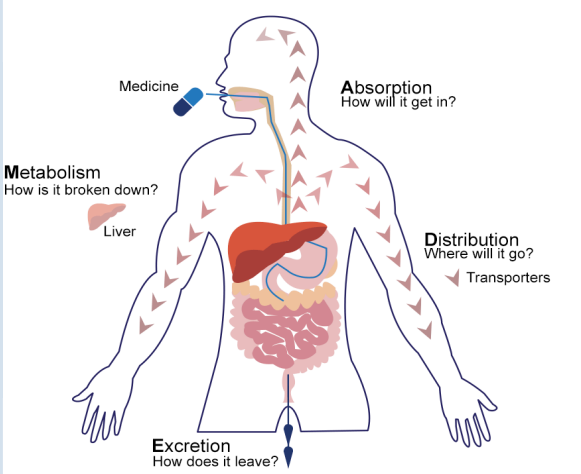
Learning outcomes

Broad

- *Understand the pharmacokinetic factors influencing drug-receptor interactions, and the nature of these effects on physiological response profiles*

Specific topics we will cover

- Different types of drug names
- Difference between pharmacodynamics and pharmacokinetics
- Drug absorption
- Drug distribution
- Drug metabolism
- Drug excretion
- Key pharmacokinetic factors



DENT3005: assessment breakdown

Assessment #	Assessment Task	Weight %	Assessment Period/ date	Module assessed	Waiver
1	SAQ	50%	30/09/25 9AM – 11AM	General Medicine and Pharmacology: all lectures content	No
2	MCQ	50%	Main Campus: Semester 2 examination period	General Medicine and Pharmacology: all lectures content	No

Recommended readings

1) NPS MedicineWise. Prescribing Competencies Framework: embedding quality use of medicines into practice (2nd Edition). Sydney, 2021 - https://www.nps.org.au/assets/NPS/pdf/NPS-MedicineWise_Prescribing_Competencies_Framework.pdf

2) Prescribing medicines in pregnancy database [Therapeutics Goods Administration] - https://www.tga.gov.au/prescribing-medicines-pregnancy-database

3) Drugs and Lactation Database (LactMed) - https://www.ncbi.nlm.nih.gov/books/NBK501922/

4) Rang & Dale's Pharmacology 9th Edition

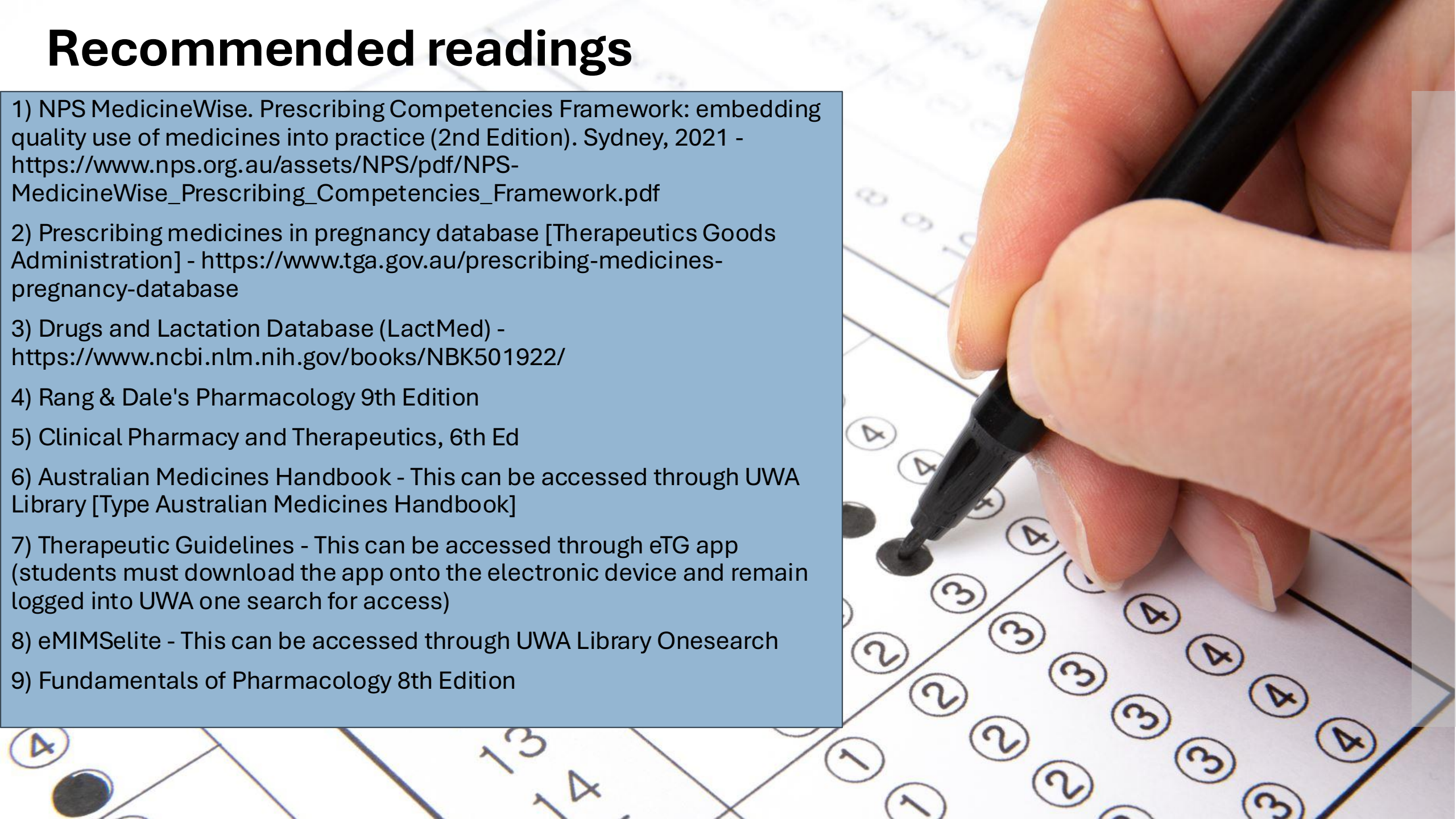
5) Clinical Pharmacy and Therapeutics, 6th Ed

6) Australian Medicines Handbook - This can be accessed through UWA Library [Type Australian Medicines Handbook]

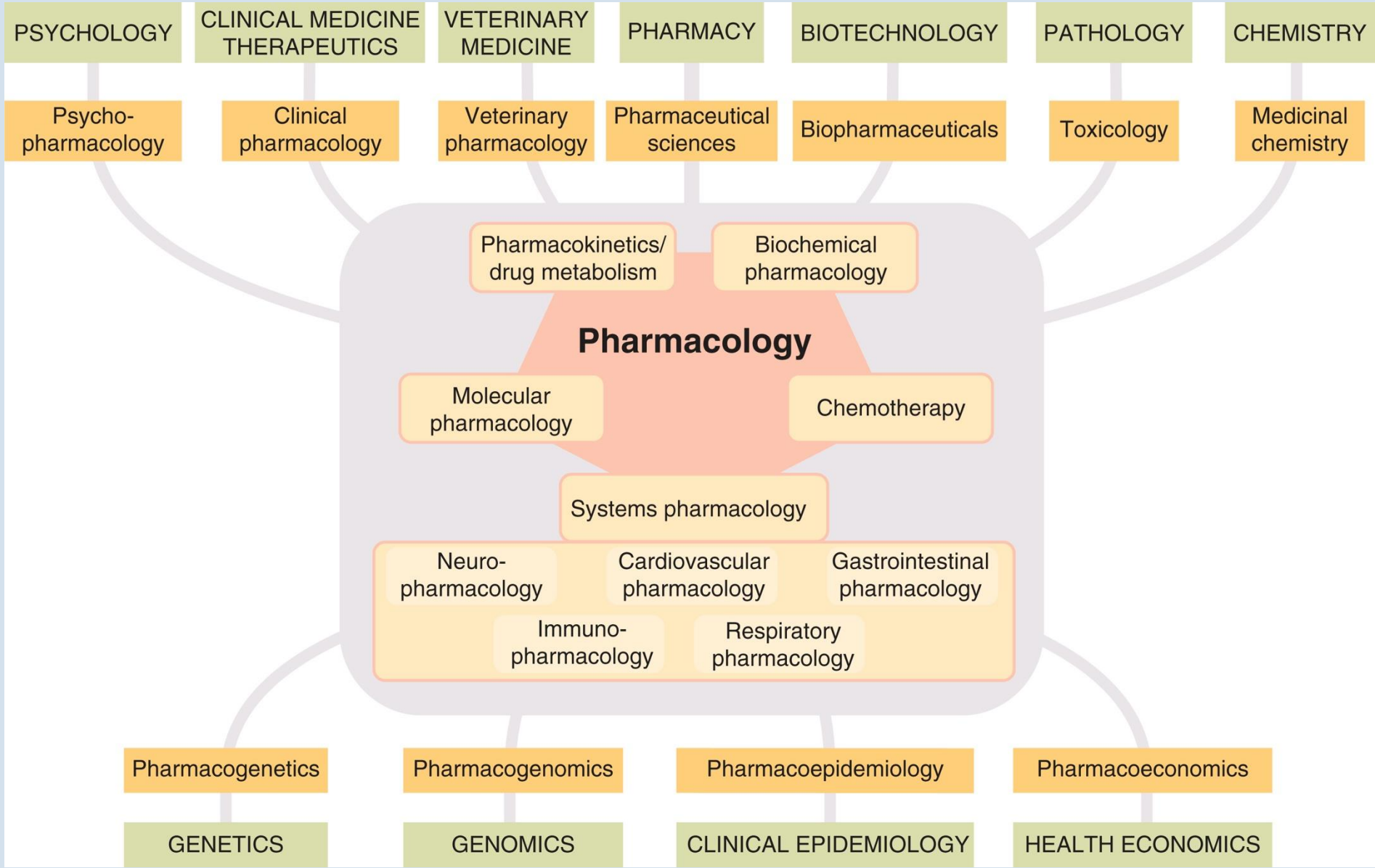
7) Therapeutic Guidelines - This can be accessed through eTG app (students must download the app onto the electronic device and remain logged into UWA one search for access)

8) eMIMSelite - This can be accessed through UWA Library Onesearch

9) Fundamentals of Pharmacology 8th Edition



What is pharmacology?

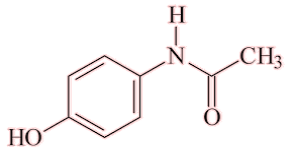


Rang & Dale's Pharmacology, Tenth Edition

Types of drug names and which one to use while prescribing?

Chemical name

- Describes the chemical structure of drugs
- Often complex



N-(4-Hydroxyphenyl) acetamide

Generic name (Most commonly used)

- Simplified drug names – often have roots & endings that provide clues to their origins, use, actions, or structure

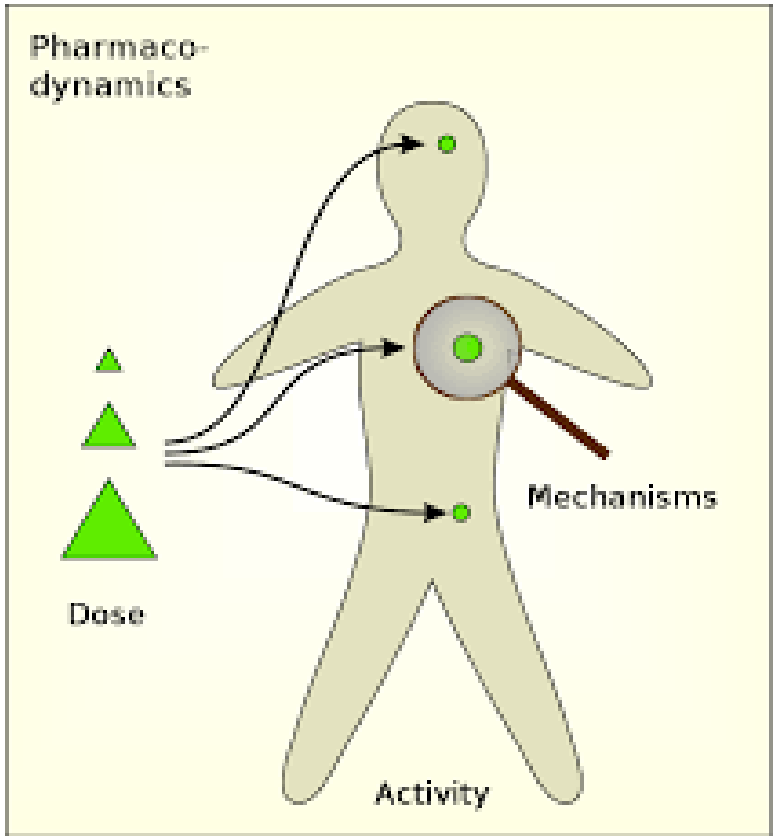
- *E.g. ibuprofen, ketoprofen, naproxen…*

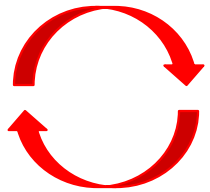
Brand name (Trade/Proprietary names)

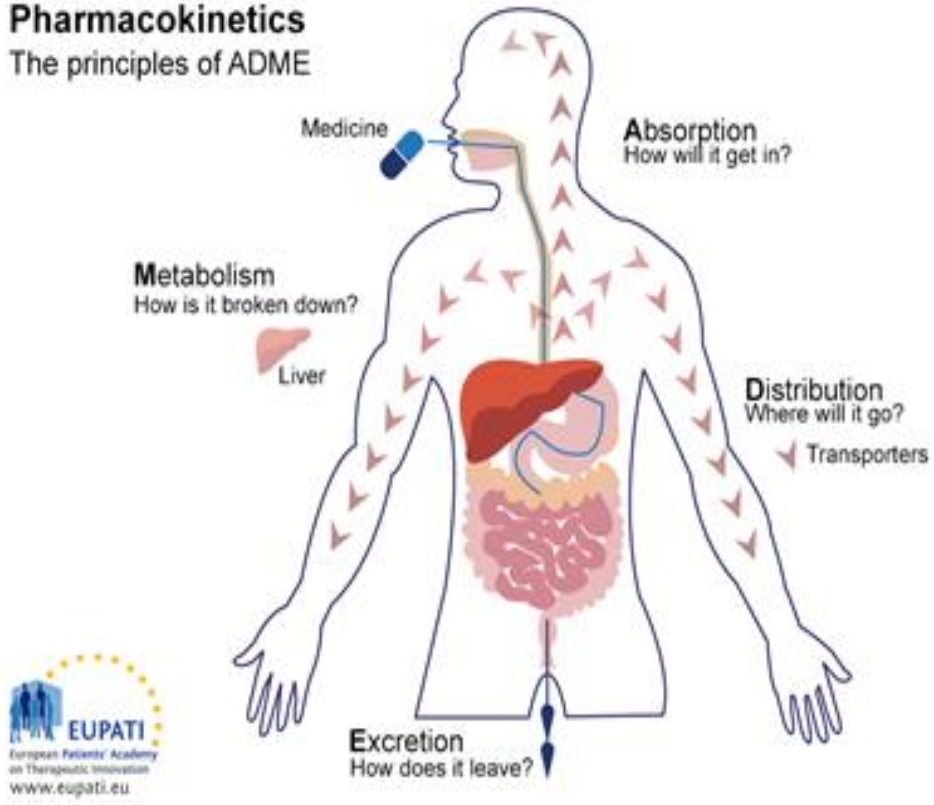
- Invented by drug companies
- Intended to be catchy and memorable

Panadol, Tylenol

Pharmacodynamics *vs.* Pharmacokinetics







Pharmacodynamics = What the DRUG does to the BODY

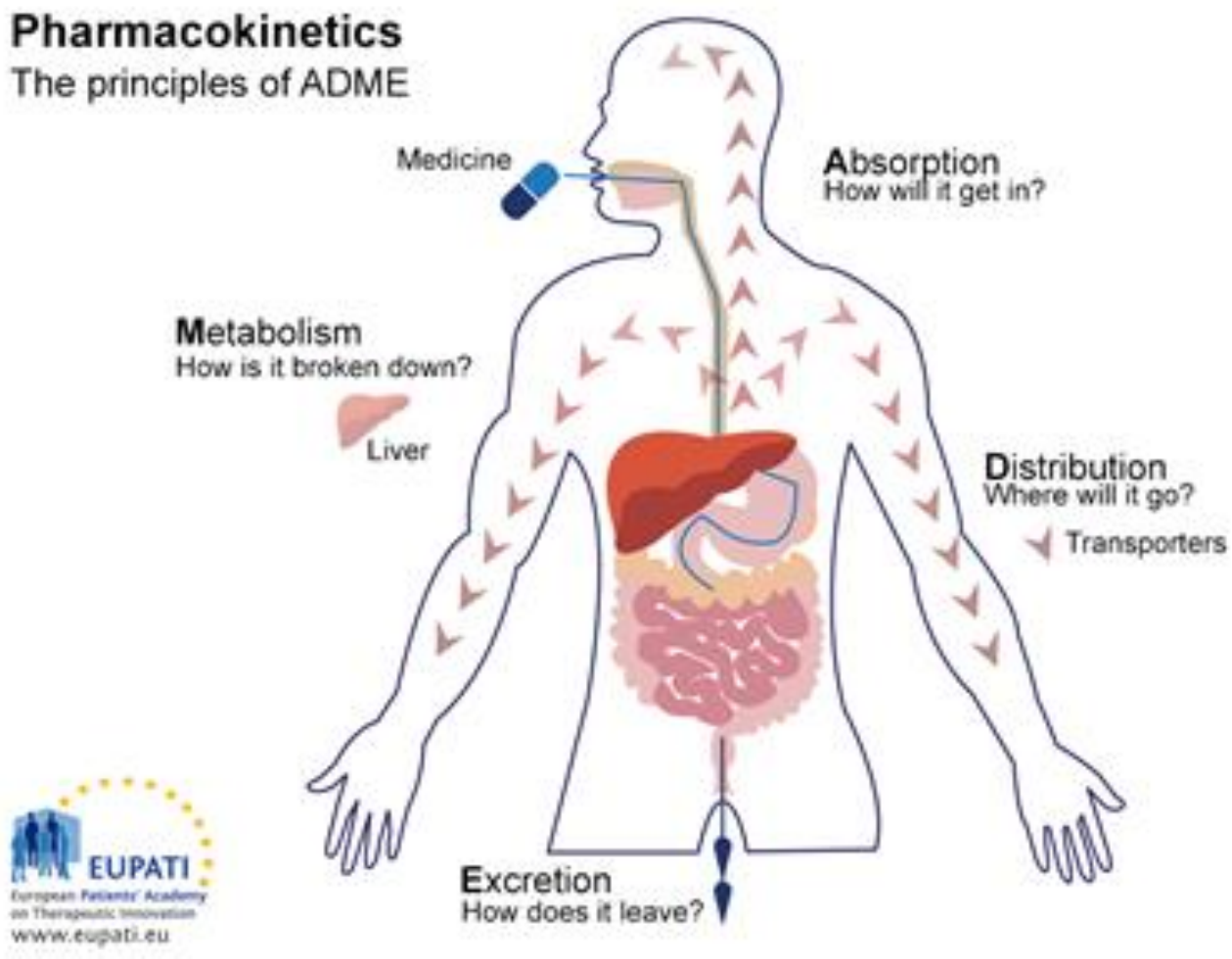
Pharmacokinetics = What the BODY does to the DRUG

Other considerations

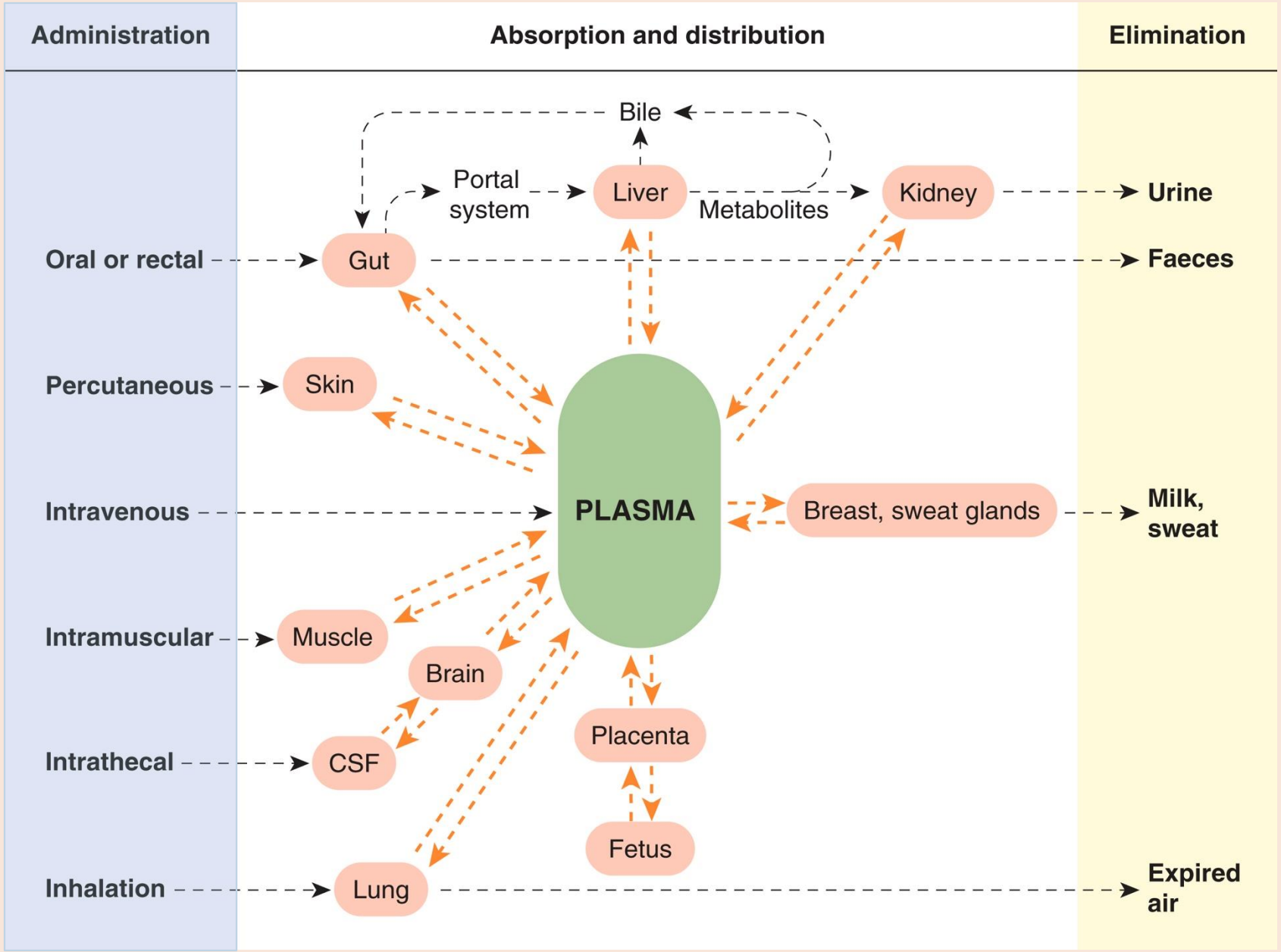
1. Efficacy
2. Selectivity
3. Safety
4. Predictability
5. Reversible actions
6. Interactions
7. Stability
8. Administration
9. Name

Pharmacokinetics

1. Absorption
2. Distribution
3. Metabolism
4. Excretion



Routes of drug absorption



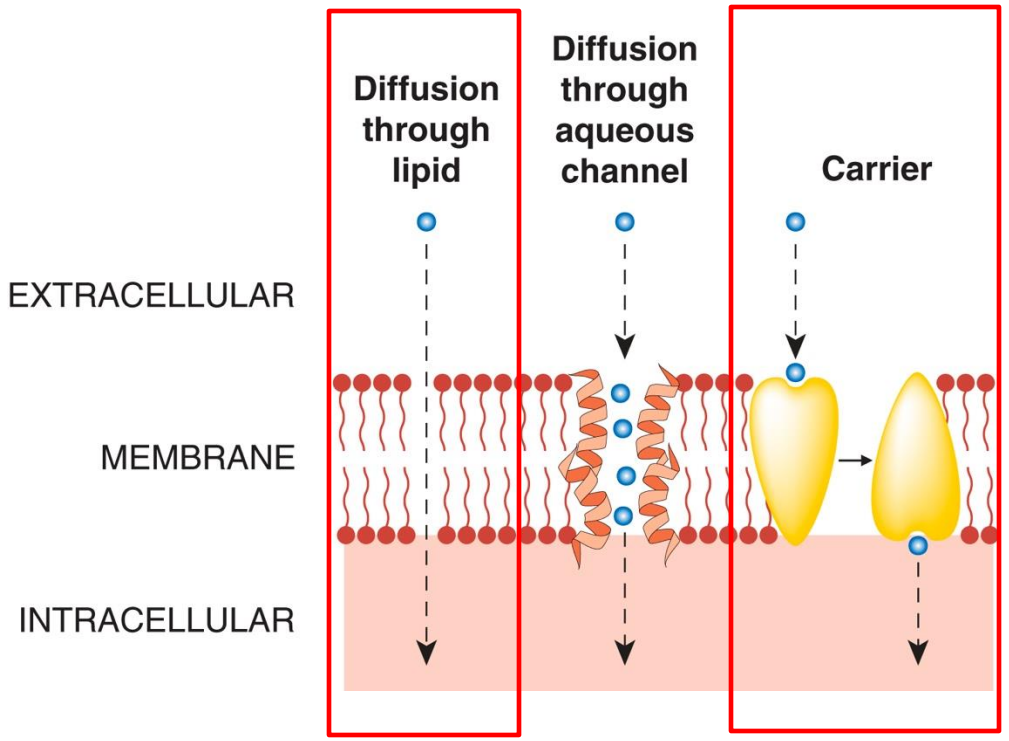
Rang & Dale's Pharmacology, Tenth Edition

Absorption

- The transfer of drugs from the site of administration into the systemic circulation.

How does it cross the cell membrane?

- **Filtration** – Paracellular uptake → Small molecules
- **Passive diffusion** – Transcellular uptake → Lipophilic
- **Facilitated diffusion by carrier proteins or transporters** →Efflux and/or Influx
- **Pinocytosis**



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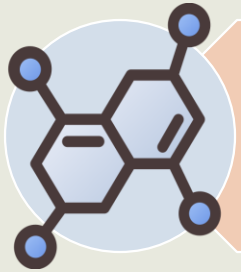
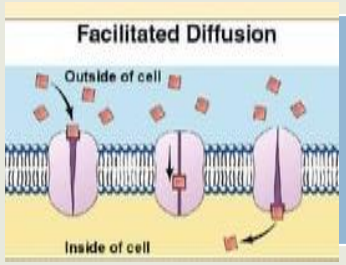
Factors affecting drug absorption



Size (Molecular weight)

Solubility

Polarity / Charge

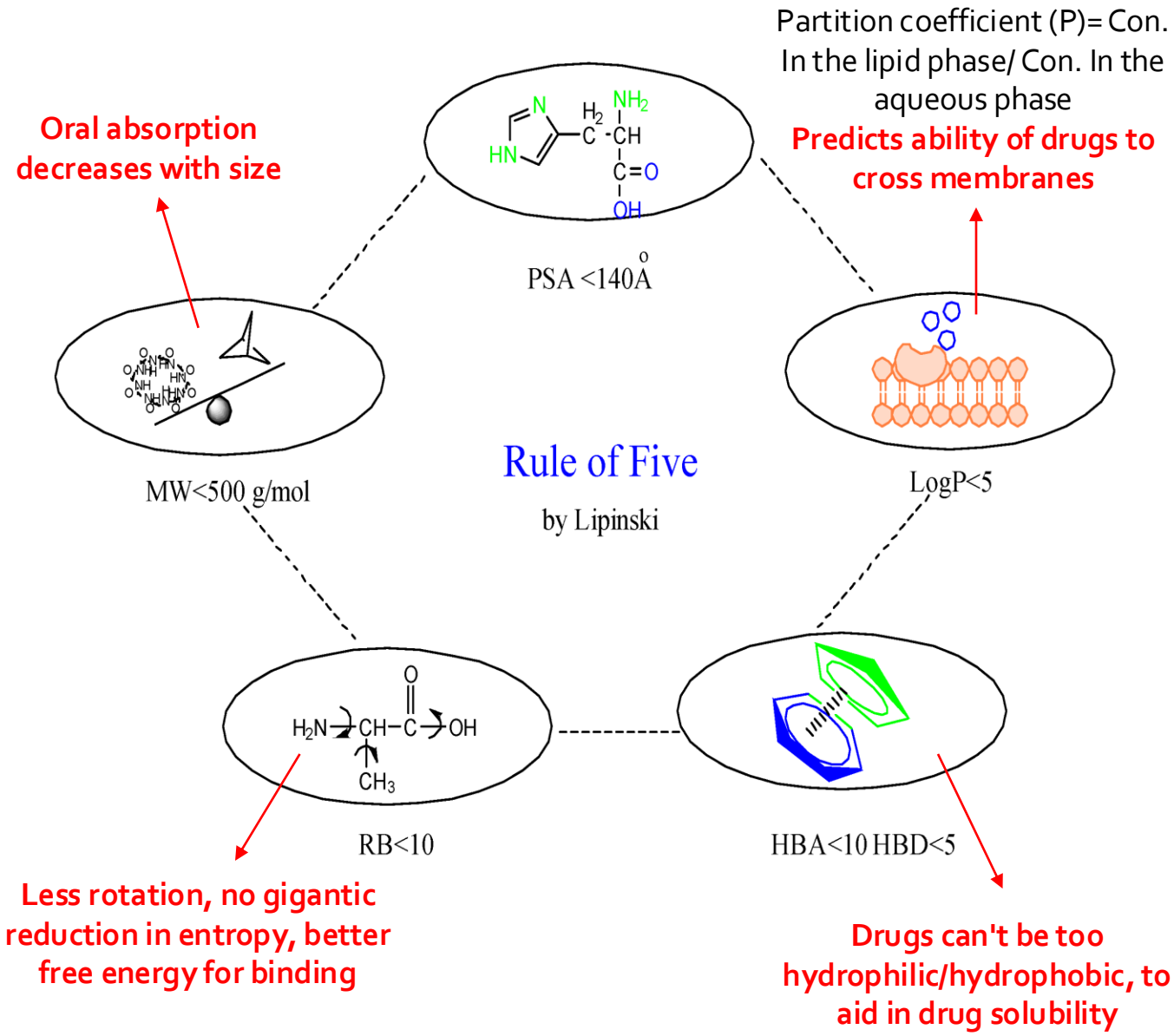


Transporters

Ideal drug properties to enhance optimal oral absorption

According to Lipinski's rule:

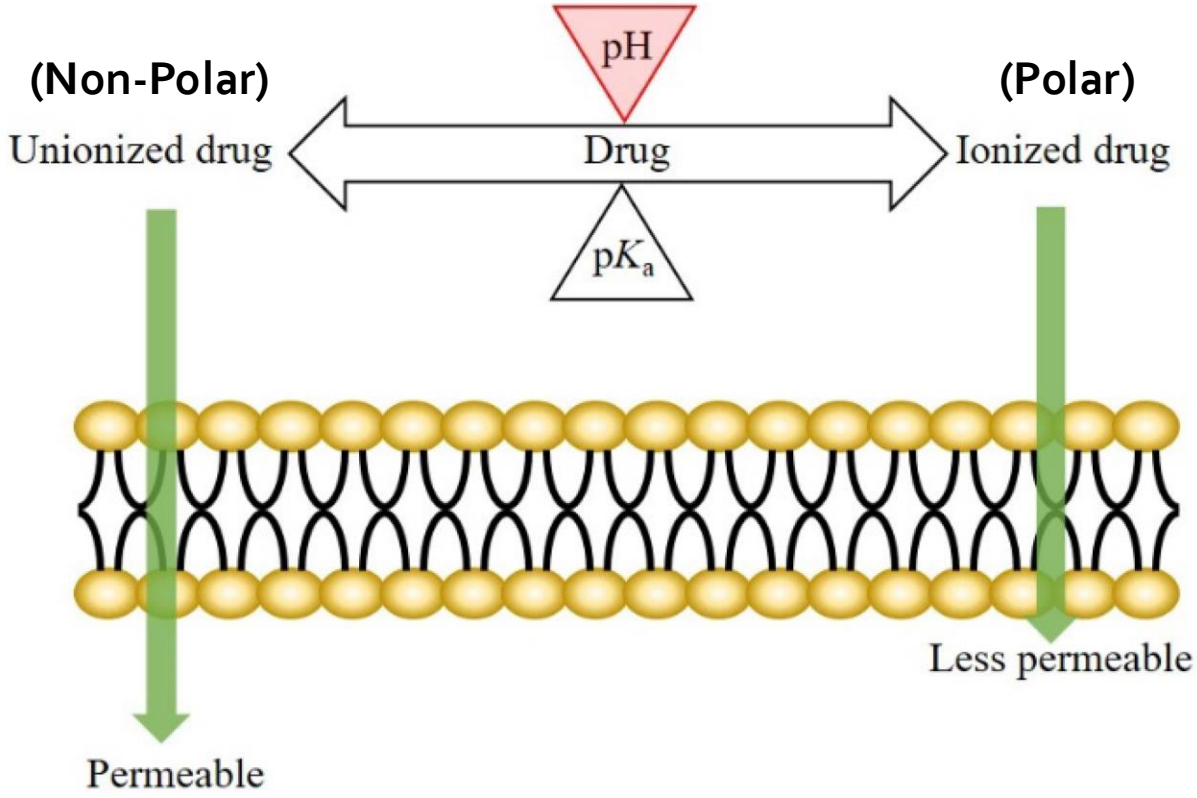
- No more than 5 hydrogen bonds
- No more than 10 hydrogen bond
- A molecular mass less than 500 Daltons (g/mol)
- An octanol-water partition coefficient log P<5
- <5 freely rotating bonds (RB)



Importance of pH!

MOST drugs exist as a weak acid or weak base

- **Acid vs Base**
  - Weak acids → negatively charged
  - Weak bases → positively charged
- **Varying pH** in different body compartments → shift in ionised or unionised states
- **Remember:** passive diffusion through membranes
  - Charge state affects absorption
- **pKa:** the pH value at which 50% of the drug is ionised



	Acid drug	Basic Drug
Acidic Environment	Non-ionised**	Ionised
Basic Environment	Ionised	Non-ionised**

Rang & Dale's Pharmacology, Tenth Edition

Strong acid in water

$HCl \rightarrow H^+ + Cl^-$

Unionized — Ionized

Strong base in water

$NaOH \rightarrow Na^+ + OH^-$

Unionized — Ionized

Strong acids/bases – Complete dissociation – highly ionized, hence poorly absorbed

Weak acid in water

$R\text{-}COOH \rightarrow R\text{-}COO^- + H^+$

Unionized — Ionized

Weak acids/bases – incomplete dissociation – unionized, absorbed

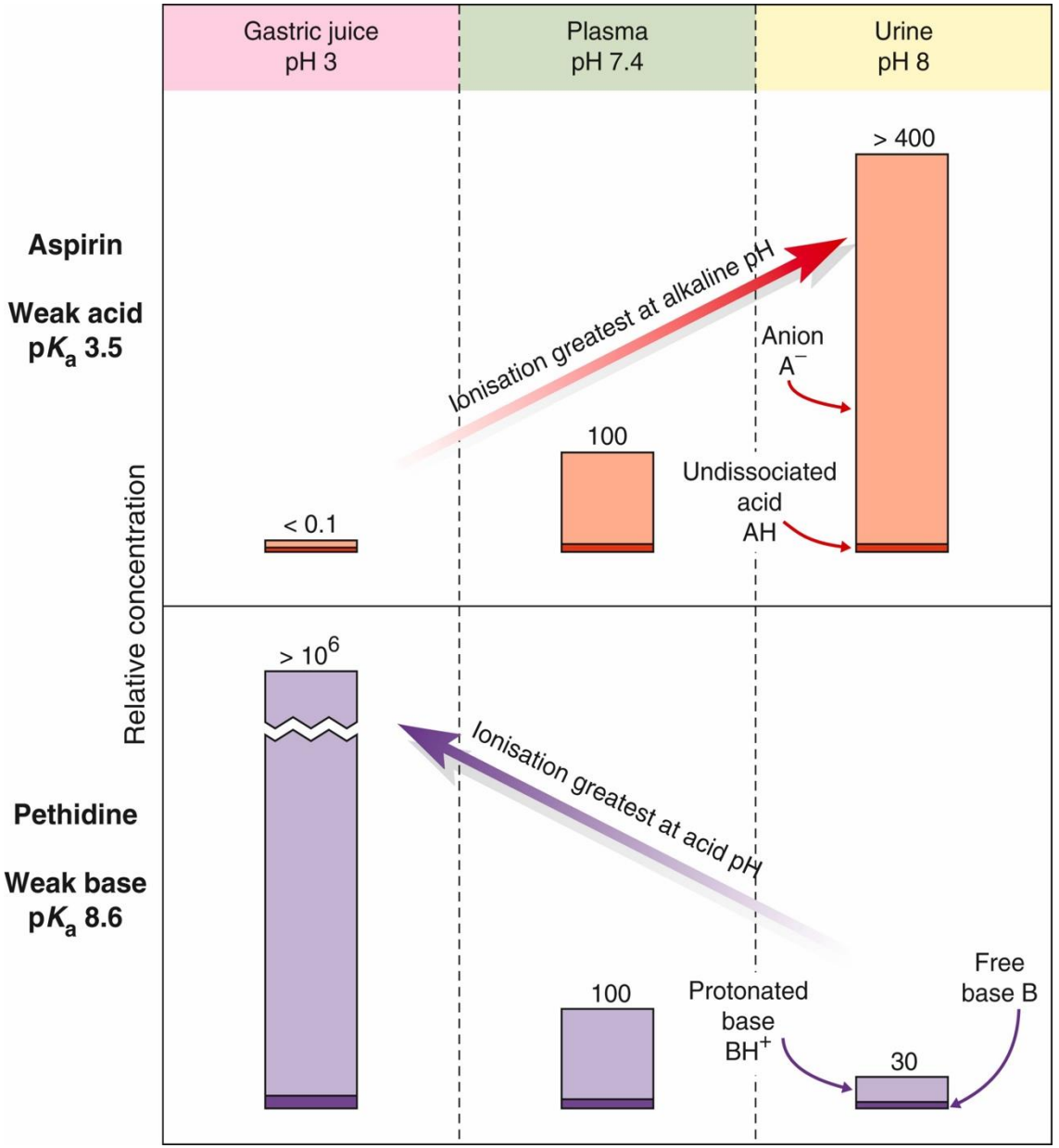
Weak acid in acidic medium

$R\text{-}COOH \not\rightarrow R\text{-}COO^- + H^+$

Unionized — H^+ — Ionized

The H+ ions will prevent the dissociation of a weak acid into ionized forms

Increased unionized form, increased conc. for absorption



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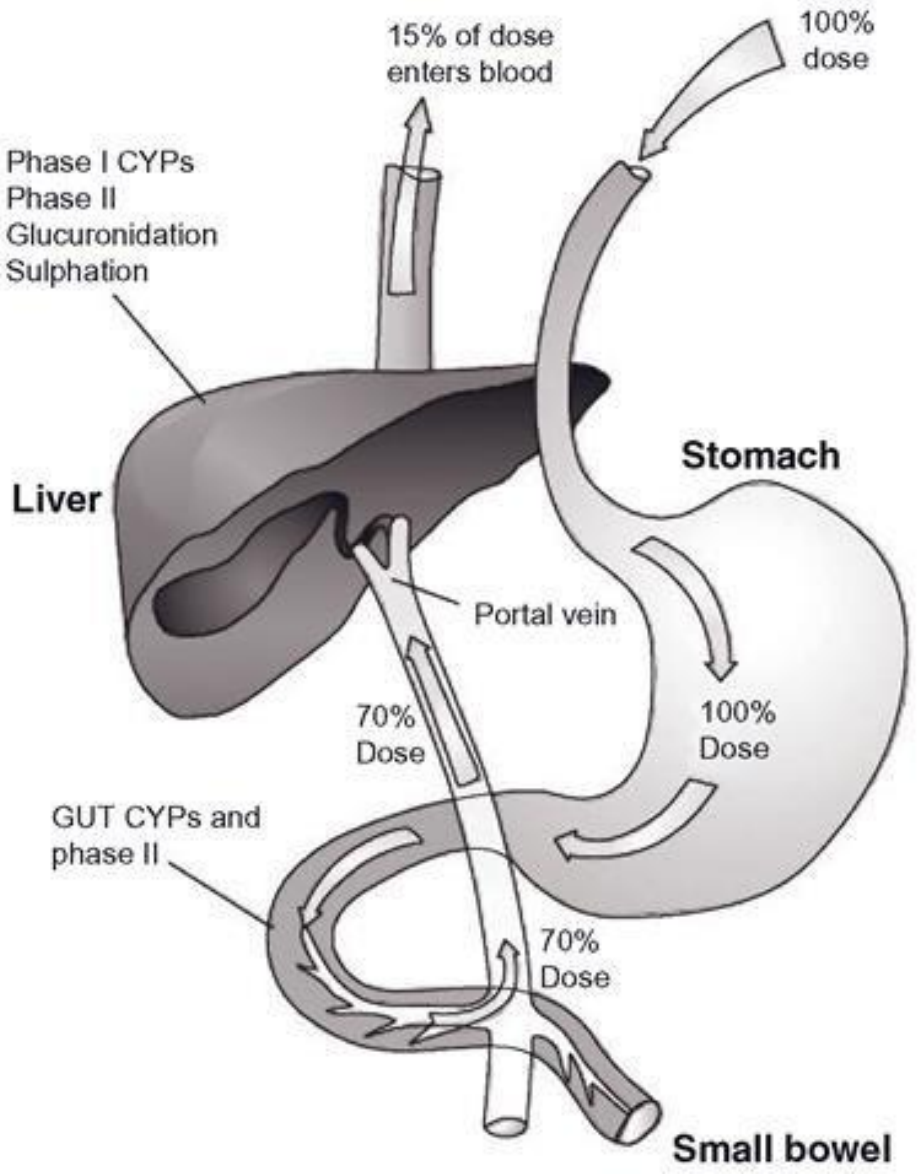
First pass effect & GI absorption



Drug properties

1) Size (MW)
2) Solubility
3) Polarity/charge
4) Formulation (capsules, enteric coating)

Physiological properties

1) Gut content
2) GI motility
3) Splanchic blood flow
4) Physicochemical interactions with gut contents
5) Genetic polymorphism

Transdermal delivery (TDD) Skin Patches: Gendelberg *et al*

Other considerations

Bioavailability

- *The fraction (F) of an orally administered dose that reaches the systemic circulation*
- Depended on enzyme activity of gut wall/liver, gastric pH, intestinal motility…
- Relates to proportion of drug reaching the systemic circulation, neglecting the rate of absorption

Bioequivalence

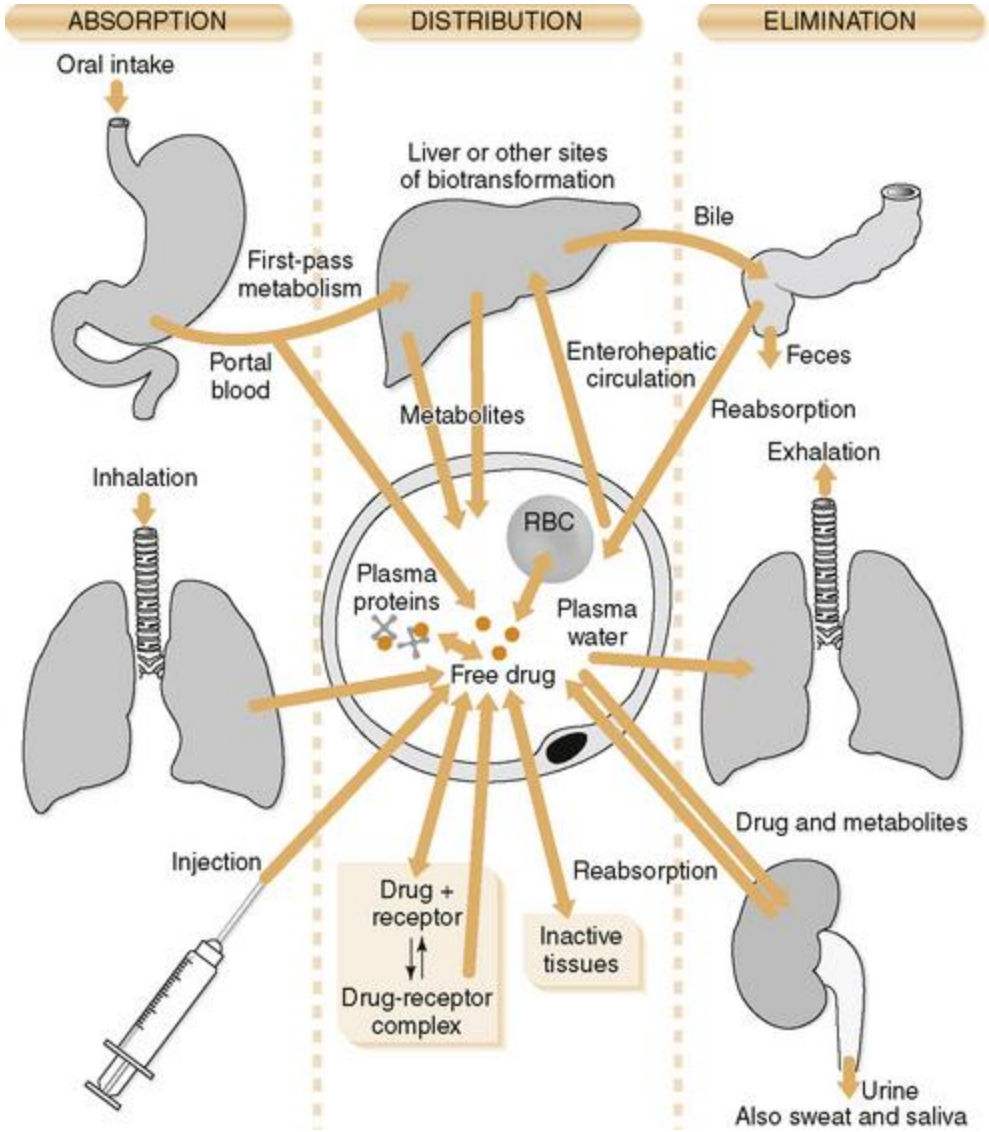
- Generic equivalents of patented products
- If we substitute one formulation for another, no clinically untoward consequence will occur

Review!

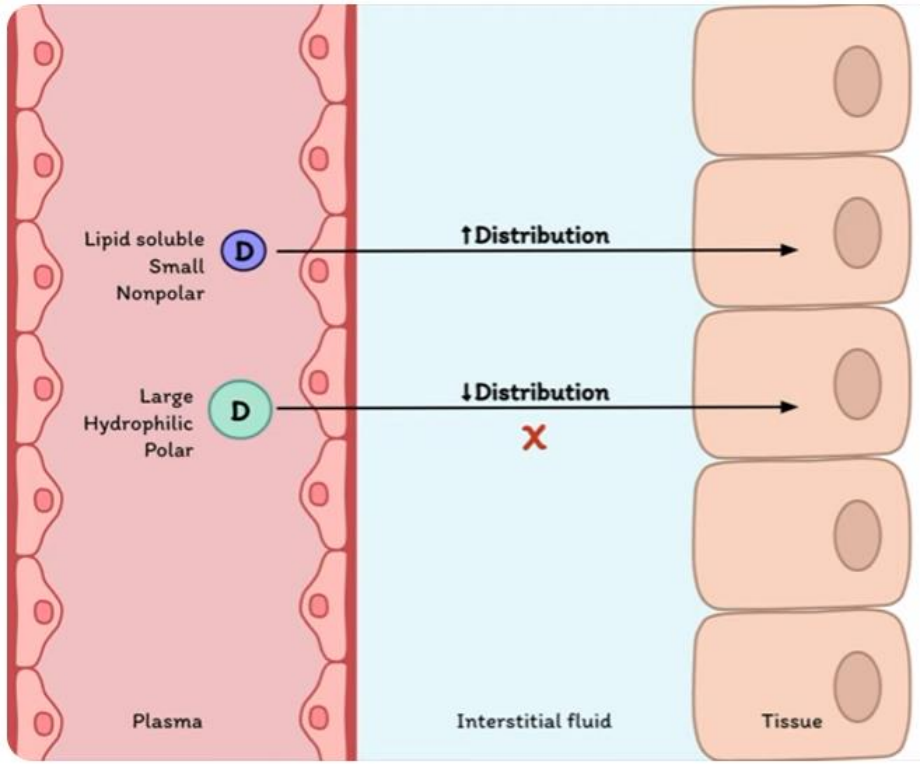
Distribution

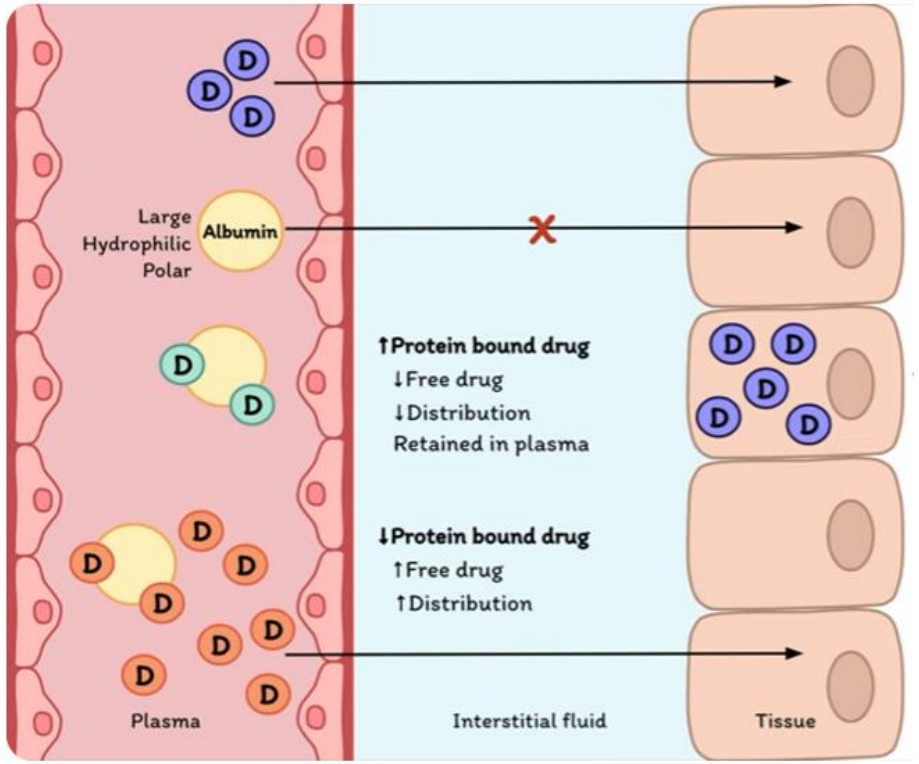
- The reversible transfer of a drug from one location (*e.g. blood*) to another (*e.g. heart, brain, or lung tissue*).

- Following absorption → drugs are dispersion
- Doesn't occur equally
- Passive diffusion
- COMPLEX



Factors affecting distribution





Solubility

- Lipophilic drugs readily cross & penetrate all tissues

Blood flow

- ↑ **Blood flow**

↑ **Distribution** (*heart, liver, kidneys*)

- ↓ Blood flow

↓ Distribution (*skin, adipose tissue*)

Plasma protein binding

- Plasma or tissue
  free drugs /affinity for binding sites/protein
- **Unbound drug → active**

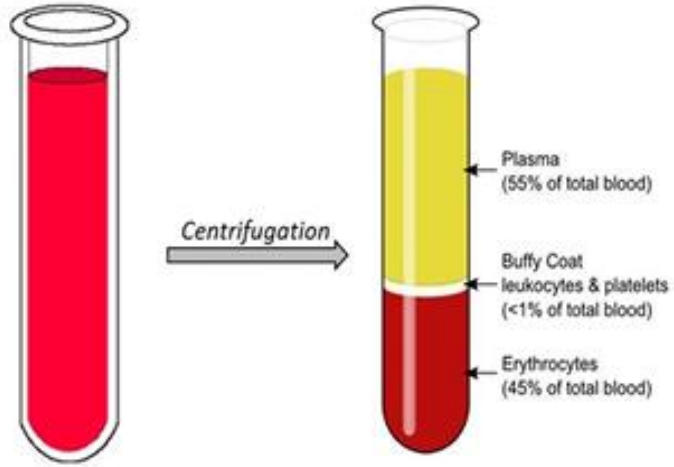
Tissue binding

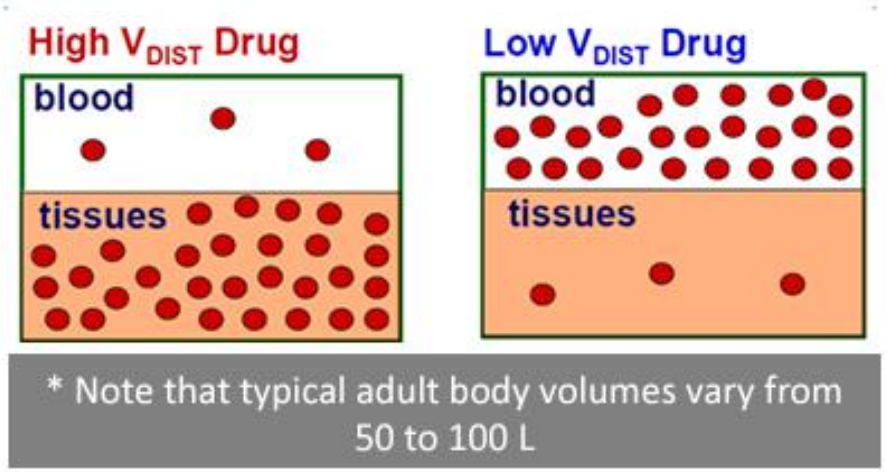
- **↓Plasma concentration ↑Distribution in tissues**

Drug distribution, EKG Science

The Volume of Distribution (V)

- **V = Dose (mg) / Plasma concentration (mg/L)**
- Diffusion of drugs to other compartments
- Approximate volume of plasma in 70Kg adult: 3L
- Vd ≤ 0.04L/kg → distribution in plasma
- Vd ≤ 0.57L/kg → distribution in ECF
- Vd larger → distribution in tissue
- Clinical use
  - Gives an idea of amount distributed in body
  - If Vd is low, haemodialysis successful
  - Calculate initial or loading dose





Other considerations

Blood brain barrier

- Very tight junctions between capillary and endothelial cells
- Impenetrable … almost
- Defense mechanism

Blood placental barrier

- Regulates transfer of molecules between and maternal circulation
- Fetal harm
- Check pregnancy!

Review!

What are some factors affecting distribution?

Which drugs will be tissue bound?

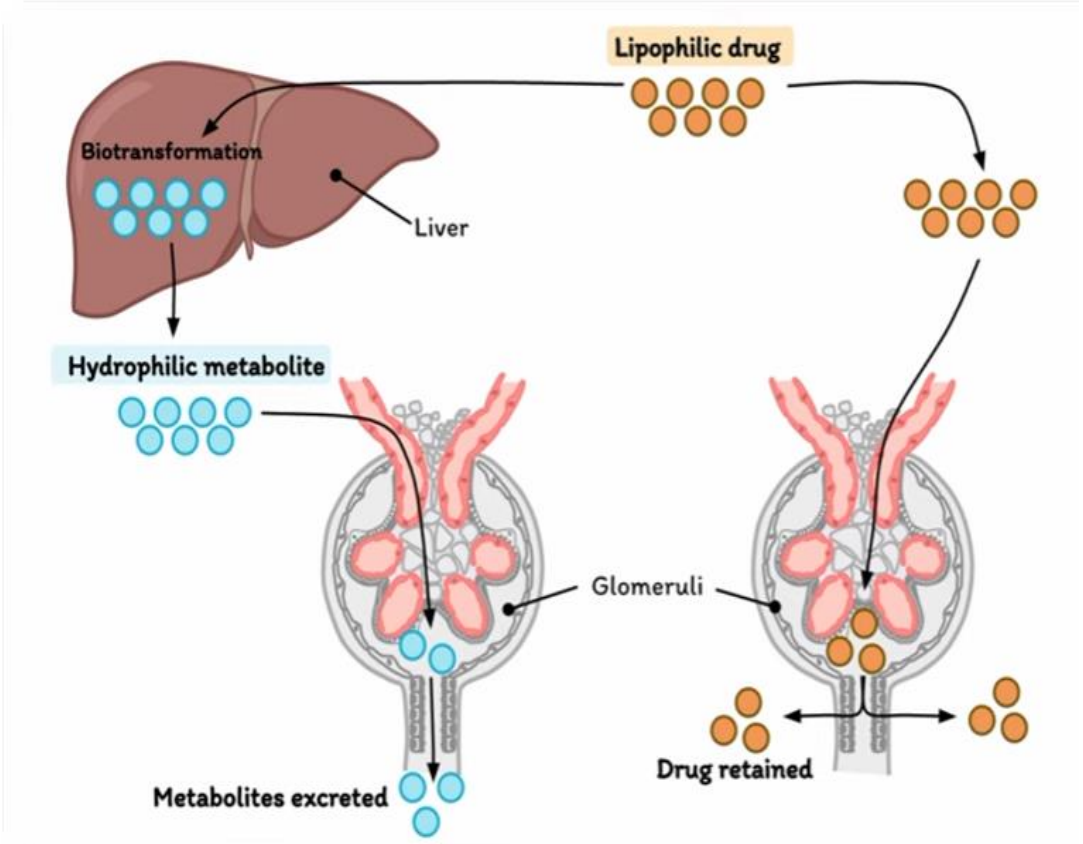
a) Phenytoin Vd = 0.7L/kg
b) Metoprolol Vd = 4L/kg
c) Fluoxetine Vd = 35 L/kg
d) Chloroquine Vd = 185L/kg

Which drug would be effectively treated with haemodialysis?

what important consideration when a patient is pregnant?

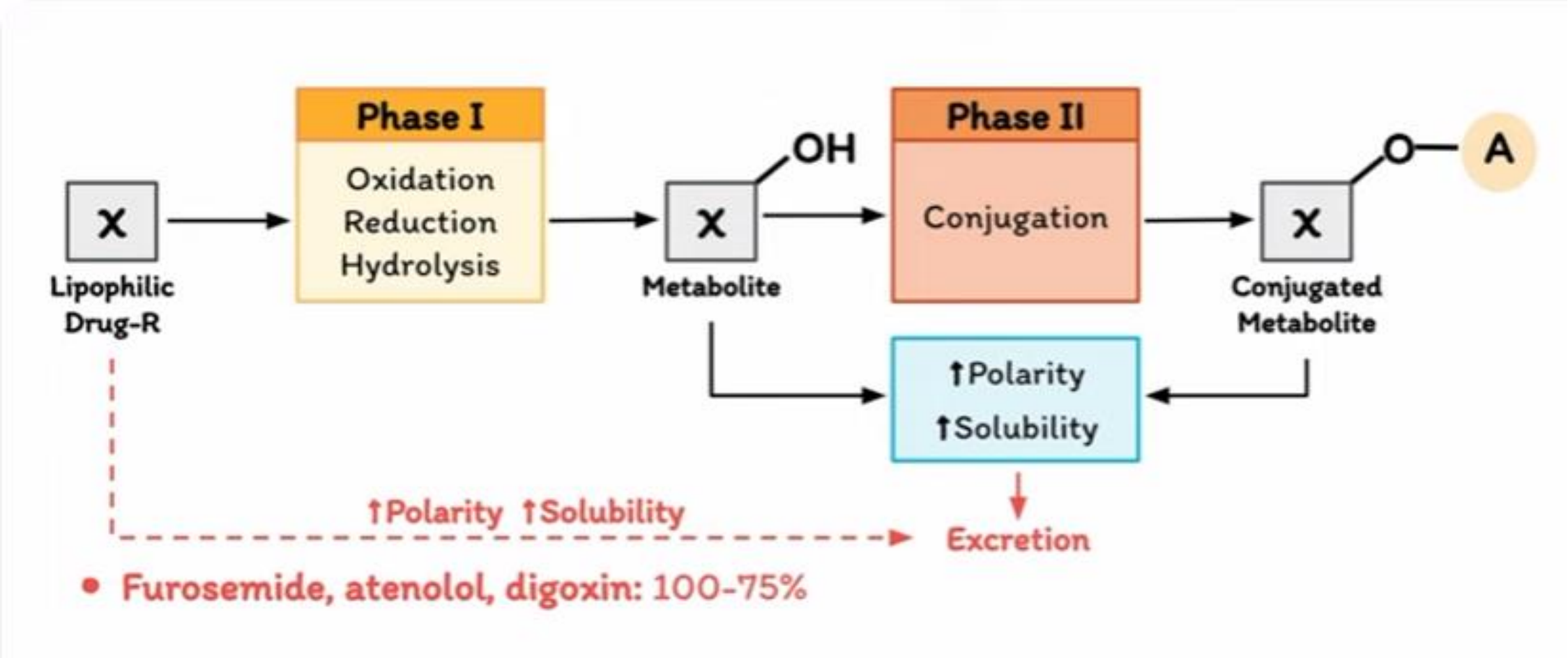
Metabolism (*Biotransformation*)

- The chemical alteration (i.e. structural modification) of drugs and foreign chemicals (xenobiotics) by drug-metabolizing enzymes (DME) in the body.
- **Make drug made more polar & water-soluble** (↓ logP)
- Facilitates excretion
- Metabolism usually decreases the half-life of drugs (e.g. blood or plasma $T^{1/2}$)
- Usually reduces biological activity
- Pro-drug – inactive drug becomes active, after body processes it (e.g codeine into active morphine by liver enzymes)



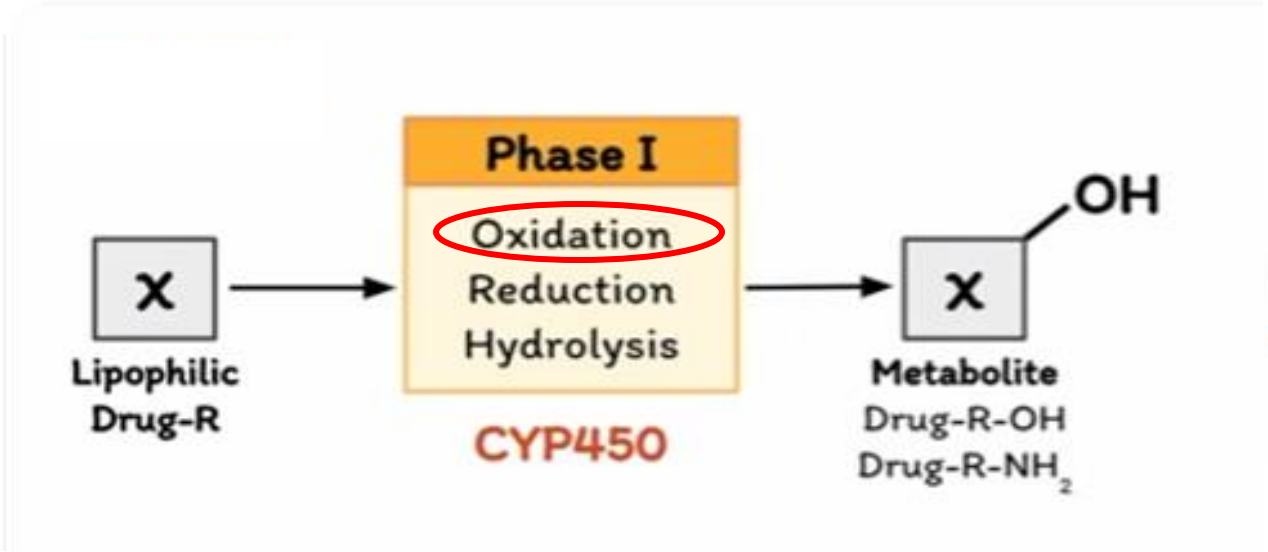
Drug metabolism, EKG Science

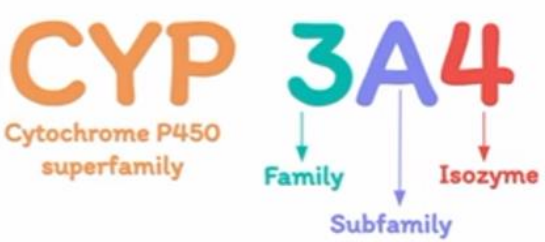
Phase I & Phase II metabolism



Lipophilic drugs are changed into more **polar** molecules; since **water-soluble** drugs can be readily **excreted** by the body

Phase I metabolism





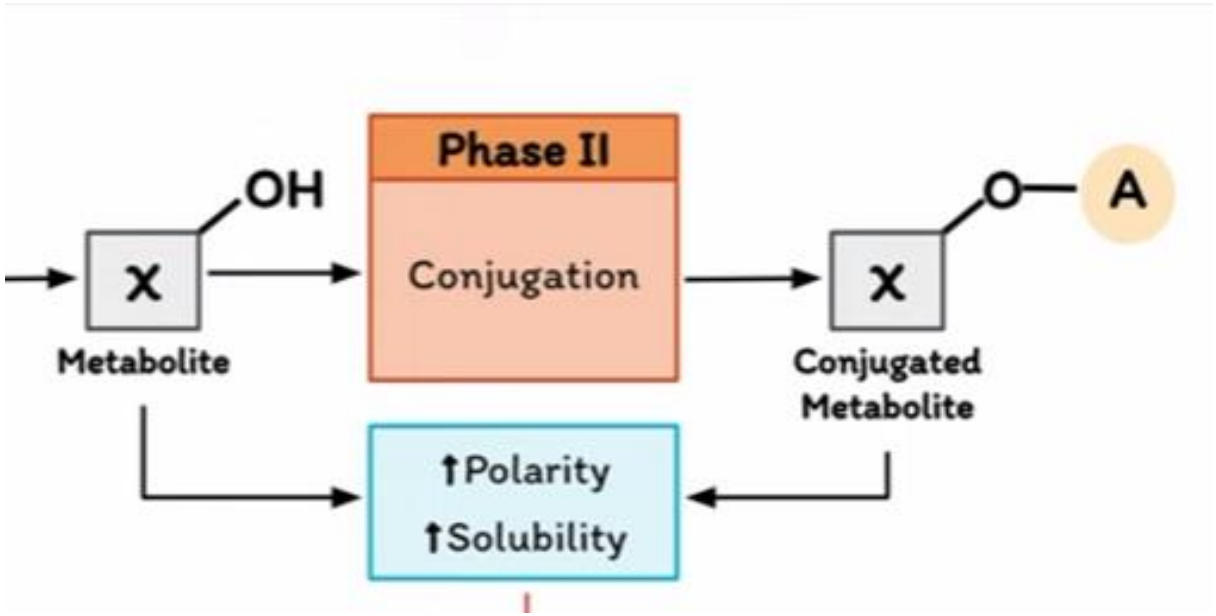
Oxidation, **reduction, hydrolysis** → active product
Main mechanism of metabolism is through **cytochrome P450 (CYP450)** system

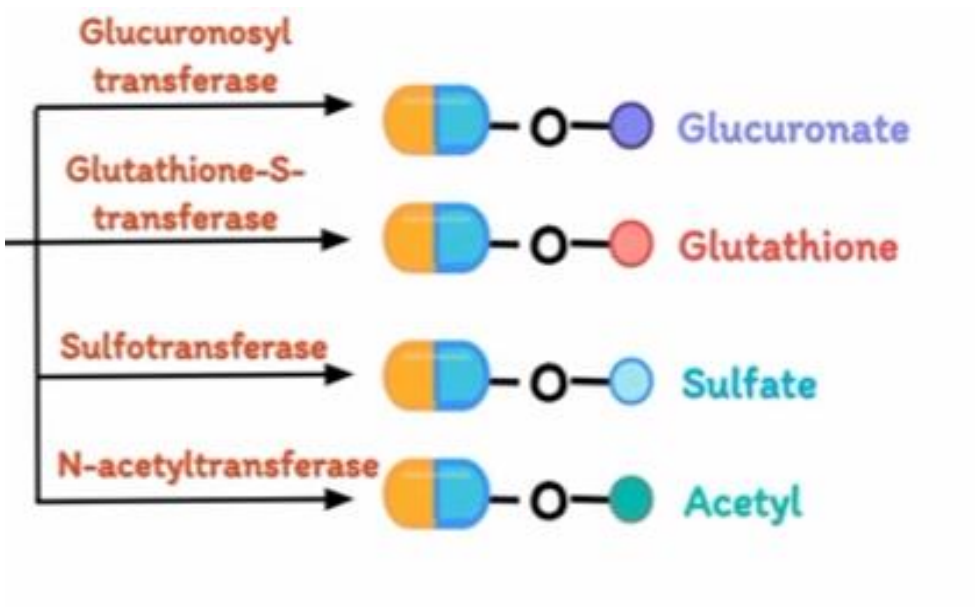
- Heme-containing enzymes
- CYP3A4 & CYP2D6

Genetic polymorphism may play a role in CYP (by causing variation in the enzyme levels)

- CYP3A4: Most abundant CYP in liver and gut wall

Phase II metabolism





Conjugation → inactive product
Mainly in liver
Groups inserted: glucuronyl, sulphate, methyl, acetyl
Result: polar product → excretion in urine

Other considerations

Concentration and types

- Genetic polymorphism
- Amount of enzymes
- Types of enzymes

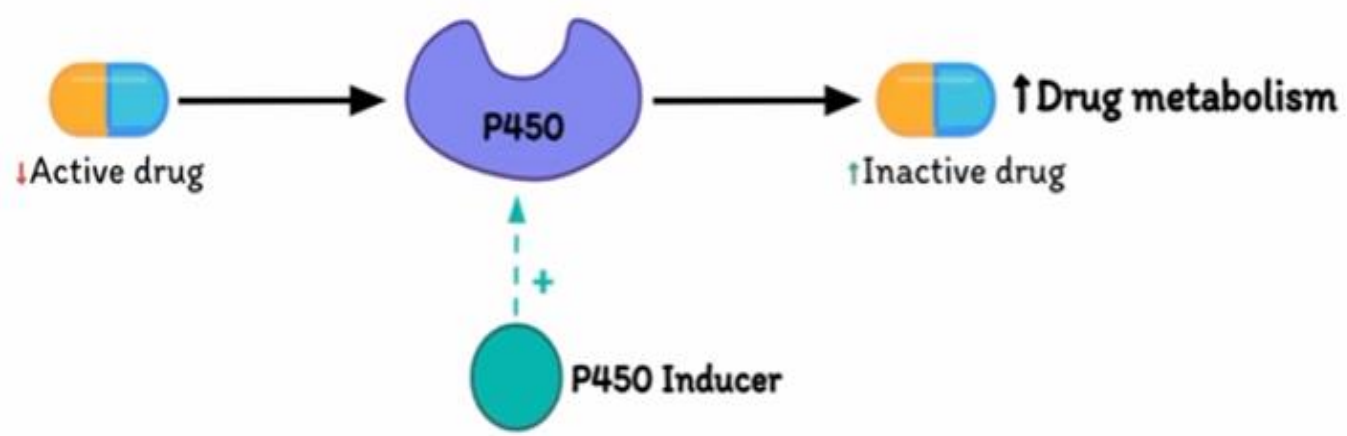
Depot binding

- Coupling of drugs with inactive sites of body → drug inaccessible for metabolism
- Eg. Highly lipid soluble drugs binding in adipose tissue will have metabolism drastically reduced

Enzyme induction/inhibition

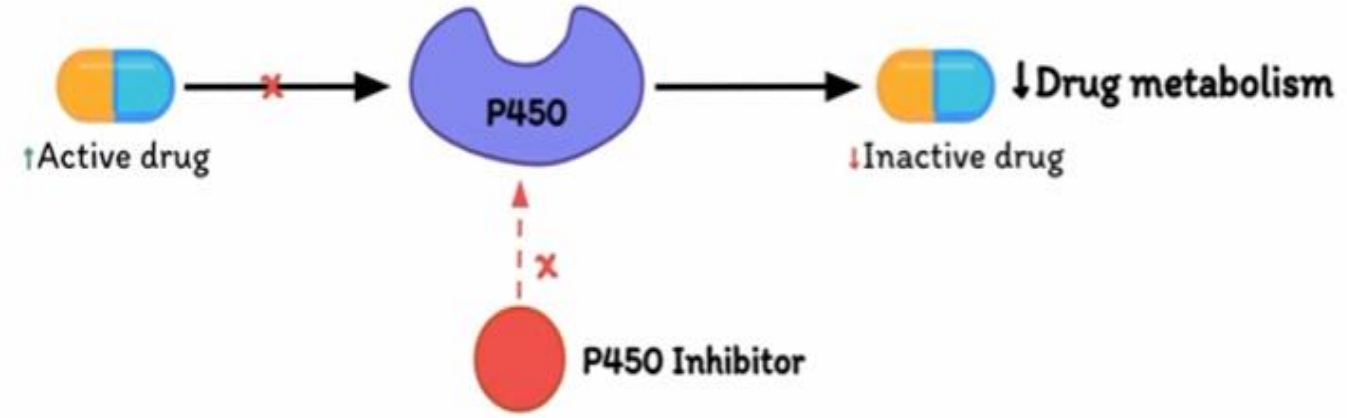
- Induction: body compensates by creating more enzymes for drug metabolism → tolerance
- Inhibition: increase sensitivity
- Competition: reduced rate of metabolism

Enzyme induction



- **Enzyme inducers**: **increase (↑)** the amount of enzymes produced
  Can **increase (↑)** drug toxicity (e.g. paracetamol)
  Low/absence of drug activity

Enzyme inhibition



- **Enzyme inhibitors:** block or slow down the action of enzymes
  Increase (↑) drug half-life
  Toxic levels

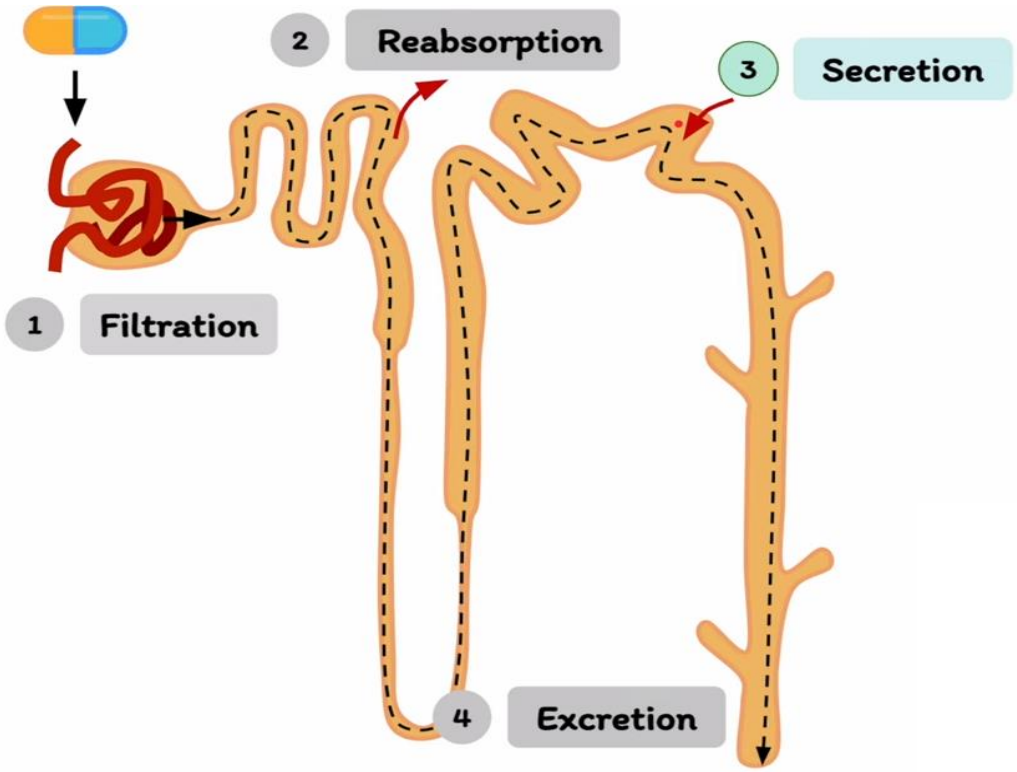
Review!

Excretion

The permanent removal of drugs from the body

Occurs via body fluids, secretions, expired air, or tissue shedding

- **Plasma half-life** reflects rate of drug elimination
- Refers to removal of **parent (unmetabolized) drug**
- Key factor in **drug pharmacology & toxicology**
- **Determines duration** of drug effect
- **Main excretion routes**:
  - **Urine (kidneys)** – most common
  - **Faeces (bile)** – also common

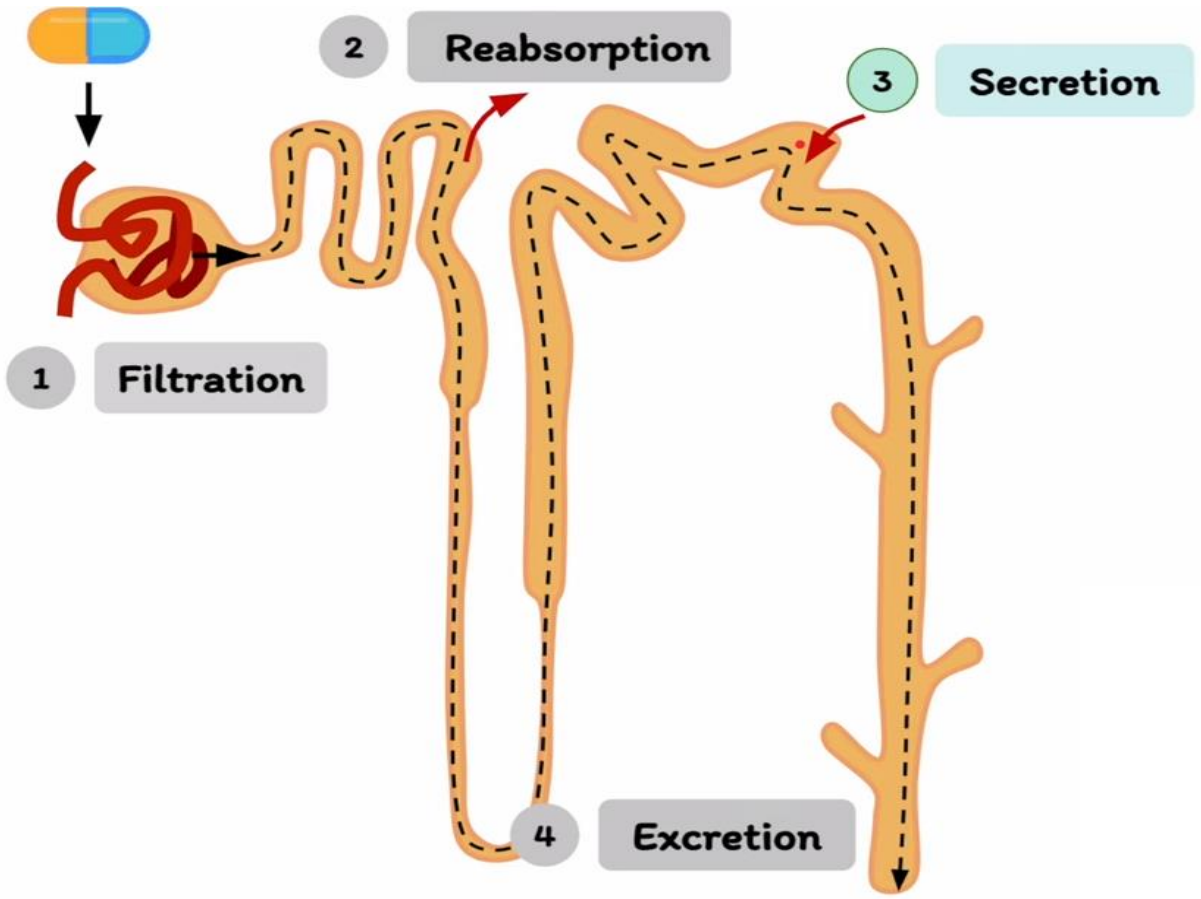


Drug excretion, EKG Science

Kidneys

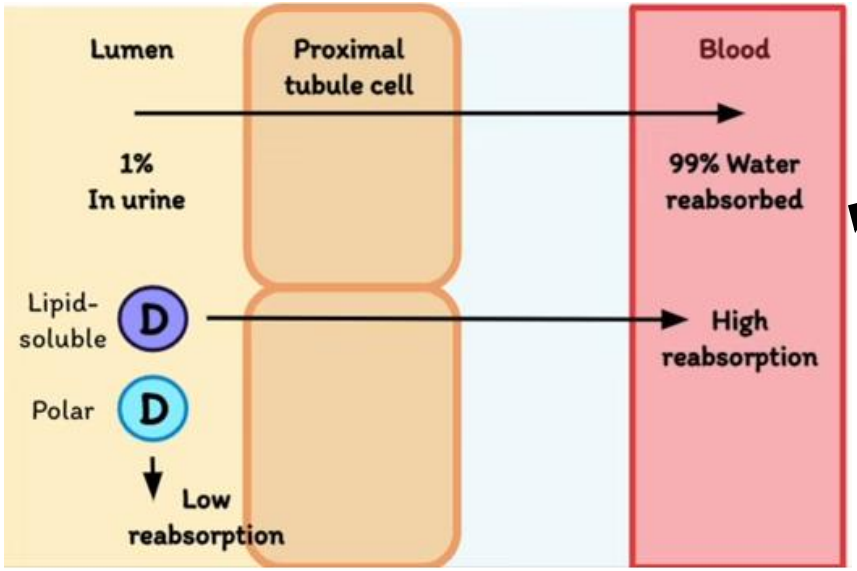
- Most common route of excretion
- Renal clearance
- 3 fundamental processes

1) Glomerular filtration
2) Active tubular secretion
3) Passive reabsorption

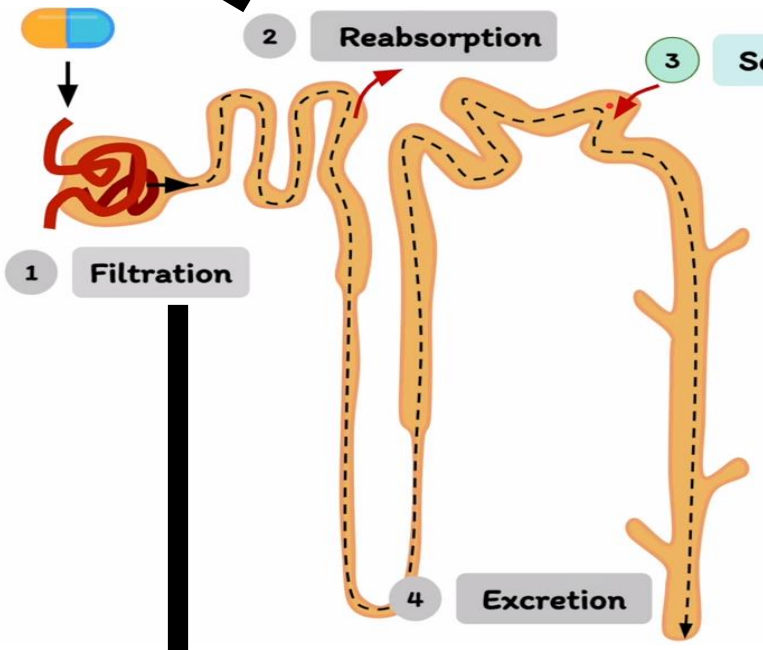


Drug excretion, EKG Science

Renal drug excretion

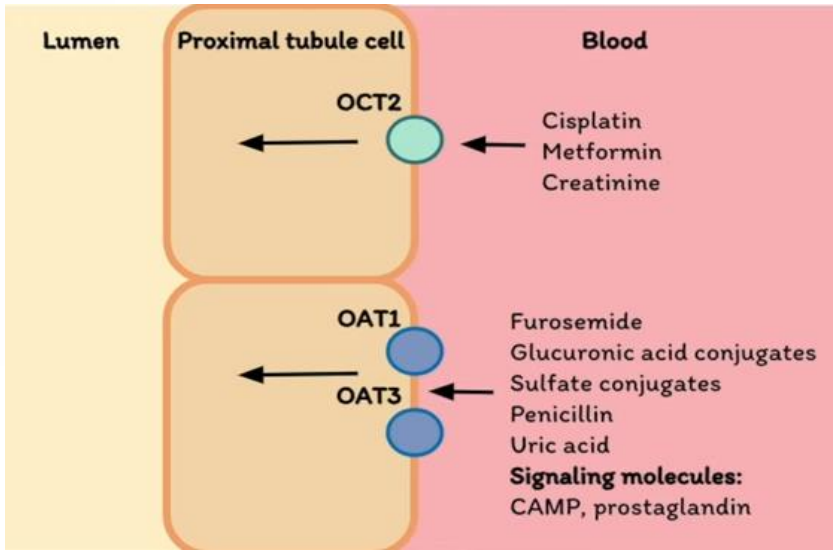


- Some passive diffuse → blood
- Small lipophilic & nonionized drugs
- **Lipid-soluble drug**: high reabsorption → Excreted poorly
- **Polar drugs:** low reabsorption → Remain in the lumen, concentrated in the urine



- Free (unbound) drugs in blood are filtered through pores in glomerulus
- Protein-bound drug remains in blood

- Energy-dependent transporters move drugs from blood into urine
- **OCT:** handles organic bases
- **OAT:** transports acidic drugs



Drug excretion, EKG Science

Other considerations

Factors affection excretion

- Age
- Weight
- Biological sex
- Kidney function

Altered kidney functions

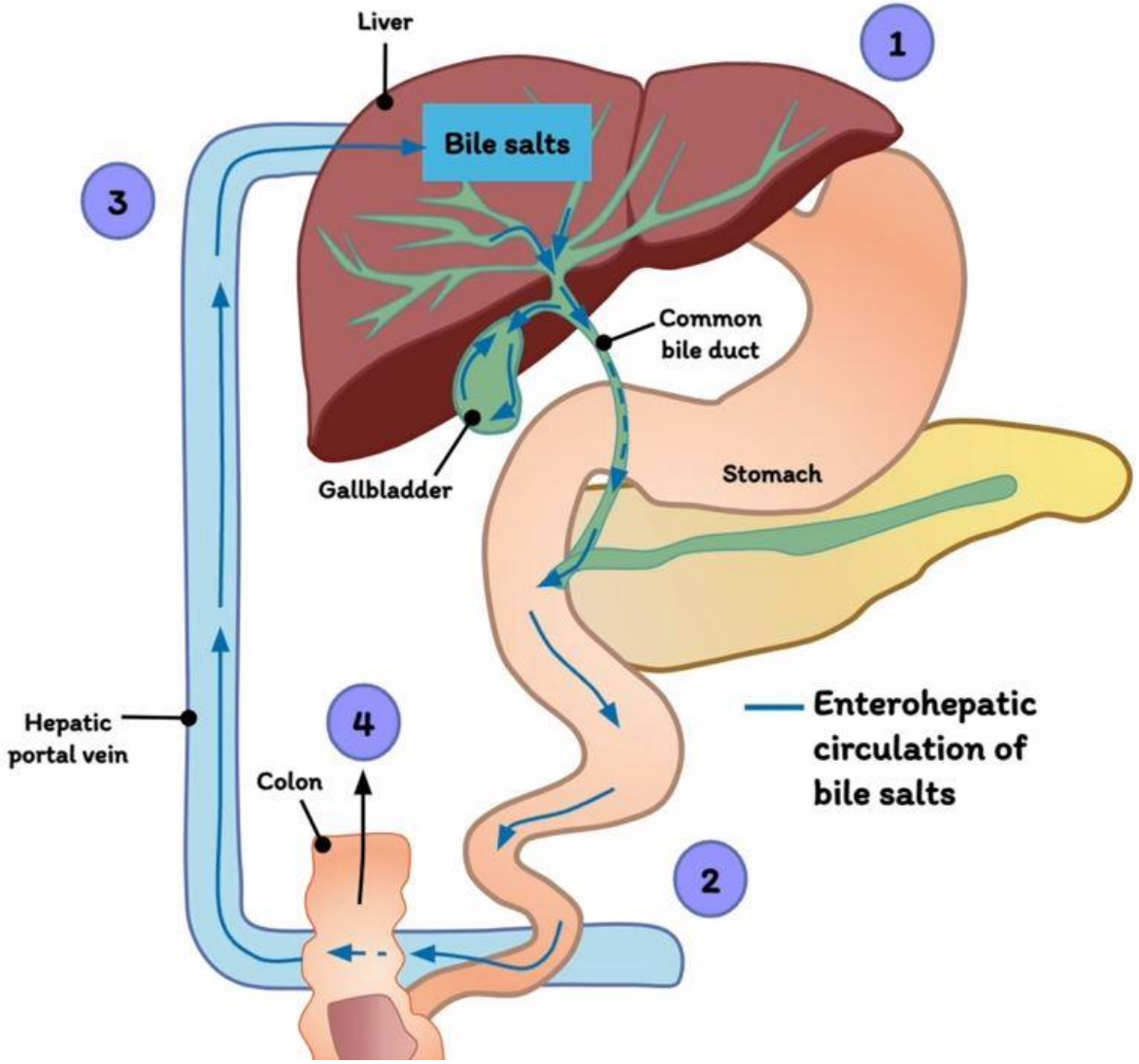
- Chronic kidney disease
- Function decreases with age
- Medical conditions eg. Heart failure

Biliary excretion & Enterohepatic recirculation

- Transfer of substances from plasma to bile
  - OAT, OCT, PGP
- Drug conjugate concentrated in bile → intestine
- Intestinal bacteria hydrolyses glucuronide → active drug
- Reabsorption of free drug → liver

Decreased liver function

- Reduced ability to excrete drugs
- Prolonged effect → toxicity



Drug excretion, EKG Science

Other routes of excretion

- Sweat
- Tears
- Reproductive fluids
- Breast milk
  - Very important to protect breastfed child from unwanted drug effects

Review!

Importance of Pharmacokinetics

Helps us ensure that maximum benefit is gained when using drugs in patients

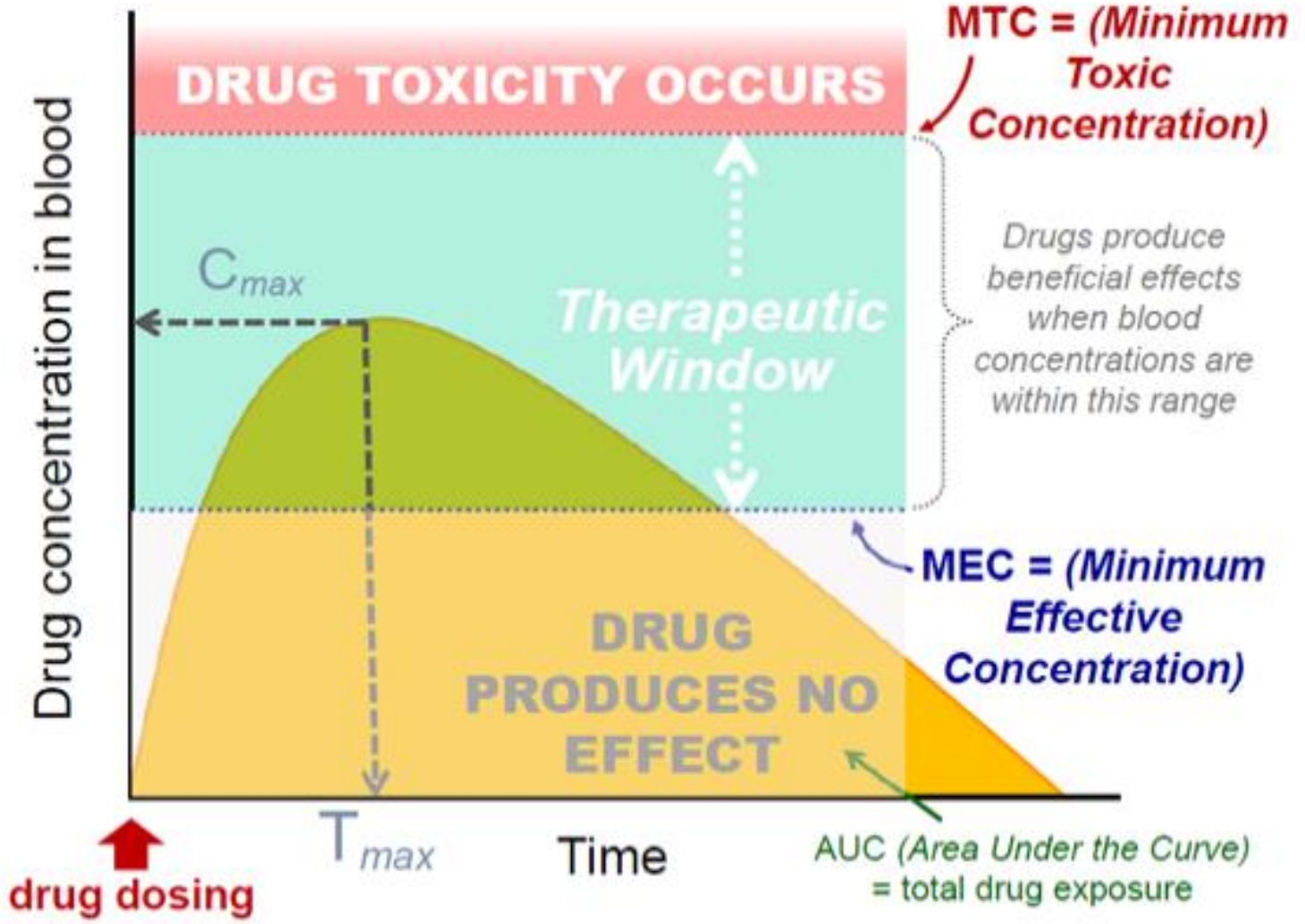
- Avoid drug **underdosing (lack of benefit)**
- Avoid drug **overdosing (unwanted toxicity)**

Ensure we administer correct doses of a drug at appropriate time intervals

Some key parameters (quantitative)

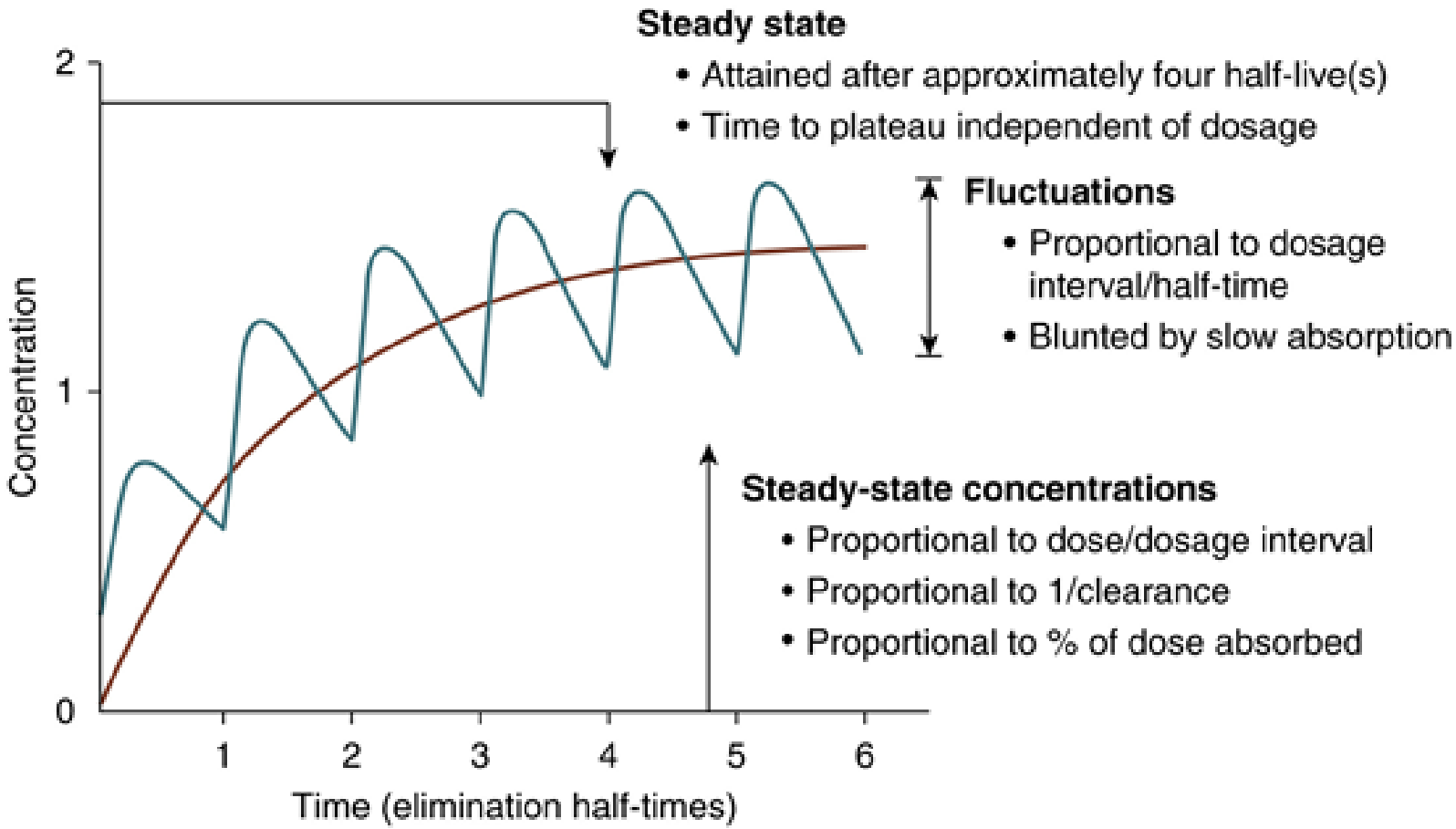
- The Therapeutic window
- First *vs.* Zero order kinetics
- Drug clearance (CL)
- Volume of distribution (V)
- Half-life (T1/2) & Elimination Rate Constant (k)
- Bioavailability (F)

The therapeutic window & plasma concentration-time profiles (single dose)



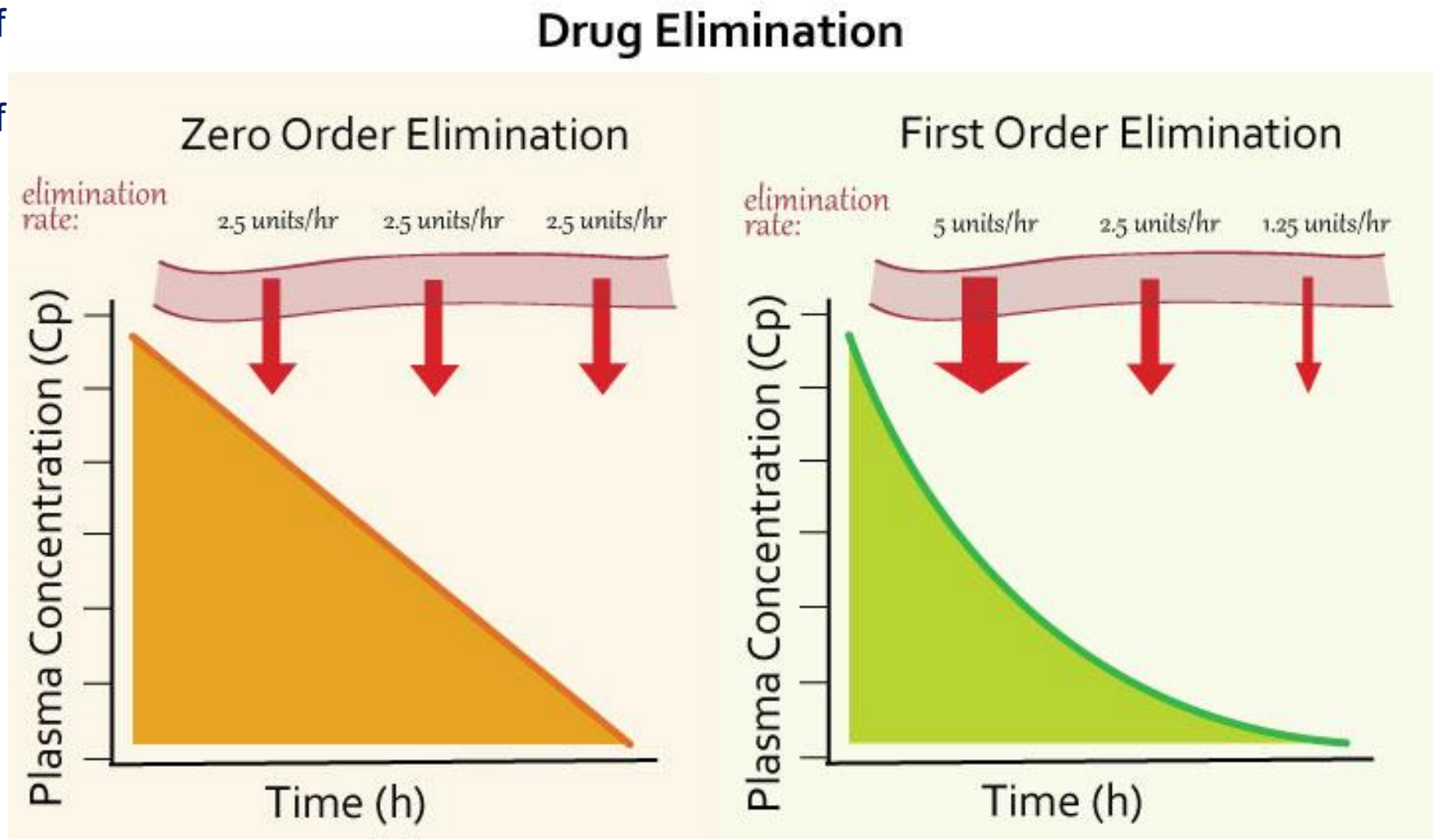
Repeated dose administration

- Dosing regimen → drug accumulation overtime
- Steady state: rate of administration = rate of elimination
- Individual variation
  - Age, weight, liver function
- Drugs properties



Elimination kinetics

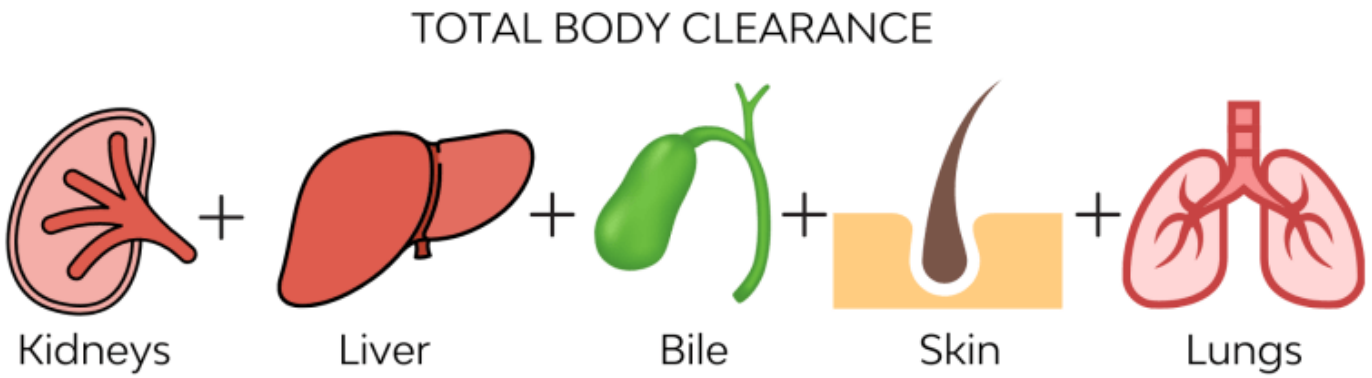
A fixed **amount** of the drug being cleared per unit of time, no matter how much is left!



A constant **proportion** of drug being cleared per unit of time

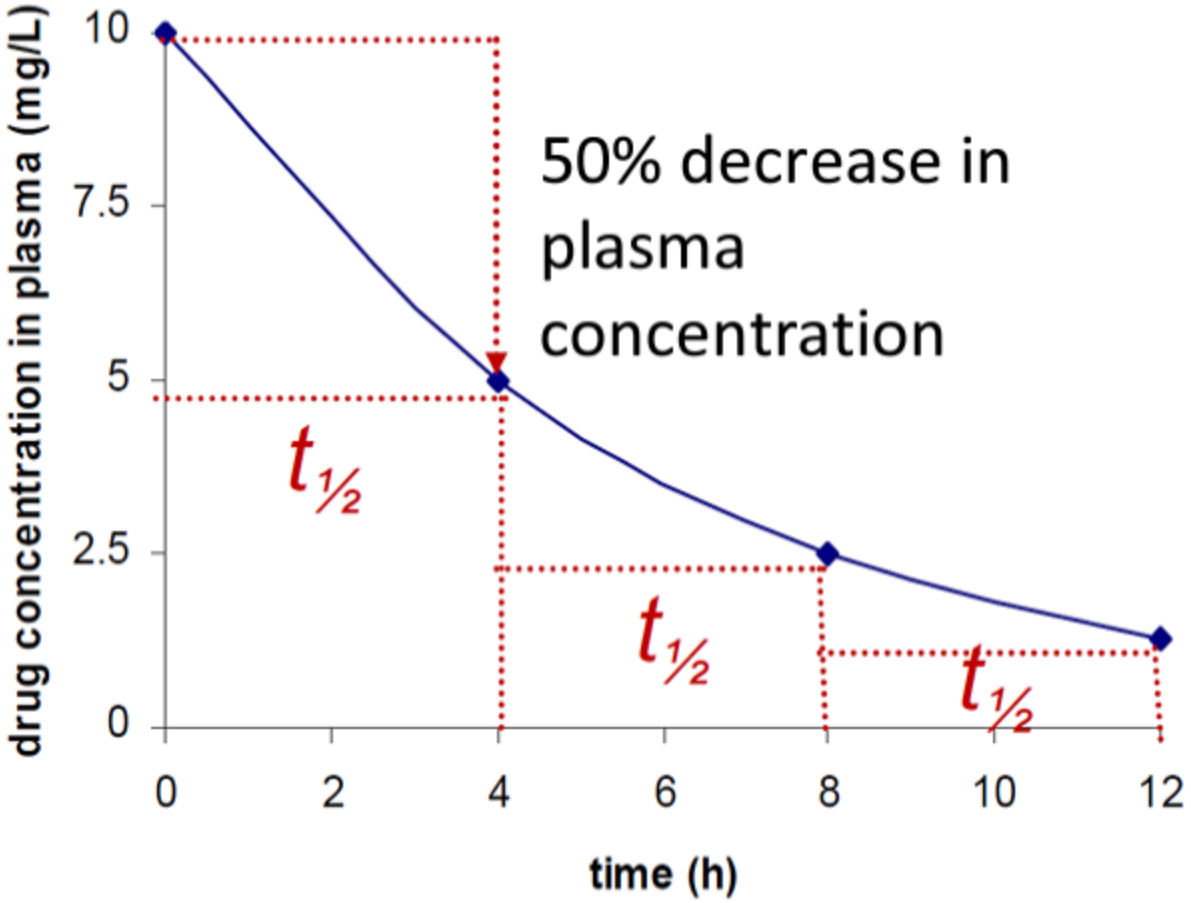
Clearance (CL)

- Clearance (CL) is the **volume of blood cleared completely of the drug per unit time**
- Units are volume per time, e.g. **L/hour or mL/min**
- Can refer to **clearance by a specific organ**, e.g. renal clearance
- Renal clearance = Renal filtration + Renal secretion – Renal reabsorption
- Can also refer to **clearance by the whole body**
- Total body clearance = sum of each organ

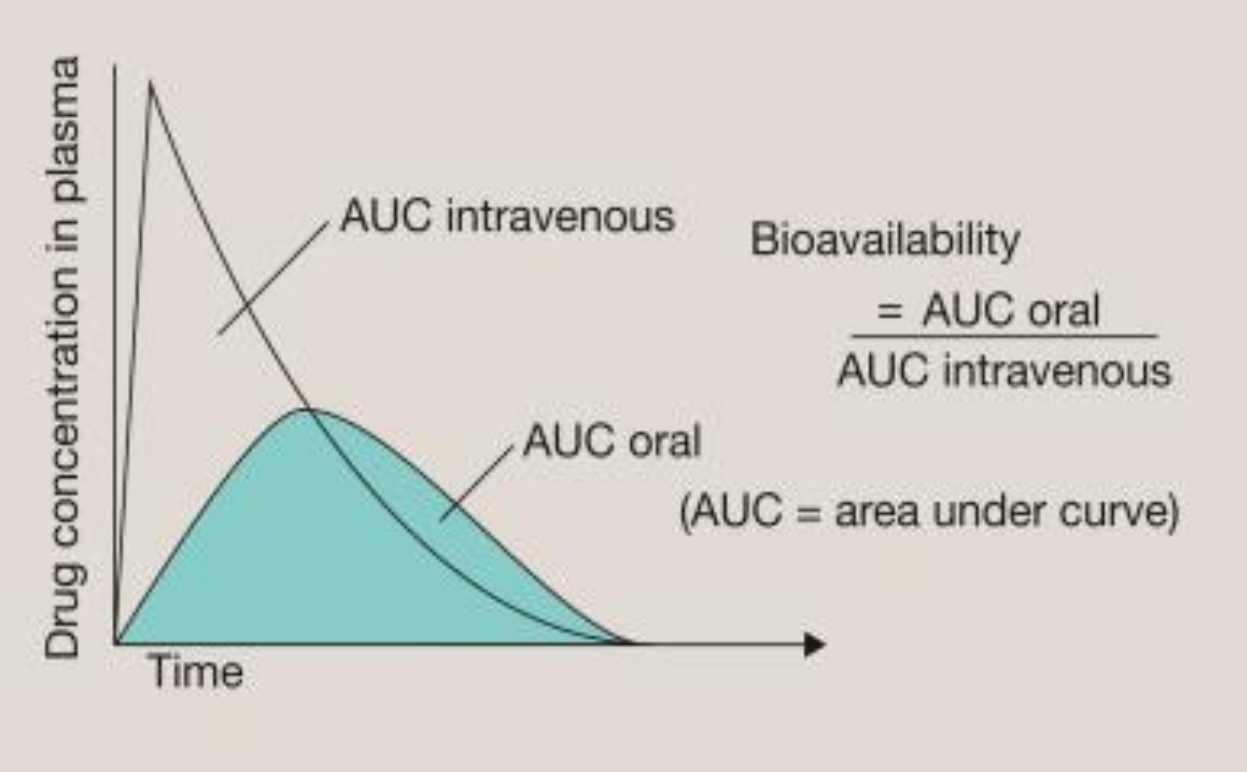


The half life ($T^{1/2}$) & Elimination rate constant (k)

- **Half-life ($T_1/_2$)**: Time for drug concentration in plasma to decrease by 50%
- **Not a fundamental PK parameter** – depends on **clearance (CL)** and **volume of distribution (Vd)**
- Follows **first-order (logarithmic) kinetics** – constant proportion removed per unit time
- Formula: **$T_1/_2 = 0.693 \times Vd / CL$**



Bioavailability (F)



Bioavailability (oral drugs)

Proportion of drug reaching systemic circulation intact

Key influencing factors in gi tract

- Membrane transporters (e.g. efflux in gut wall)
- First-pass metabolism (gut wall & liver)
- Stability to gastric acids/enzymes
- Drug formulation (e.g. pill composition)
- Gut motility
- Presence of food (affects pH, absorption, motility)

Some take home message

- Drugs are able to penetrate membrane barriers by several mechanisms
- More lipid-soluble a drug is, the more likely it is to penetrate the lipid environment of membranes
- Distribution of weak acids and weak bases depends on pH and pKa of drugs
- Drug transporters play notable roles in the small intestine, liver, kidneys, and capillaries
- Each route of drug administration has its own absorption characteristics
- Liver is the most important organ for drug metabolism, employing many key enzymes, most notably the cytochrome P450 enzymes
- Drug inhibitors and drug inducers can affect cytochrome P450 enzymes
- The kidneys are the most important organs for excreting drugs
- First-order Kinetics = constant percentage of drug is eliminated per unit time
- Zero-order kinetics = Constant amount of drug is eliminated per unit time
- Drugs differ from another in their volumes of distribution, half-life, and clearance

Review!

References

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