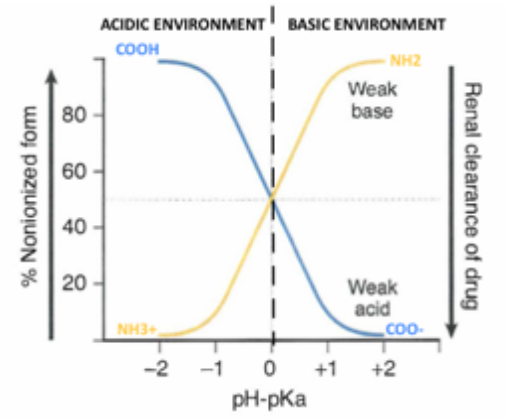
Pharmacokinetics

ACID-BASE, IONIZATION

WEAK ACIDS: *aspirin, phenobarbital, penicillin, cephalosporins, loop & thiazide diuretics*
WEAK BASES: *morphine, local anaesthetics – 'caines', amphetamines, PCP*

Weak Acid	R–COOH (crosses membranes)	⇌	$R–COO^- + H^+$ (better cleared)
Weak Base	$R–NH_3^+$ (better cleared)	⇌	$R–NH_2 + H^+$ (crosses membranes)

Absorption/elimination of a weak acid drug	$pK_a = pH - \log \frac{\text{concentration of ionized acid } (A^-)}{\text{concentration of nonionized acid (HA)}}$
Absorption/elimination of a weak base drug	$pK_a = pH - \log \frac{\text{concentration of nonionized base (B)}}{\text{concentration of ionized base } (BH^+)}$



	PERCENTAGE IONIZATION	
pH - pKa	ACIDS	BASES
-3	0.1	99.9
-2	1	99
-1	10	90
0	50	50
1	90	10
2	99	1
3	99.9	0.1

A drug has a pKa of 8 and is administered to a patient with stomach pH of 2. **pH – pKa = 2-8 = -6** → *This means that 99.9% of the drug is ionized & will not be absorbed in the stomach.*

***ELIMINATE** the **IONIZED** form of the drug – water-soluble: Opposite environment of the drug*
- Weak acid in BASIC ENVIRONMENT
- Weak base in ACIDIC ENVIRONMENT

***ABSORB** the **NON-IONIZED** form of the drug – lipid-soluble, can cross membranes: Same environment of the drug*
- Weak acid in ACIDIC ENVIRONMENT
- Weak base in BASIC ENVIRONMENT

***To increase ionization (Elimination) of a Weak Base, ACIDIFY the urine** – NH_4Cl, vitamin C, & cranberry juice*
**i.e. OD on amphetamines*

***To increase ionization (Elimination) of a Weak Acid, ALKALINIZE the urine** – Na**HCO_3**, acetazolamide*
**i.e. OD on aspirin*

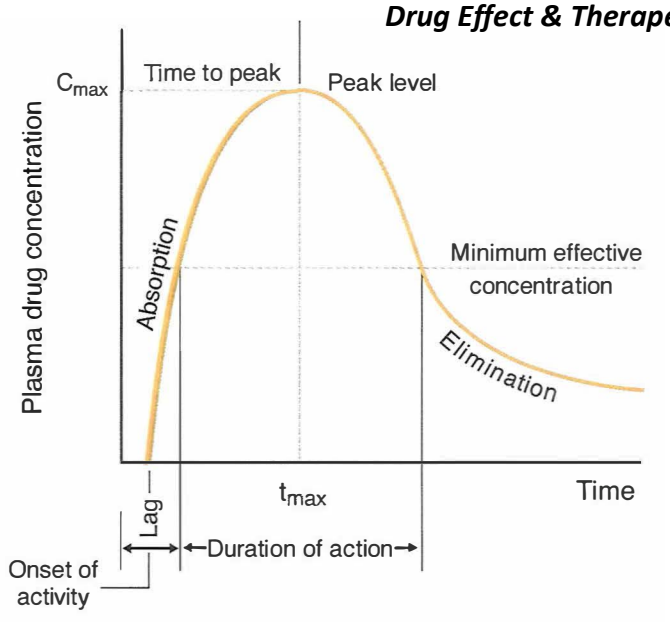
ABSORPTION: *Process of entry* of a drug into the systemic circulation from the site of its administration

**IV administration does NOT involve absorption & there is no loss of drug (bioavailability = 100%)*

THUS, IV is NOT the fastest route of absorption.... ***INHALATION is the fastest route of absorption!***

Plasma Concentration vs. Time – EXTRAVASCULAR ROUTE

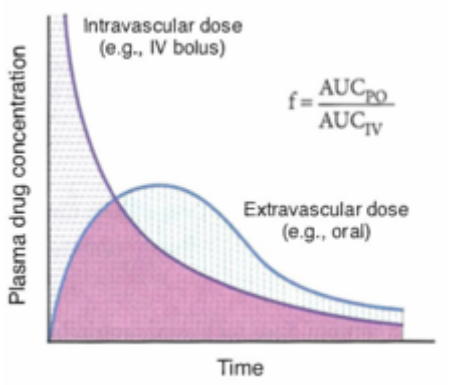
Drug Effect & Therapeutic Window



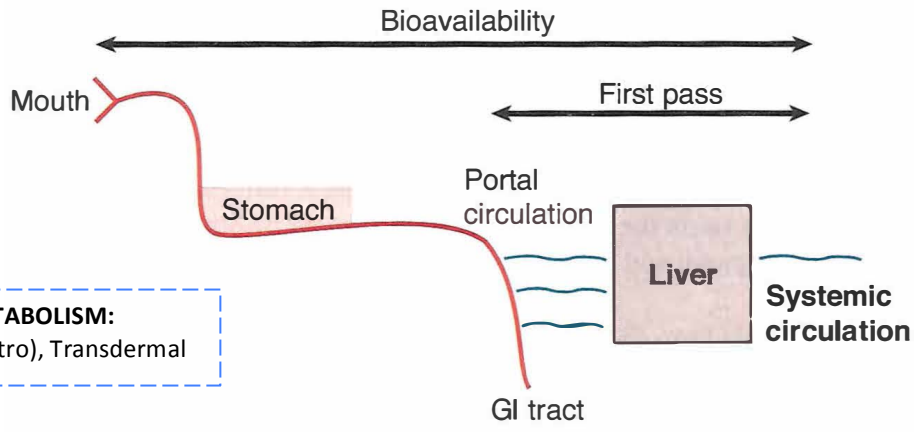
C_{max} = maximal drug level obtained with the dose.
t_{max} = time at which C_{max} occurs.
Lag time = time from administration to appearance in blood.
Onset of activity = time from administration to blood level reaching minimal effective concentration (MEC).
Duration of action = time plasma concentration remains greater than MEC.
Time to peak = time from administration to C_{max}.

BIOAVAILABILITY: *Measure of the fraction of a dose that reaches the systemic circulation*

**BIOEQUIVALENT = same bioavailability + same plasma profile superimposed curves)*



FIRST-PASS EFFECT: *Drugs given PO are absorbed into Portal Circulation & initially distributed to LIVER*



NO FIRST-PASS METABOLISM:
IV, Sublingual (Nitro), Transdermal

What makes it here is the 'bioavailability'

BIOTRANSFORMATION (Metabolism): *Metabolic conversion of drugs to more water-soluble metabolites that are more readily excreted*

Drug → Inactive metabolite(s) (MOST DRUGS)

Drug → Active metabolite(s) *BENZOS

Prodrug → Drug Levodopa —> dopamine; Enalapril —> enalaprilat

PHASE 1 REACTIONS: *Modification of the* drug moleculecule via *oxidation, reducation, or hydrolysis*

- Cytochrome P450 isoenzymes are major enzymes involved in phase I reactions
- **INDUCERS**: ↓ substrate level of drug
- **INHIBITORS**: ↑ substrate level of drug
  - GRAPEFRUIT JUICE: inhibits 3A4, which inhibits statin metabolism & thus, increases statin concentration in plasma

Table I-1-2. Cytochrome P450 Isozymes

CYP450	Substrate Example	Inducers	Inhibitors	Genetic Polymorphisms
1A2	Theophylline Acetaminophen	Aromatic hydrocarbons (smoke) Cruciferous vegetables	Quinolones Macrolides	No
2C9	Phenytoin Warfarin	General inducers*	—	Yes
2D6	Many cardiovascular and CNS drugs	None known	Haloperidol Quinidine	Yes
3A4	60% of drugs in PDR	General inducers*	General inhibitors† Grapefruit juice	No

* General inducers: anticonvulsants (barbiturates, phenytoin, carbamazepine), antibiotics (rifampin), chronic alcohol, St. John's Wort.

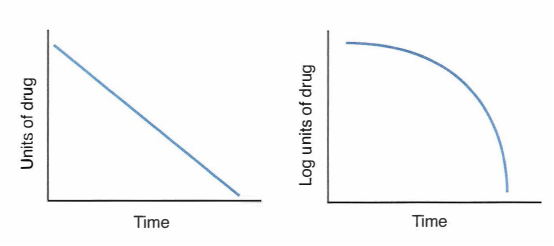
† General inhibitors: antiulcer medications (cimetidine, omeprazole), antimicrobials (chloramphenicol, macrolides, ritonavir, ketoconazole), acute alcohol.

PHASE II REACTIONS: *Conjugation with endogenous compounds via the activity of* ***transferases***

1. **Glucuronidation:** Diazepam, Digoxin, Morphine, Chloramphenicol
   - CHLORAMPHENICOL TOXICITY: Grey Baby Syndrome due to low levels of glucuronosyl transferase
2. **Acetylation:** Sulfonamides, INH
   - Genotypic variations
   - Drug-Induced SLE by slow acetylators with hydralazine: *Stop drug & SLE goes away*
3. **Glutathione:** GSH
   - Depletion of GSH in the liver associated with acetaminophen hepatotoxicity

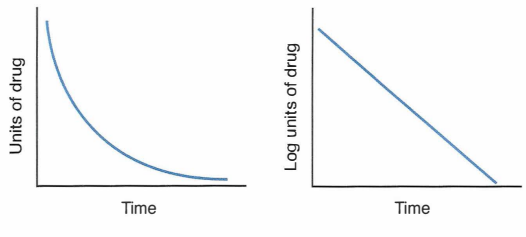
ZERO ORDER KINETICS: *Think 'saturation kinetics'*

- Fixed amount of drug eliminated per unit time
  - **RATE OF ELIMINATION = CONSTANT**
- **Independent** of plasma concentration
- Variable half-life
- **Phenytoin, Ethanol, Aspirin, Salicyclates – PEAS***



FIRST ORDER KINETICS

- Constant fraction of drug eliminated per unit time
- Concentration dependent: *rate falls as plasma levels fall*
- **Clearance is CONSTANT** & **HALF-LIFE is CONSTANT**
- *Most drugs*



Rate of administration $R_A = \dfrac{\text{dose} \times (\text{bioavailability F} \times \text{salt form S})}{\text{dosing interval } \tau}$

V_D is LOW when high % of drug is bound to plasma protein ($\uparrow C_p$)
V_d is HIGH when high % of the drug is sequestered in tissues ($\downarrow C_p$)

Volume of distribution $V_d = \dfrac{\text{total amount of drug in body}}{\text{plasma concentration}}$

**If V_d is given in L/kg, you have to multiple by the patient's weight – if no weight given, assume 70kg*

$= \dfrac{\text{dose} \times (\text{bioavailability F} \times \text{salt form S})}{\text{plasma concentration } C_p}$

***Rule of Thumb:** Loading dose = 2 x Maintenance Dose*
This is how it will be on the exam!

Loading dose Loading Dose = (Cp x Vd)/(F x S)

Loading dose (maintenance form) $LD = 1.44 \times t_{1/2}/\tau \times MD$

# of half-lives	1	2	3	4
% remaining	50%	25%	12.5%	6.25%

Half-life ONLY FOR FIRST ORDER KINETICS! $t_{1/2} = \dfrac{0.693 \times V_d}{Cl}$ or $t_{1/2} = \dfrac{0.693}{k_e}$

% drug remaining after t time $(0.5)^{t/t1/2}$

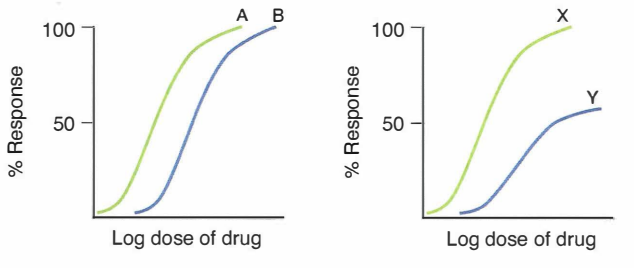
Clearance $Cl = \dfrac{0.693 \times V_d}{t_{1/2}}$ or $Cl = k_e \times V_d$

Concentration of a drug at steady state $C_{ss} = \dfrac{\text{rate of administration } R_A}{\text{clearance Cl}}$

Pharmacodynamics

AFFINITY: the nearer the curve to the y-axis, the greater the affinity; parallel curves
POTENCY: shows relative doses of 2+ agonists to produce the *same magnitude of effect* can compare if 2 curves do not cross
EFFICACY: effectiveness; the dose required to produce a certain effect; shown by max height reached by the curve;

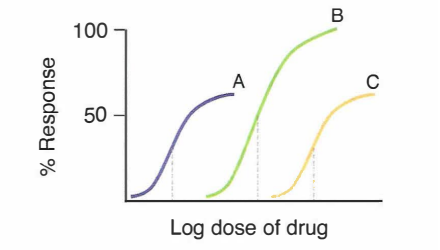
Parallel = same receptor
Affinity A > Affinity B
Efficacy A = Efficacy B

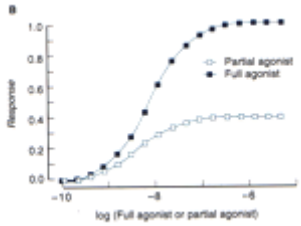


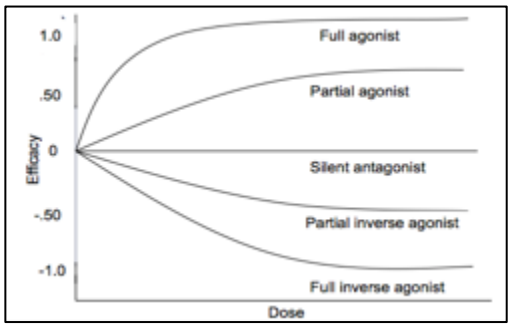
Not parallel = Diff. receptors
Potency X > Potency Y
Efficacy X = Efficacy Y

AGONIST: when binding to the receptor gives a response *(full, partial inverse)*

- FULL AGONIST: produce a maximal response; maximal efficacy
- PARTIAL AGONIST: incapable of eliciting maximal response; less effective
  - *Can act as an antagonist – competition for receptor*
- INVERSE AGONIST: produces an opposite effect of the agonists; *stabilizes the inactive state reducing signal transduction below basal levels*

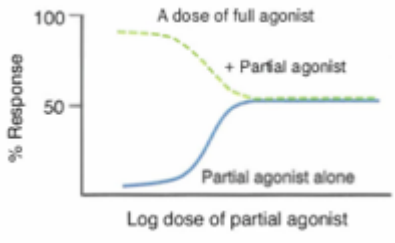


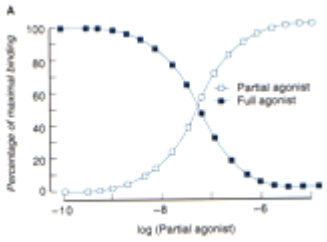


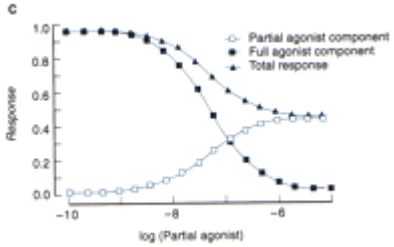


A, C = PARTIAL
B = FULL

Highest efficacy: B
Highest potency: A (A>C; B>C)
Can't compare potency of A & B because their curves cross, but you can compare at a specific dose. At low doses, A>B & at high doses, B>A.



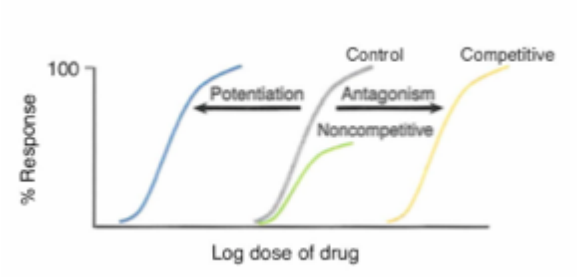




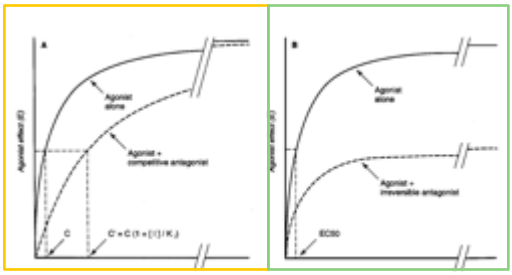
As the partial agonist replaces the full agonist from the receptors, the receptor is reduced – *Partial agonist is acting as ANTAGONIST*

Example: Epinephrine, Pindolol (β-blocker, partial agonist), & heart beat

ANTAGONIST: binding to the receptor is NOT associated with a response; the drug only has an effect by **preventing** an agonist from binding the receptor; *stabilizes the equilibrium condition*

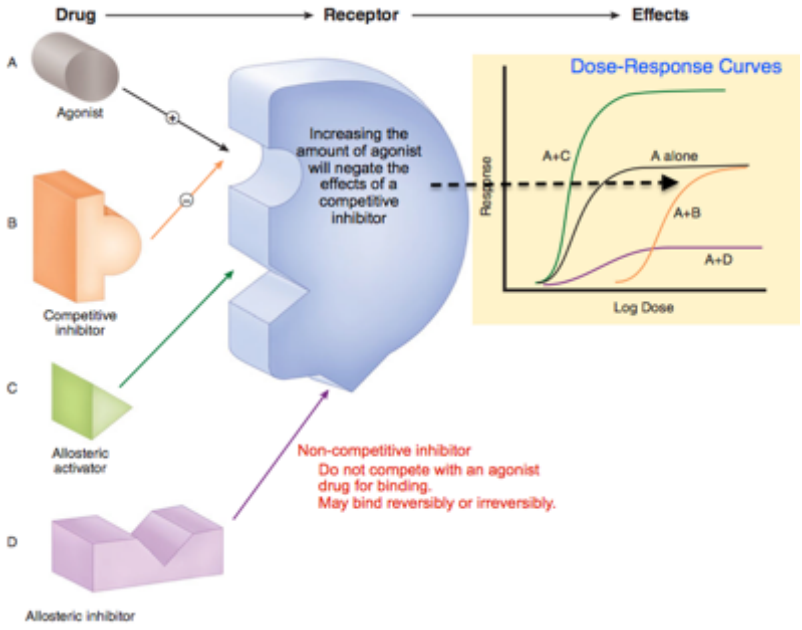


COMPETITIVE: ↓ POTENCY *(shift right, ΔED50)*
POTENTIATION: ↑ POTENCY *(shift left)*
NON-COMPETITIVE: ↓ EFFICACY *(shift down)*



TYPES OF ANTAGONISM:

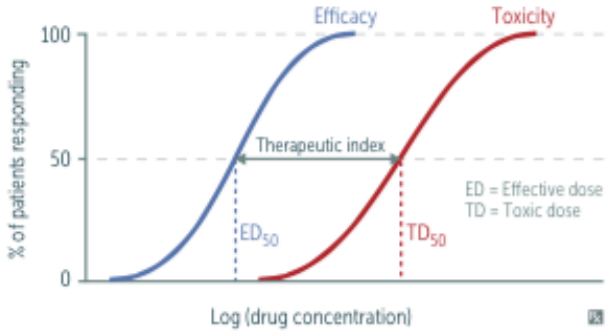
- **PHARMACOLOGIC:** SAME RECEPTORS
  - **COMPETITIVE**: *Atropine, propranolol*
    - Occupies receptor of agonist without activating it
    - Parallel shift in dose-response curve for agonist
    - Overcome with increasing dose of agonist
  - **NON-COMPETITIVE**: *Aspirin,* ***phenoxybenzamine***
    - Non-parallel shift to right
    - Can only be partially overcome with increasing dose of agonist
- **PHYSIOLOGIC:** DIFFERENT RECEPTORS
  - Two agonists with OPPOSING actions antagonize each other
  - *Phenylephrine (vasoconstrictor) + Nitroglycerin (vasodilator)*
- **CHEMICAL**: NO RECEPTORS (*Acts directly with the agonist)*
  - Formation of a complex between effector drug & another compound
  - *Protamine binds to heparin to reverse its actions*



THERAPEUTIC INDEX: how effective a drug is in producing the desired effect relative to toxicity

- Both ED50 and TD50 are calculated from quantal-dose response curves, which represent the frequency with which each dose of drug elicits the desired response or toxic effect in the population
- **ED50:** dose required to produce a therapeutic effect in 50% of the population
- **TD50:** dose required to produce a toxic effect in 50% of the population
- **SAFER DRUGS HAVE HIGHER TI VALUES**
- **DRUGS WITH NARROW/LOW THERAPEUTIC INDEX:** Warfarin, Lithium, Digoxin, Theophylline, Gentamycin, Amphotericin B

$$\text{Therapeutic index} = \frac{TD_{50}}{ED_{50}}$$



Drug Development

Pre-clinical	Phase 1	Phase 2	Phase 3	Phase 4
Animals Safety & biologic activity	**~20 Healthy volunteers** ***THIS IS NOT PATIENTS** *Safety, minimum effective dose (pharmokinetics)*	**100s Selected PATIENTS** *Therapeutic efficacy*	**Large # Selected PATIENTS** *Safety & efficacy* *Overall benefit-risk ratio* ***SIDE EFFECTS**	**Post-marketing surveillance – Patients given drug for therapy** *Adverse reactions*

IND application for FDA Safety Review

NDA Review