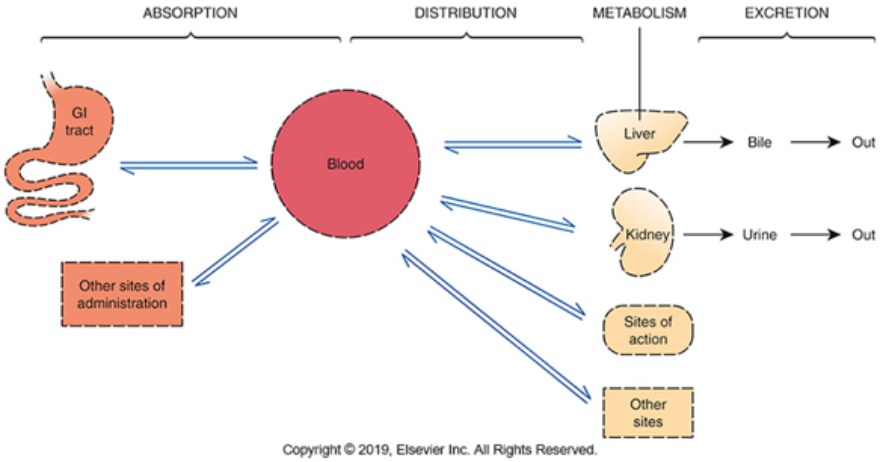
Pharmacokinetics (Ch. 4)

By definition it is what our body does to the drug

- Absorption
- Distribution
- Metabolism
- Excretion
- Response timeline



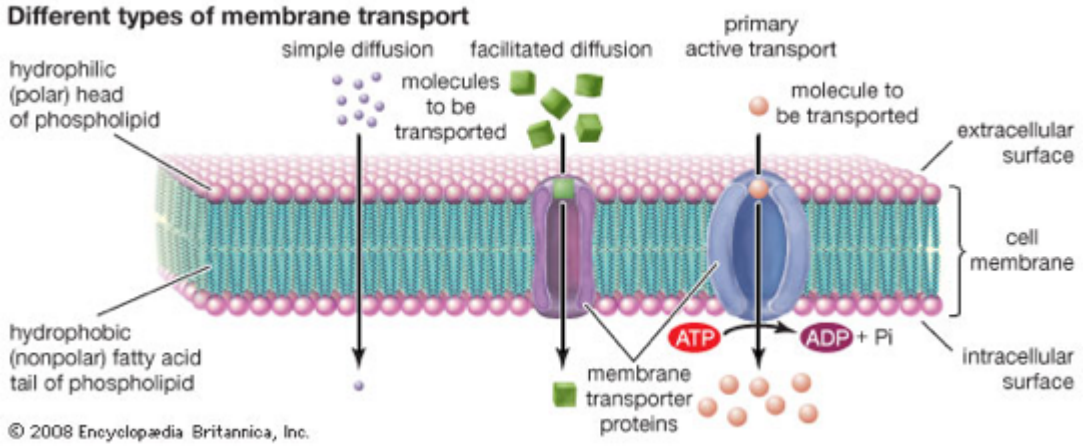
Absorption

When the drug is taken from the outside world and then reaches the bloodstream

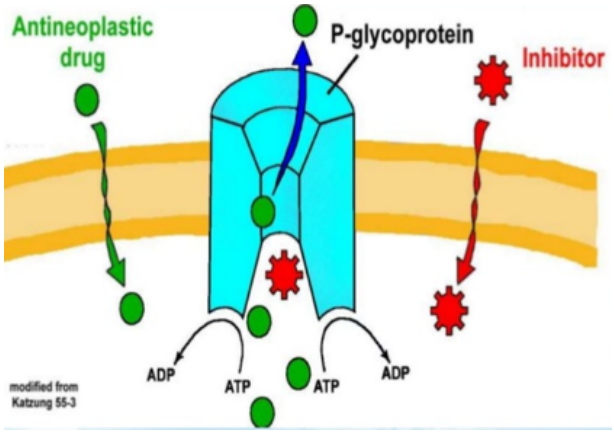
Drug membrane transport

Review:

- lipid-soluble/non-polar molecules can diffuse across plasma membranes
- water-soluble/polar molecules must use transport proteins



Water-soluble/polar diffuse more slowly because it requires transport proteins (MDR-1 protein). It is a protein whose job is to get harmful things out of cells (outward active transporter - protective origin). It takes different drugs, and pumps it out of the cells (see antineoplastic drug on picture below). However, it doesn't know the difference between drugs that want to cure you from drugs that want to harm you. From an evolutionary perspective, this is very good, because there are potentially things that can harm us. But when you want to give



someone a drug to help them (good stuff) it will get rid of it. So in order to give this medication, we need to block this protein, to avoid it getting rid of the drug.

Different drugs interact with this MDR-1 protein to different extents. If it interacts a lot with this protein a lot, it will affect the absorption. Some don't interact much with it, therefore their absorption is independent of the MDR-1 protein.

Some organs have an abnormally large amount of MDR-1 proteins, because they are the entry points:

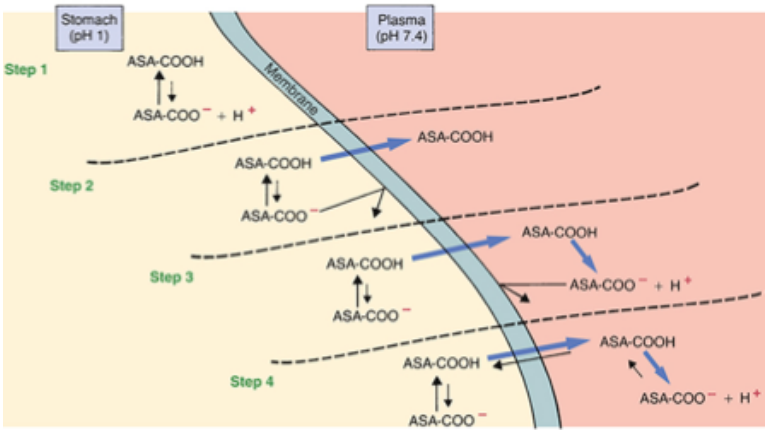
- Intestines
- Kidneys
- BBB
- Placenta

pH & Ion Trapping

Drug\Environment	Acidic	Alkaline
Strong Acid	Polar/Ionized	
Weak Acid	**Non-Polar/Unionized**	**Polar/Ionized**
Weak Base	**Polar/Ionized**	**Non-Polar/Unionized**
Strong Base	Polar/Ionized	

Certain drugs can be characterized as weak acids or weak bases. We don't care about strong acids and strong bases so much, because they remain (polar) all the time. Weak acids and weak bases, change based on their environment. A weak acid will be polar if the environment is alkaline, and non-polar in an acidic. The opposite is true of weak bases. So it can be two faced.

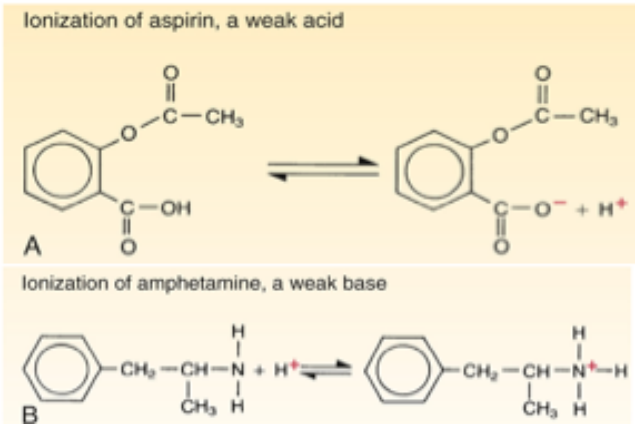
- Ex: a weak acid in an acidic environment becomes non polar: in an acidic environment, do you want to make this environment even more acidic? No. Therefore a weak acid will become non –polar, and therefore won't add to the acidity. If the environment is alkaline, the acid says i can neutralize this environment, so now I can become polar. Opposite is true of weak bases.



Ion trapping: the process whereby a drug accumulates on the side of a membrane where the pH most favors its ionization.

Aspirin (weak acid): a weak acid in the stomach (acidic environment), it will be non-polar. Is non-polar easier to absorb? Yes, because it is lipid-soluble, easily diffusing across the membrane into the bloodstream. The bloodstream is alkaline, so the aspirin becomes polar, and because it becomes polar, it stays stuck in the bloodstream, it doesn't cross back over (ion trapping). If aspirin makes it into the intestine, where the environment is relatively alkaline, they change to their ionized form. As a result, absorption of aspirin is impeded.

This greatly favors the absorption of certain drugs (weak acids), but disadvantages weak bases.



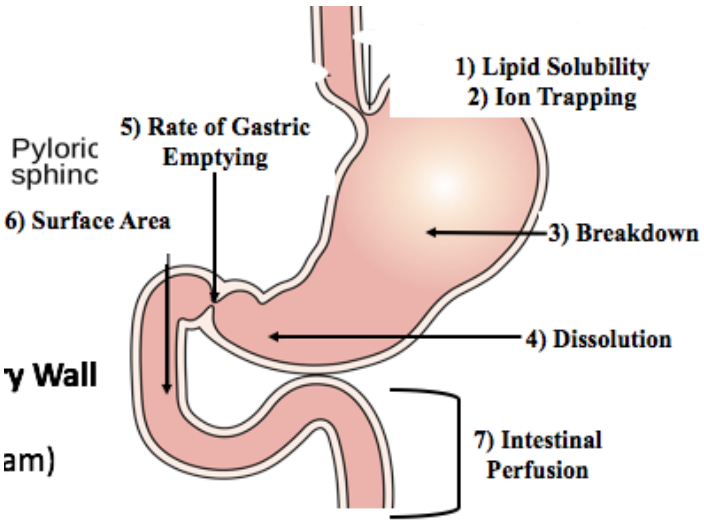
When we want to save someone from a drug overdose, changing the pH of the urine will help excrete more of the drug.

<u>Absorption factors (Per Os)</u>

- Rate/speed of absorption → onset of effects is influenced by the physical and chemical properties of the drug itself and the physiologic and anatomic factors at the absorption site.

- Magnitude/amount → peak effect intensity
- Intestines → through the cell membrane & capillary wall → portal vein (aka bloodstream)
- The absorption factors will also affect the peak effect intensity

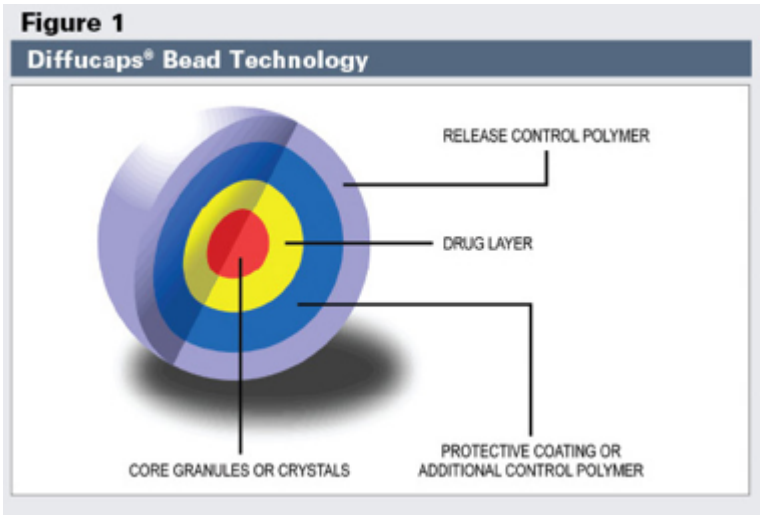
*Example of exam question: would this factor affect absorption?

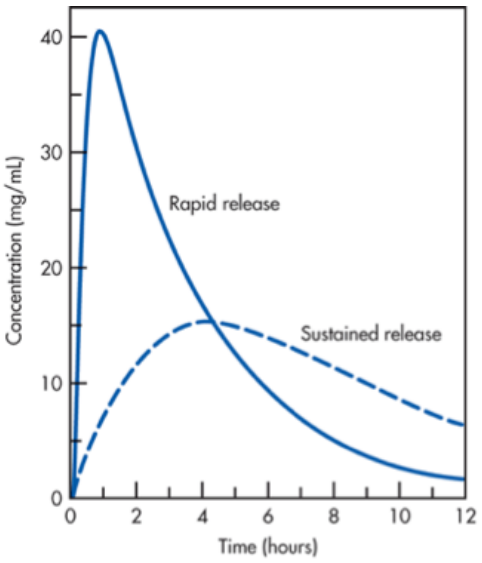


1. **Lipid solubility**: lipid-soluble drugs are absorbed more rapidly because they can readily cross the membranes.
2. **Ion trapping** (pH partitioning): absorption will be enhanced when the difference between the pH of plasma and the pH at the site of administration is such that drug molecules will have a greater tendency to be ionized in the plasma.
3. **Rate of dissolution**: rate of dissolution helps determine the rate of absorption. Rapid dissolution drugs have a faster onset than drugs formulated for slow dissolution.
4. **Surface area**: a major determinant in the rate of absorption → the larger the surface area, the faster absorption will be. Therefore, drugs are usually absorbed faster in the small intestine than in the stomach due to larger surface area created by the microvilli.
5. **Blood flow**: drugs are absorbed more rapidly from sites where blood flow is high because blood containing a newly absorbed drug will be replaced rapidly by drug-free blood, thereby maintaining a large gradient between the concentration of drug outside the blood and the concentration of drug in the blood. The greater the concentration gradient, the more rapid absorption will be.

<u>Per Os Formulations</u>

Formulation	Advantages	Disadvantages
Tablets	Standard Reference Kinetics	None of the advantages
Enteric-Coated	No Stomach Degradation Protect Gastric Epithelium	↑ Absorption Variability Failure to dissolve altogether
Sustained-Release	Steady Absorption Rate ↓ # of Daily Doses	More Expensive ↑ Absorption Variability





Routes of administration (p.29-32)

Route	Abs. Barriers	Abs. Pattern	Advantages	Disadvantages
Intravenous (IV)	None	Instantaneous	• Rapid Onset (emergencies!) • Precise Concentration Control (Bypass 1st pass) • Allows use of irritant drugs & large fluid volumes	• Irreversible • Expensive & Inconvenient • Poor Self-Administration • Risk of overload; Embolism • Water-Soluble Drugs ONLY
Intramuscular (IM) Subcutaneous (subcut)	Capillary Wall (weak barrier)	Water-Soluble = Rapid Poorly soluble = Slow	Allows use of poorly soluble drugs & depot preparations	• Inconvenient • Possible Discomfort or Injury • Poor Self-Administration
Oral (PO)	GI Epithelial + Capillary Wall	Slow & Variable	• Easy, Good Self-Administration • Convenient & Inexpensive • Potentially Reversible (Safer!)	• Variable Drug Concentrations • First-Pass Inactivation • Possible Nausea & Vomiting • Conscious & Cooperative Patients ONLY

Extra routes:

- Inhalation → drugs for respiratory airways/direct injections at target sites (ex: brain, knee joint, etc)
- Topical → skin, nose, eyes, ears, rectum & vagina & rectal suppositories → local effects

Choice of administration route & formulas

- Choice of administration route & formulation depends on a multitude of factors
  - Practicality & availability
  - Schedule of administration
  - Price
  - Patient state & compliance
  - Drug properties
- In most situations: if possible, PO tablets are preferred to parenteral routes (safer) ***

- Good pharmacokinetics foundation means:
    - Understand choice of administration route & formulations for specific drugs
    - Anticipate situations where administration route/formulation should be reviewed, adapted or changed

Distribution

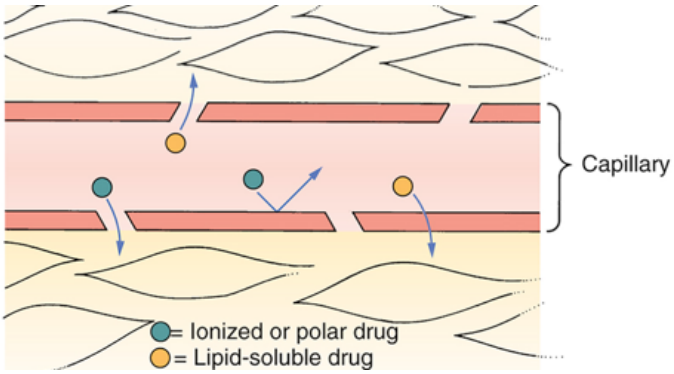
Is the movement of drug to cells & tissues

Once the drug is in the bloodstream, it now needs to be distributed to different organs.

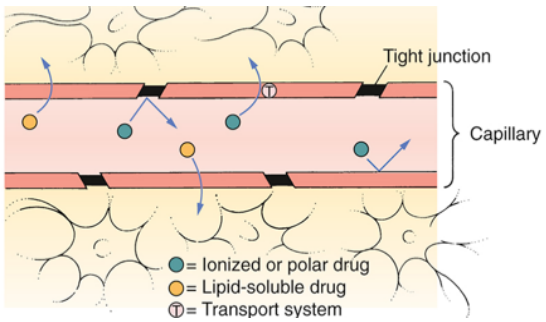
<u>Distribution barriers & factors</u>

Factors that affect distribution:

1. Drugs carried via bloodstream → rate at which drugs are delivered to a particular tissue is determined by blood flow to that tissue.
    a. think of sympathetic/parasympathetic phases, it varies accordingly.
2. Exit vasculature through capillary beds → plasma proteins
    a. Drugs pass between capillary cells rather than through them, movement into the interstitial space is not impeded.

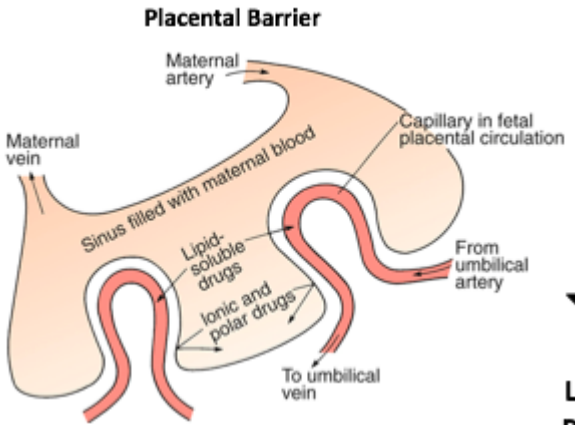


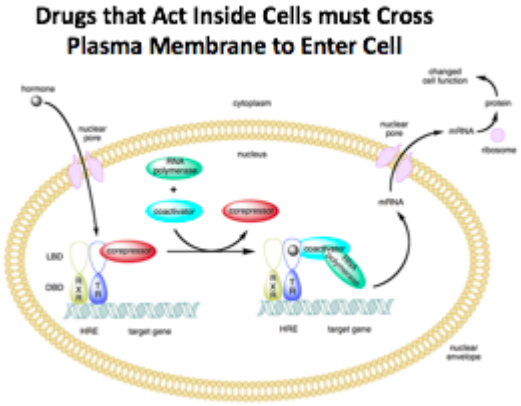
    b. you do not want a drug that binds to plasma protein. It will just attach to the PP and travel aimlessly throughout your bloodstream. It won't have an effect
3. Cross optional barriers (ex: BBB, placenta; plasma membrane)
    a. Capillary beds: because of the slits, polar drugs cross through those slits.
    b. BBB: The capillaries in the BBB are composed of tight junctions between the cells. These junctions are so tight that they prevent drug passage. Consequently, to leave the blood and reach sites of action within the brain, a drug must be able to pass through cells of the capillary wall. Only drugs that are lipid-soluble or have a transport system can cross.



Optional Barriers

Same factors affecting absorption across GI epithelium apply to placental barrier & plasma membrane.



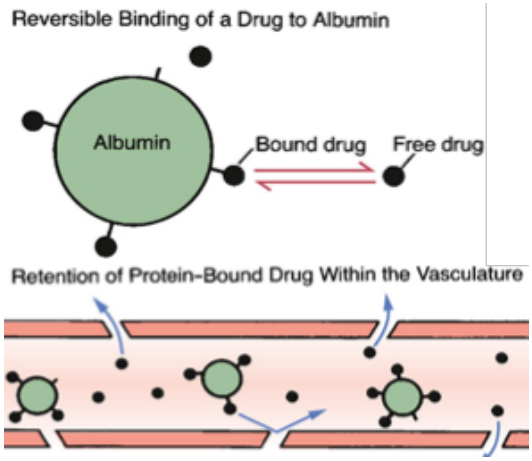


Drugs that are lipid soluble/non-polar have more ease crossing the placenta, but if they cross, they stay there (ion trapping).

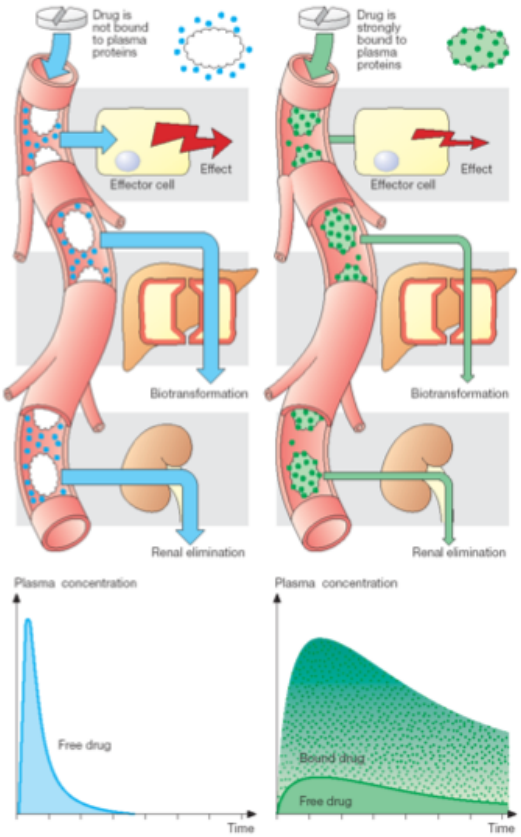
Hormones have easy access through barriers.

Plasma Proteins

- Key therapeutic concepts
  - Albumin-bound drugs = trapped in bloodstream because albumin never leaves the bloodstream (too big to pass through the slits)
  - Source of potential drug interactions: each molecule of albumin has only a few sites to which drug molecules can bind. Because the number of sites is limited, drugs with the ability to bind albumin will compete with one another for those sites. As a result, one drug can displace another from albumin, causing the free concentration of the displaced drug to rise. By increasing levels of free drug, competition for binding can increase the intensity of drug responses. If plasma levels rise sufficiently, toxicity can result.
  - Major determinants:
    - Albumin levels
    - Drug-albumin affinity
- Albumin has the most significant effect. Albumin is synthesized by your liver.



- The black dots (drug) that are free, and free to leave the bloodstream. While those that are bound to the albumin protein, are trapped inside the bloodstream. As a result, bound molecules cannot reach their sites of action or undergo metabolism or excretion until the drug-protein bond is broken. This prolongs the distribution phase and increases the half-life.
- Free drug concentration is what matters!!!
- Plasma-bound drugs are like players on the bench: ready to play but irrelevant at the moment



- Blue graph: this one has almost no interaction with albumin, so it has a short duration of action, but a large effect.

- Green graph: this one has interaction with albumin, so it has a longer duration of action, but a smaller effect.

Metabolism

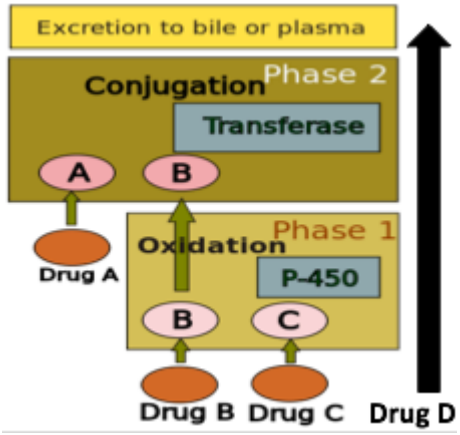
Alteration of the drug's chemical structure

Hepatic Enzymes

Hepatic enzymes will play a major role in the metabolism phase. There are 2 primary phases.

2 Main Goals:

1. Inactivation of drug
2. Promote excretion

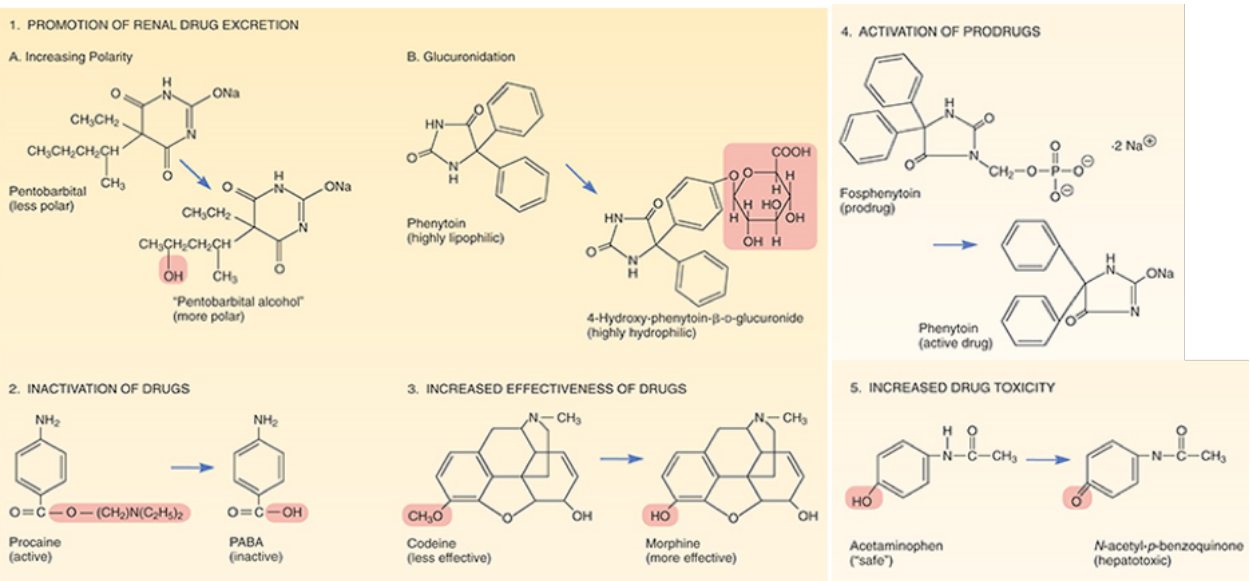


- Phase 1 enzymes: job of the phase 1 enzymes, is to perform redox reactions (turn off the drugs/inactivate).
- Phase 2 enzymes: conjugation reaction with transferase - they transfer a particular chemical group onto the drug. The goal of phase 2 is to promote excretion (making the drug more water soluble, making it into the urine and ready to be excreted).

**Drugs A, B, C, D are the different scenarios possible.

Why does drug A not go through phase 1? It's probably already inactivated, but just needs to be made water soluble to be excreted.

Therapeutic consequences



#1: Promotion of renal drug excretion (phase 2 reactions) - drugs are made more hydrophilic (water soluble) to be excreted more rapidly. Lipid-soluble drugs cannot be excreted by kidneys.
#2: Inactivation of drugs (phase 1 reactions)
#3 Increased effectiveness of drugs

- Codeine: is an example of an off drug. It goes to the liver, and turned into morphine (turned on), then morphine will have pain relief effects. Then morphine will be inactivated.

#4 Activation of prodrugs - are drugs that are pharmacologically inactive as administered and then undergoes conversion to its active form via metabolism
#5 increased drug toxicity –if your liver isn't functioning properly, instead of turning off a drug, it will turn it into a super drug (harmful).

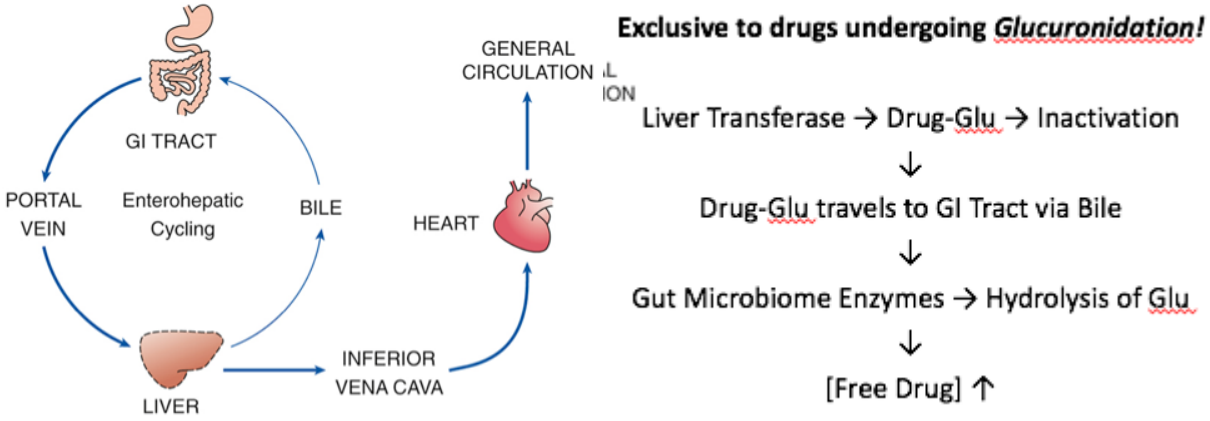
Special metabolic considerations

- **Age** will affect the metabolism/efficiency of the liver enzymes, especially in infants under the age of 1 and older adults.
- **Competition** between drugs and enzymes - if a pt is on two drugs and both are metabolized by the same enzyme, well we only have so many of that one enzyme, so the drugs will have to wait in line to be metabolized, thereby decreasing the rate at which one or both agents are metabolized → can increase to dangerous level
    - Ex: drug A gets metabolized first, but in the meantime drug B is still having some effects while waiting to be metabolized.
- **Induction & inhibition**
    - Induction: drugs that act on the liver to increase rates of drug metabolism. Induction of drug-metabolizing enzymes can have 2 therapeutic consequences.

        - First, if the induced is also a substrate, by stimulating the liver to produce more drug-metabolizing enzymes, the drug can increase the rate of its own metabolism, thereby necessitating an increase in its dosage to maintain therapeutic effects.
        - Second, induction of drug-metabolizing enzymes, the drug can accelerate the metabolism of other substrates used concurrently, necessitating an increase in their dosages.
    - Inhibition: are drugs that act on the liver to decrease rates of drug metabolism. They also cause therapeutic consequences because slower metabolism can cause an increase in active drug accumulation, leading to adverse effects and toxicity.
- **1st pass effect** – is only applied to drugs that are administered orally because it only happens when the drugs are absorbed from the GI tract, they are carried directly to the liver via the hepatic portal vein. That means the drugs that are ingested go to the liver first, before reaching the heart. So they go through a round of metabolism even before getting into the systemic circulation.
    - ex: morphine cannot be given orally because it gets metabolized so rapidly. They get turned off immediately in the liver before going systemic. So a large percentage of morphine would go to waste. Therefore, morphine is given parenterally, to bypass the 1st pass effect.
- **Nutrition**: some of the foods/vitamins you eat can have an effect on the efficacy on the metabolism phases. Also, hepatic drug-metabolizing enzymes require a number of cofactors to function. In the malnourished patient, these cofactors are deficient, causing drug metabolism to be compromised.

<u>Enterohepatic Recirculation</u>

There is a cycling that happens between the liver and intestines. It is exclusive to drugs undergoing glucuronidation (example of phase 2/conjugation).



Liver transferase adds Glu to certain drugs, inactivating them. They can then enter the bile and then pass to the duodenum and interact with your gut microbiome. Some enzymes in the gut microbiome are able to "chop/remove" (hydrolyze) Glu from drugs, reactivating it. Because the free drug is more lipid soluble than the glucuronidated form, the free drug can undergo reabsorption across the intestinal wall, followed by transport back to the liver, where the cycle can start again.

Taking Abx will decrease your gut microbiome. If you have a decrease in gut microbiome, this will decrease the amount of Abx that will be reactivated, and therefore the efficacy of the drug will go down.
When taking Abx at the same time as another drug, you might need to take more of that other drug in order to have better efficacy because of the reduced microbiome.

- Ex: oral contraceptives while on Abx (it reduces the effects of the oral contraceptive)

Excretion

Drug removal from the body

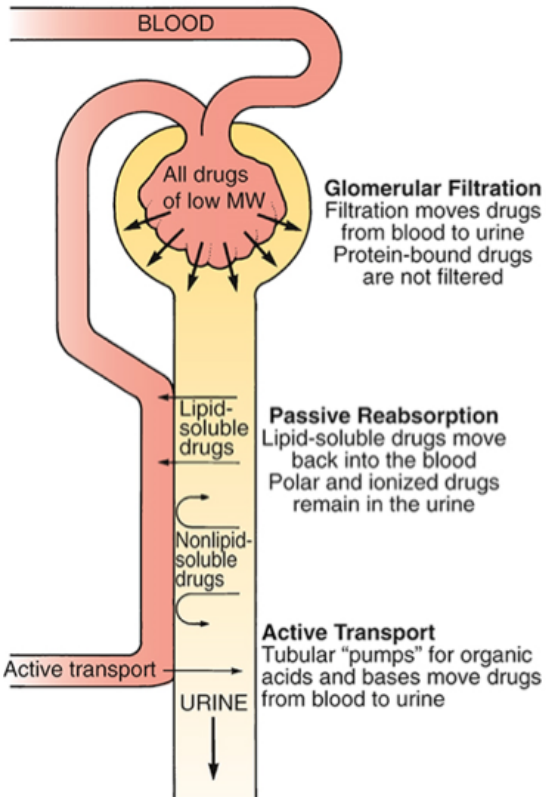
Metabolism + Excretion =

<u>Renal Excretion</u>

- Excretion = GF + TS - TR

Factors affecting renal excretion:

- Age:
  - Renal function decreases with age
  - Kidneys in newborns are not fully developed, limiting their capacity to excrete drugs.
- pH - Ion trapping: pH dependent ionization can be used to accelerate renal drug excretion. Recall that passive tubular reabsorption is limited to lipid-soluble compounds. Because ions are not lipid soluble, drugs that are ionized at the pH of tubular urine will remain in the tubule and be excreted.
  - We can manipulate the urine pH in such a way to promote the ionization of a drug, decreasing passive reabsorption back into the blood.



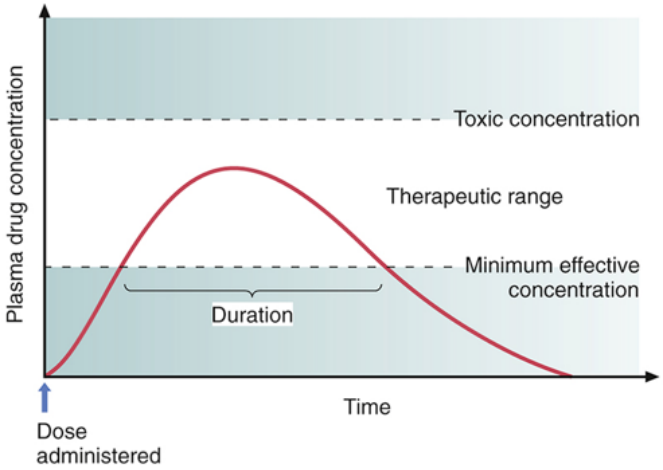
- Tubular transporter competition:
    - If you have 2 drugs, and they both need to be secreted in the tubules by the same protein, they'll have to compete. This causes accumulation of one of the 2 drugs, leading to toxicity.

Non-renal Excretion

- Lungs
    - Alcohol ~ 10% (breathalyzer)
    - Anesthetics
- Breast milk
    - Lipid-soluble/non-polar drugs enter breast milk more easily, and therefore in larger amounts
    - Patient education of breastfeeding women!
- Bile/feces, saliva & sweat
    - Therapeutically insignificant
    - Useful for drug detection testing

Drug Response Timeline

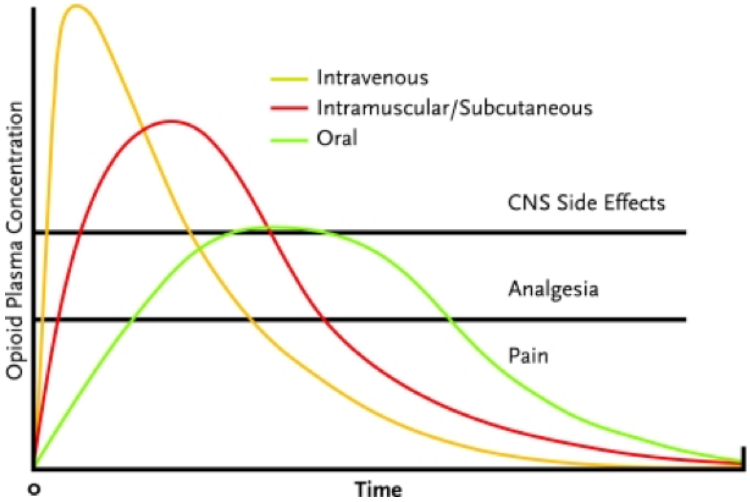
Plasma Drug Concentration



- Plasma drug levels correlate with therapeutic/toxic responses → Practical!! Measuring plasma levels is much easier than measuring directly at the site of action (ex: brain cells, heart cells, etc)
- Therapeutic objective:
    - maintain therapeutic range
    - Avoid toxic concentrations
    - Wider range = safer drugs
    - Narrow = increased toxicity risks

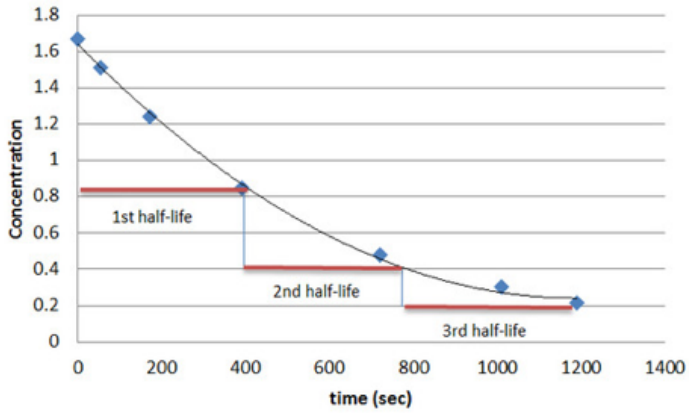
- Minimum effective concentration: the plasma drug level below which therapeutic effects will not occur.
- Toxic concentration: toxicity occurs when plasma drug levels climb too high
- Therapeutic range: is the range where there is enough drug present to produce therapeutic responses but not so much that toxicity results.
    - Certain drugs have a large gap between their floor and ceiling levels. However, some drugs have a very small therapeutic window, making it difficult to administer safely.
        - Ex: acetaminophen has a wide therapeutic range (about 30x greater than MEC)
        - Ex: lithium has a very narrow therapeutic range (about 3x greater tham the MEC)
- Drug behavior (graph line) influenced by kinetics:
    - Absorption → time until MEC
    - Distribution → peak height
    - Metabolism & excretion → duration length (T1/2)

<u>Drug Concentration x Administration Route</u>



- Orally is the safer route, the slope is softer, it stays more in the analgesia section of the graph.
- Watch out for:
    - Onset
    - Peak
    - Duration

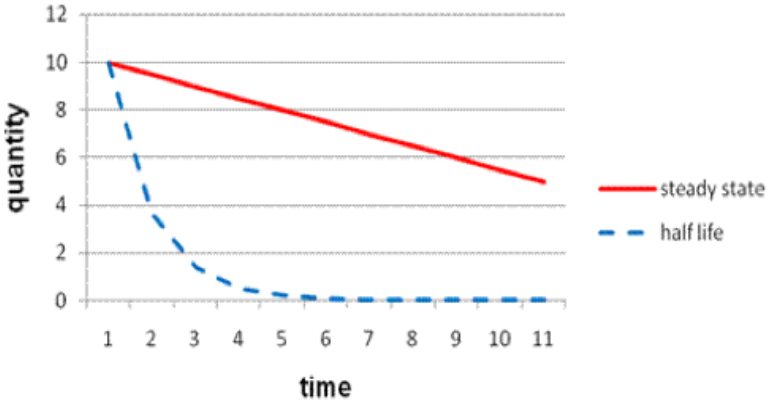
Half life



$T_{1/2}$ determine Dosing Schedule
Long $T_{1/2}$ = Long Intervals (ex.: 2mg/day)
Short $T_{1/2}$ = Short Intervals (ex.: 2mg/3 hours)

- It's the time it takes for the drug levels to drop by 50%. 1.6mg is the start. Half of 1.6 is 0.8mg so it drops to 0.8mg on the graph (1st half life). They it will drop to 0.4mg (2nd half life). Every 400s your drug level is decreased by half.

First-Order vs. 0-Order Kinetics



Example: 1st-order kinetic drug with 3 hours half-life vs. 0-order kinetic drug with 2mg/hour half-life

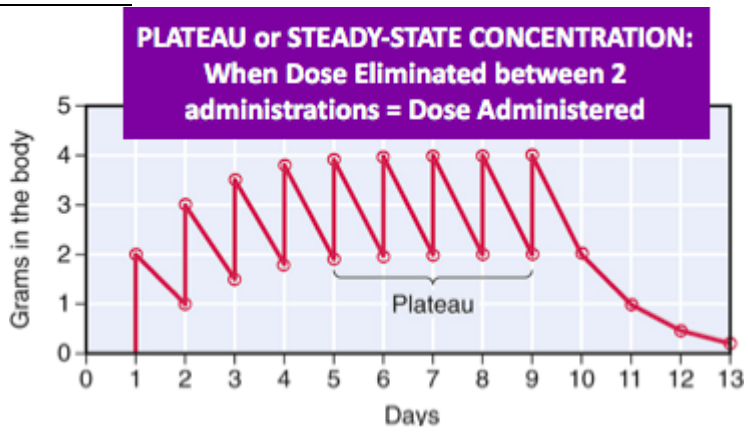
Hours ($T_{1/2}$)	1st-Order (mg)	1st-Order (mg)	Zero-Order (mg)
0 (0)	10	50	50
3 (1)	5	25	44
6 (2)	2.5	12.5	38
9 (3)	1.25	6.25	32
12 (4)	0.62	3.12	26
15 (5)	0.31	1.06	20

- Blue dotted curve(first order kinetic): is your typical half-life curve.
  - Ex: morphine
  - removed quicker
- Red curve (0-order kinetic):
  - ex: alcohol
  - risk of toxicity

All drugs can exhibit both behaviors. It all depends on concentration.

- 1st order drugs = impossible to saturate in real life
- 0-order drugs saturate so fast = impossible to observe 1st order

Repeated Doses: Plateau Levels



- What causes drug levels to reach a plateau? If a second dose of a drug is administered before all of the prior dose of a drug is administered before all of the prior dose has been eliminated, total body stores of that drug will be higher after the second dose than after the initial dose. As succeeding doses are administered, drug levels will climb even higher.
    - Took about 4 half-lives to reach the plateau
- The drug will continue to accumulate until a state has been achieved in which the amount of drug eliminated between doses equals the amount administered. When the amount of drug eliminated between doses equals the dose administered, average drug levels will remain constant and plateau will have been reached.
- Loading dose is a larger dose to reach the plateau quicker, then you give maintenance doses, smaller doses, to keep in the plateau.
- Not all drugs can be given as a loading dose due to the high risk of toxicity.
- **Rule of thumb**:
    - When repeated doses follow a regular schedule (ie. same dose at same interval), plateau is reached = 4 half-lives
- Key = Constant doses
    - Increasing dosage but keeping it constant only elevates the plateau but does not shorten the time it takes to reach it. It takes the same amount of time to reach the plateau, whether it be a small dose or large dose.
- Expert nurse question: let's say you wanted to reach a plateau between 2mg and 4mg. What could be done to reach it faster?

Drug Levels Management

- Reducing fluctuations techniques → narrow peak and trough range
    - Continuous infusions - plasma levels are kept constant
    - Depot preparations - releases the drug slowly and steadily
    - Dosage & interval reduction → reduce both the size of each dose and the dosing interval (keeping the total daily dose constant) ex: 1g, 2x/day vs 2g 1x/day
- Achieving plateau/steady-state faster → loading dose & maintenance dose
    - Loading dose = larger initial dose to reach the peak value fast (ex. 4g on the 1st day)

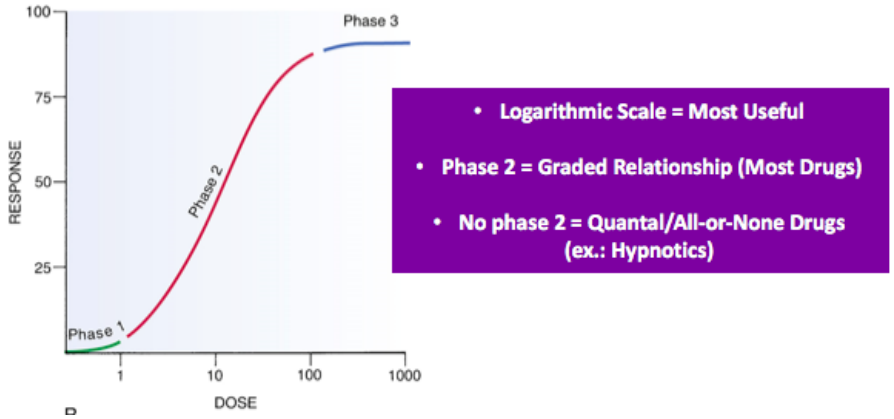
- Maintenance dose = regular dose at regular intervals to maintain plateau phase (ex: 2g/day afterward
- Most useful for drugs with long half-lives

- Drug discontinuation → short half-lives are safer than long half lives
  - 4 half-life rule = When a drug is discontinued, it takes about 4 days (4 half-lives) for most (94%) if the drug to leave the body.
  - Toxicity management is complex & hard when half-life is long → **favor short half-life whenever possible!!**

Pharmacodynamics: what drugs do to our body? (Ch. 5)

Dose-Response Curves (DRC)

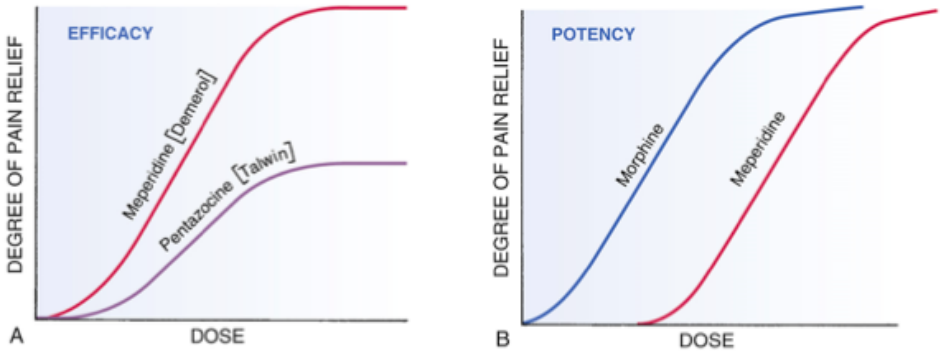
DRC: What is the response of the drug at different doses? Dose response relationships determine the minimum amount of drug needed to elicit a response, the maximum response a drug can elicit, and how much to increase the dosage to produce the desired increase in response.



- This shows, as the dosage increases, the response becomes progressively larger.
- Phase 1 (no response phase): you get the drug in your body, but the dosage is not high enough to produce a meaningful response.
- Phase 2: an increase in dose elicits a corresponding increase in the response. Some drugs don't have a phase 2, meaning that they don't have an effect (all-or-none)

Efficacy vs. Potency

Efficacy vs. potency – two very independent concepts.



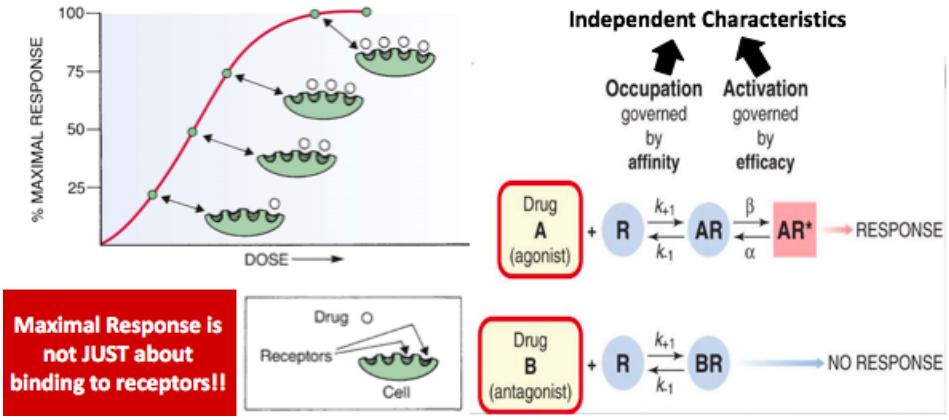
- Efficacy: the largest effect that a drug can produce → height of the curve
  - Mepiridine is more effective than Pentazocine, because the response is much greater than Penta (higher curve).
- Potency: the amount of drug we must give to elicit an effect → relative position of the curve along the x-axis
  - morphine/meperidine have the same efficacy (same height in curve). Morphine is much more potent than Meperidine because you have a smaller dose than you would need for Meperidine to reach the same effect.
- N.B. a drug with very high maximal efficacy is not always more desirable than a drug with lower efficacy. Recall, you want to match the intensity of the response to the needs of the patient.

Drug Receptors

- The drug has an effect on the body because it interacts with receptors.
- Receptors are useful to communicate different messages throughout the body.
- Drugs don't do anything more than what your body can already do.
  - Ex. NE increases HR. A drug can also be given, that will bind to the same receptor, increasing your HR. Or it can bind to the receptor, and block the action of NE, thereby preventing stimulation of the heart

Affinity vs. Efficacy (p.49)

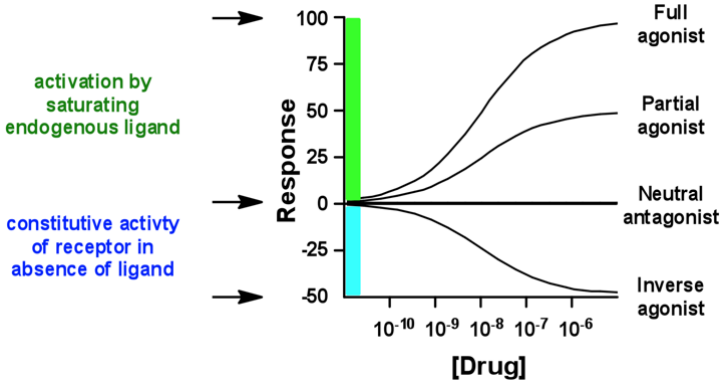
- Efficacy: maximum dose response you can get. When the drug binds to the receptor, does it activate it?
- Affinity: physical binding of the drug
  - Ex: Morphine interacts on opioid receptors. But heroine, also an opioid, is more potent because it has a much higher affinity for the opioid receptor than morphine.



- Oxycodone is a moderate opioid because it has a lesser affinity than morphine does for the receptors.
- Occupation is governed by affinity – because a drug can have a high affinity, meaning it will bind to the receptor, but not necessarily have a high efficacy (it might not activate, and it will just sit there occupying space).
- Activation is governed by efficacy.
- These characteristics are independent of each other.
- The curve is an s-shaped curve – at 25% maximal response, you have one receptor that is occupied. At 50%, you have half the receptors that are occupied, and therefore have half the response. At 100% you then fall into a plateau phase where if you continue giving medication, you don't get a bigger response because all the receptors are occupied already.

<u>Agonists vs. Antagonists</u>

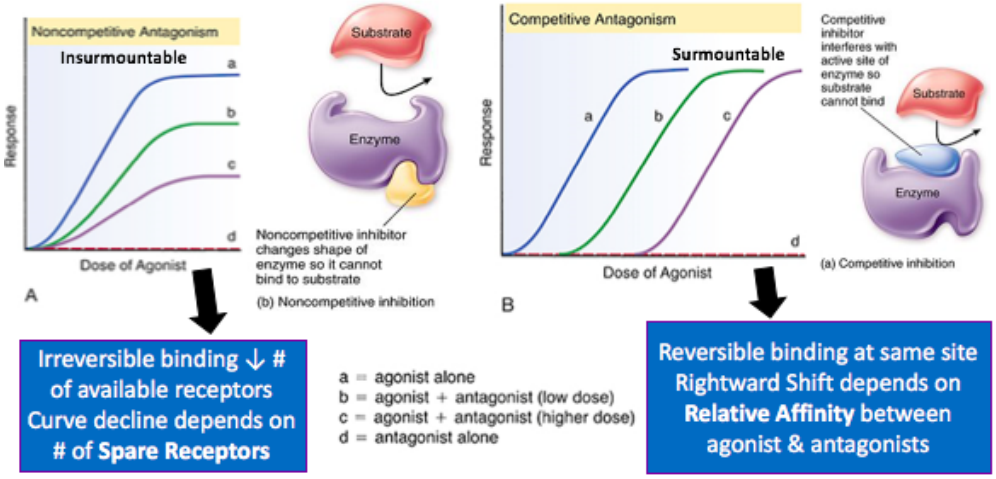
- This has to do with efficacy



- Agonist: a drug that is able to activate the receptor (has both affinity and high intrinsic activity)
  - ex: morphine is an agonist of the opioid receptor
- Full agonist: a drug that can get to the maximum response (ex. Mepiridine).
- Partial agonist: a drug that can get to only a partial response (ex. Pentazocin)
  - Can also act as an antagonist. For example, if the patient is already receiving Mepiridine (a full agonist), and then we give a large dose of Pentazocin, it will then occupy the opioid receptors and prevent their full activation by Mepiridine.

- Antagonist: a drug that prevents the activation of receptors. The response of an antagonist is determined by the amount of agonist present.
- Neutral antagonist: a drug that has affinity to the receptor (so it binds), but has no effect, the response is zero.
- Inverse agonist: response is negative –a drug that binds to the same receptor, causing a response that is opposite of what the receptor normally does. Only works on receptors that are already working (vs. those that are asleep), you can upregulate or downregulate. Example: a receptor that lowers BP, inverse agonist will increase BP.

<u>Antagonists Type</u>



(on the picture:substrate is the drug, enzyme is your target, yellow is your antagonist)

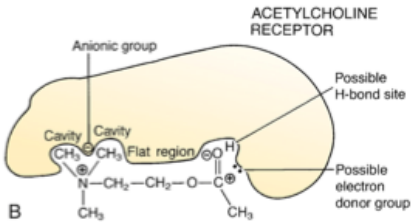
- Two types of antagonists:
  - **Insurmountable (non competitive) antagonist**: the antagonist binds to a receptor/enzyme (target) at a different site than the drug (substrate). They are not fighting for the same site/spot. When they bind to the receptor, it causes the enzyme to change its shape, preventing the substrate from being able to bind to the other site, because now the shape has changed. Called insurmountable because it doesn't matter how much more of the drug you give, because your receptors have a different shape, nothing can bind there anymore. And therefore, your response decreases with increased dose of agonist. Spare receptors are the number of receptors you have in extra. So let's say we have 100 pain receptors, but only need 10 receptors to have the maximum response. Now if the antagonist binds to 20 receptors, well you still have 10 receptors available to give the maximum response. But now if you add more antagonists, and have eliminated 95 of the receptors, you can't reach the maximum response because of a lack of spare receptors.
    - In other words: the effect of irreversible binding is equivalent to reducing the total number of receptors available for activation by an agonist.
  - **Surmountable antagonists (competitive antagonists)**: that's when the antagonist binds to the same site as your drug. The affinity is what determines

who will bind to the site. The one with the highest affinity will get to bind more often. If they both have the same affinity, binding will be by random chance or by whichever is present in more quantity. The more drugs you have present, the bigger the chance of it binding to the site. To get to maximal response, we want to flood, this means adding more of one substance by increasing the dose of the drug, this increases the odds of the drug binding to the site. There will be less antagonist present, and therefore less chance of it binding to the site.

- In other words: competitive antagonists produce receptor blockade by competing with agonists for receptor binding

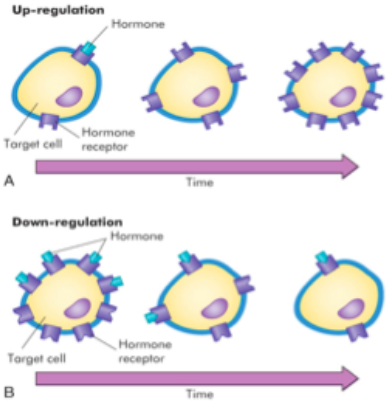
<u>Receptor Selectivity vs. Sensitivity</u>

- Receptor selectivity: has to do with is your drug monogamous or non-monogamous? Does it bind to just one receptor or to multiple receptors? The more selective a drug is, the smaller the affinity it has for different receptors. Whereas, the smaller the selectivity means that it can bind to a wider range of receptors. The more selective a drug is, the better we are at predicting its effect (meaning it will bind to one receptor and we know what that response will be). Versus if it less selective, it binds to many different types of receptors, and this entails a larger amount of side effects because each receptor it binds to will have different outcomes.



A Single Receptor can regulate multiple processes (produce multiple effects)

Ex.: Opioid Receptors
Pain, Respiration, Bowel Movement

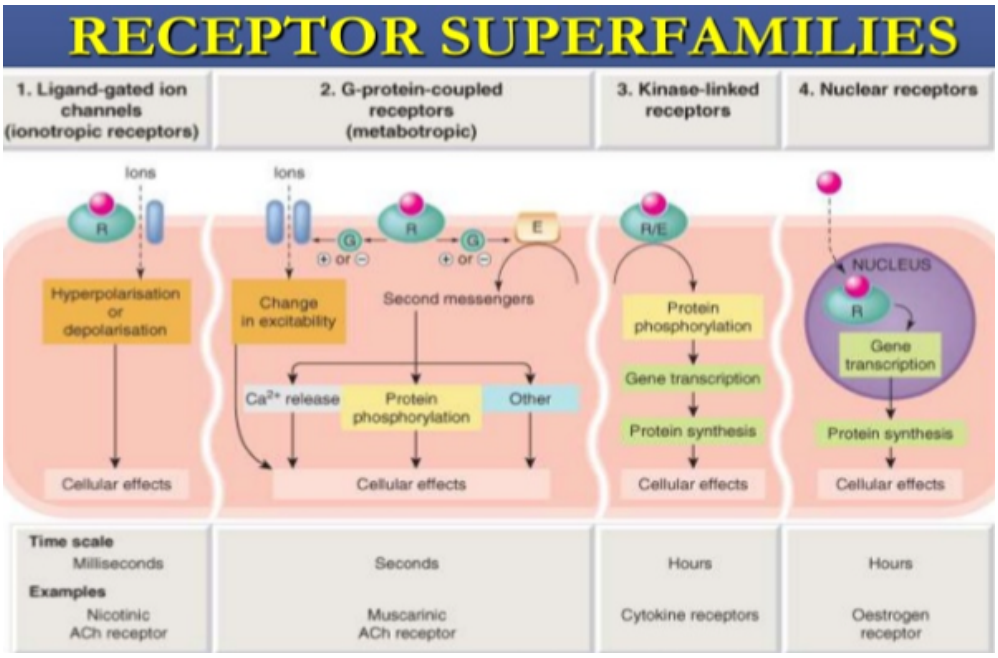


- Red box example: opioid receptors are not only found just for pain, they also regulate respiration (found in the medulla), bowels, etc.
- Sensitivity: what's the impact of the drug on the # of the receptors overall. How sensitive are you to a certain drug? Your sensitivity level can fluctuate over time by processes known as 'upregulation and downregulation'. Where your body adjusts the # of receptors based on what's happening.
    - Downregulation: when the receptors of a cell are continually exposed to an agonist, the cell usually becomes less responsive (ie. desensitized/refractory), meaning it has undergone downregulation. This is your body's way of restoring homeostasis by removing some of the receptors to decrease the activation level, to bring it back to the way it was before.

- Upregulation: continuous exposure to antagonists has the opposite effect, causing the cell to become hypersensitive (supersensitive). One mechanism that can cause hypersensitivity is synthesis or more receptors.

4 Main Receptor families

Know the 4 receptors, don't need to know them in detail.



1.Ligand-gated ion channel: sodium channels, potassium channels

2.G-protein-coupled receptors (will go over this later)

3.Kinase-linked receptors: cytokine, insulin receptors

4.Nuclear receptors (aka hormone receptors): takes hours to have an effect because it has to produce or eliminate proteins which takes days. (big changes, longer to see effects)

Pay attention to time scale and the different cellular effects
From left to right, they are going in increasing time scale.

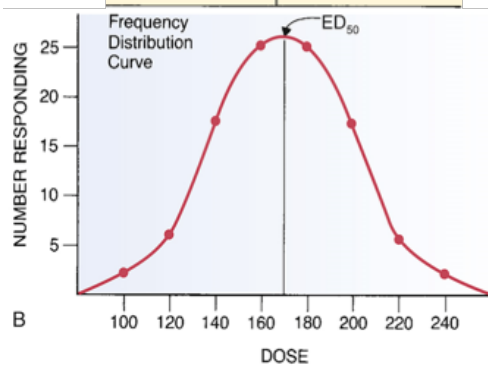
Non-Receptor Targets

- Chelating Agents → physically neutralize/trap chemical molecules
  - Antacids → acts by binding to H+ ions and neutralize them
  - Resins (ex. coesevelam) → Target cholesterol
  - Dimercaprol → target heavy metals (antidote!!)
- Laxatives → chemical molecule retention
  - Magnesium sulfate → acts by osmotic water retention in GI tract
- Antiseptics (ex. Ethyl alcohol) → results from precipitating bacterial proteins
- Protective coats → prevent chemical cell injuries
  - Sucralfate → coat stomach lining to prevent/protect GI ulcers
  - Sunscreens → coat skin cells to prevent/protect UV-induced injuries
- Anti-mitotic agents (anti-cancer) → prevent cell cycle stages
  - Taxanes → stabilize microtubules to inhibit cell division

Interpatient variability

Inter-patient variability refers to giving two patients the same dose of the same medication, but they won't have the same response to it.

Dose of Drug (mg)	Number of Subjects Responding at Each Dose
100	2
120	6
140	17
160	25
180	25
200	17
220	6
240	2



One of the measures we have is the ED50 (effective dose for 50% of individuals): it's the dose that achieves the therapeutic objective in 50% of the individuals. It is the standard initial dose for 1st exposure. This is a guideline to help you question the initial dose given to a patient if it differs by more than 20% (see example on p.52).

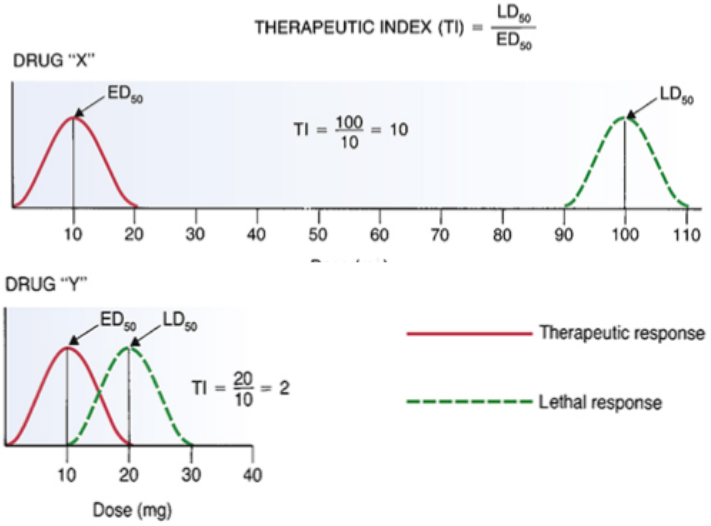
Nursing clinical implications:

1. Only question initial dosage if differs from ED50 by more than 20%
2. Evaluate response closely following initial few doses. Pt might need an increase or decrease in dosage.
3. ED50 = average effective dose! Effective for some, ineffective or toxic for others
4. Recommend adjusting dosage accordingly if necessary

Drug Safety: Therapeutic Index (TI)

Therapeutic index: value to illustrate the range between minimal effective dose and toxicity.

- LD50 (animal studies): lethal dose in 50% of individuals
- TD50 (human studies): toxic dose in 50% of individuals
- Larger TI - safer drugs; Smaller TI - relatively unsafe drugs.



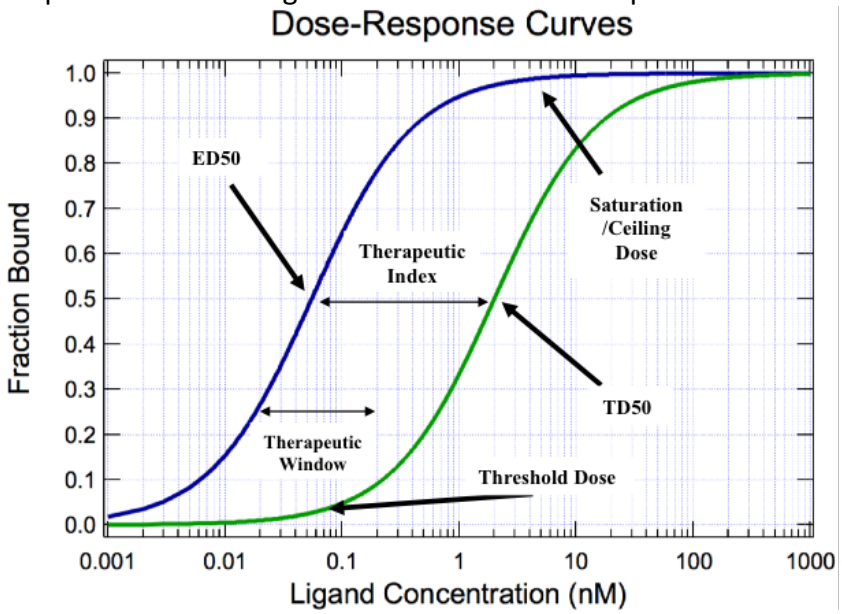
The larger the distance between those two curves, safer the drug. (ie. Drug X)
The smaller the distance between the curves, the more risky it is to give a lethal dose. (ie. Drug Y).

The curves for Drug Y overlap. This overlap tells us that the high doses needed to produce therapeutic effects in some people may be large enough to cause death

- Ex. Alcohol has a very low therapeutic index, very toxic. Alcohol's TI = 4. If discovered today, it would never be legalized.

Therapeutic vs. Toxic curves

Here, we can compare the same drug's toxic curve to the therapeutic curve.



- Ceiling dose: what is the dose after which you have no more efficacy
- Threshold dose: what's the minimum dose to give to get an effect
- Therapeutic window: it is similar to the therapeutic index. But the chances of getting into the toxic window is much less than if were looking at the therapeutic index (it looks at the TD50). The therapeutic window typically doesn't go higher than the 10%.
    - Therapeutic effect of one patient can be the toxic effect of another. Ex: constipation to treat diarrhea (therapeutic) vs opioid constipation (toxicity). It all depends on what you are trying to treat.

Individual Drug Response Variations

Age & Body Weight

- Age - Generally, for a same dose:
    - drug response of infants & elderly > adults
    - Specific variations discussed next week
- Body weight
    - Concentration = quantity/volume
    - Water:fat ratio affects distribution of drugs
        - %body water & %fat have an impact since there are drugs that are water soluble vs. lipid soluble.
        - You would give a larger dose of lipid soluble drug (because there's a lot of fat) or low dosage of water soluble drugs (because there's less water).

- Larger individuals usually require larger doses

	Infants	Adults	Elderly
%Body Water	↑	↔	↓
% Fat	↓	↔	↑

%Body Water	Lean	Average	Obese
Males	70	60	50
Females	60	50	42

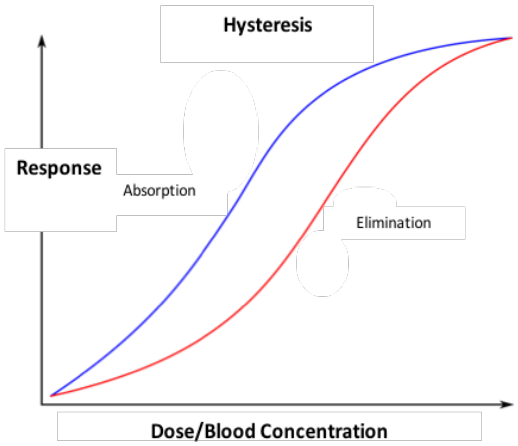
Pathophysiology

The physiology and the pathology of your patient can alter some of the kinetic and dynamic parameters. Example:

- Kidney failure → decreased excretion = increased half life
  - the half-life of the drug is 1.5h. Versus someone in renal failure, the half-life is 25h.
- Liver failure = multiple adverse effects
  - Increased toxicity of drugs or decreased efficacy of pro-drugs (drugs that need to be activated = failed treatment)
  - Decreased plasma proteins = increased response of drugs with high plasma protein affinity
- Diarrhea/constipation
  - Absorption rate alterations
- Acid-base imbalances
  - Exacerbation of ion trapping/pH partitioning
- Altered electrolytes concentrations
  - Ex: digoxin toxicity (dysrhythmias) increases if serum potassium level is low

Tolerance

Tolerance is the concept of decreased drug response from a repeated dose, because your body becomes habituated to feeling the effects of the drug. So it builds a resistance to the drug. That's why you need to give a bigger dose to feel the effects, then you build more resistance, etc. This pushes the response curve to the right.



Tolerance doesn't develop for all the different effects of the drug at the same rate.

- Ex for opioids: the tolerance for pain relief increases a lot but the tolerance for constipation doesn't really happen. So you keep increasing the dose to reach the same pain relief, however by doing so, you increase the effects of constipation.

Some tolerances are dynamic in nature: if it changes the # of receptors, sometimes the tolerance is metabolic/dynamic (kinetic tolerance).

Pharmacodynamic tolerance:

- Long-term receptor regulation (changes in # of receptors)
- Usually increased MEC/rightward shift of DRC
- May decrease maximal efficacy

Hysteresis: special short-term (single dose) dynamic tolerance

- Ex: depletion of enzymatic cofactors for drug response

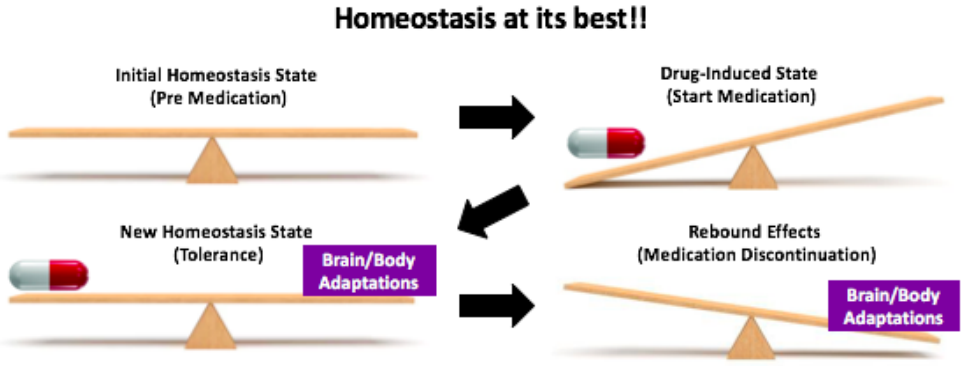
Metabolic (kinetic) tolerance:

- Altered (increased or decreased) drug metabolism
- Usually decreased duration of response

Tachyphylaxis: special short-term kinetic tolerance (completely unabsorbed molecule or metabolized super fast)

<u>Withdrawal/rebound effects</u>

When a patient is becoming very tolerant to a drug, the withdrawal effect is when symptoms arise when you stop giving the drug.



At first, when you are not on a drug, everything is in balance (homeostasis). When you introduce a drug into a person, this causes imbalance. Your body tries to adapt to that to restore homeostasis. The body's adaptations try to match the effects of the drug. But when you remove the drug, your body's adaptations are still present (rebound effects)

** Rebound effects should be opposite of drug effects

- Ex: alcohol = depressant → alcohol withdrawal sx = muscle tremor; hyperactivity

Placebo effect

Fraction of drug response based on patients' attitude & expectations of the Rx. Your brain tricks your body into feeling better

Pharmacogenomics

Combines genetics and pharmacology: it studies the effects of genetic variations on drug response.

- Increased metabolism → decreased therapeutic action
- Decreased metabolism → increased toxicity
- Increased receptor activity or population → increased therapeutic effects
- Increased risk of allergic reactions

There are some drugs (as indicated in the table on slide 52) where genetic testing is highly recommended prior to giving a drug because it has a significant impact on the person depending on whether if they have this gene instead of that gene.

Sex & Race-related variations

Sex-related differences: no data on women before 1997. Now required to participate in clinical trials. Some practical examples:

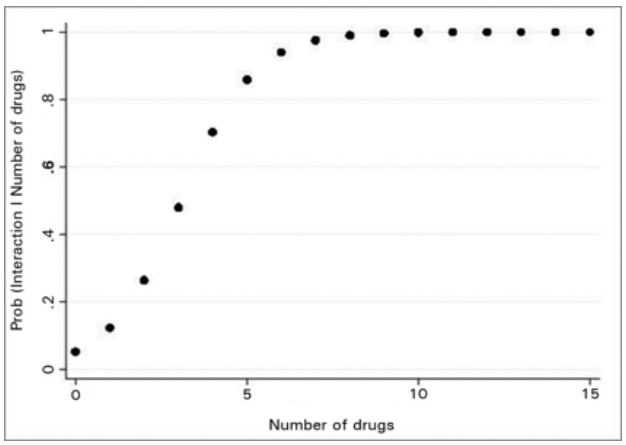
- Digoxin increases mortality of women only
- Women alcohol metabolism is lower
- Opioid pain relief efficacy in women > men

Race-related differences: 'race' = shared genetic & psychosocial factors

- Ex: BiDil = only approved for African-Americans, but likely that it would also benefit others!
- Asian: have difficulty metabolizing alcohol → get drunk faster

Comorbidities & Polypharmacy

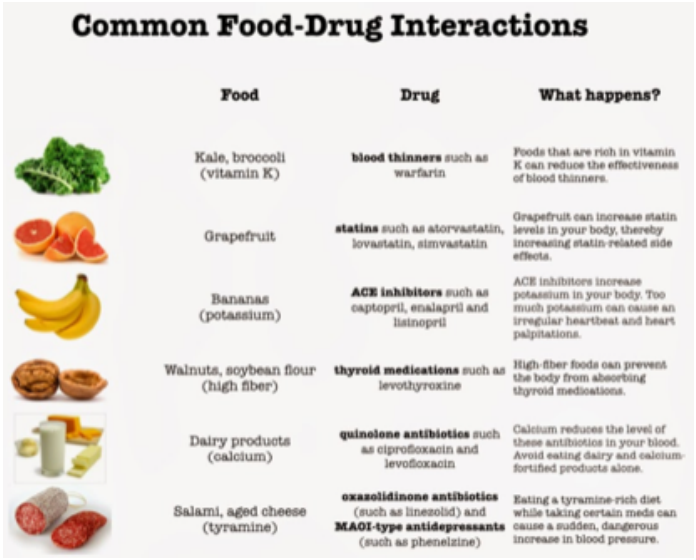
- Comorbidities: patient with 2+ conditions requiring Tx
    - Ex: patient with asthma & hypertension → if you give beta-blocker for HTN, it could cause bronchoconstriction and worsen asthma
- Polypharmacy:
    - associated with comorbidities
    - Frequent in elderly
    - Significant increased risk of drug interactions
    - At 5+ drugs, you are 100% likely to have drug interactions



Diet & Patient adherence

Diet effects on drug response:

- Healthy diet increases therapeutic benefits
- Drug-food interactions (ex: grapefruit juice)
- Decreased plasma proteins (ex: starvation)



Patient adherence:

- 30-60% of patients do not adhere correctly
- Problematic with elderly (memory loss)
- Patient education is key!!!

Recap of individual variations

- Watch for distribution differences due to BMI
- Consider effects of pathologies on drug response (especially liver and kidney diseases)
- Watch out for decreased DR and increased toxicity with long-term medications
- Minimize placebo effect by conveying optimistic (but realistic!) expectations about Rx
- Verify if known genetic, race or sex-related characteristics exists for the Rx
- Consider the patient as a whole (holistic approach)
- Good patient education (diet, drug adherence, expected effects) to optimize therapeutic objective