Introductory Lecture: Terms, Pharmacodynamics, Pharmacokinetics.

Textbook:

Lippincott's Review of Pharmacology 6th or 7th Edition: There are some readings in this book I will assign that I do not cover in my lengthy handouts. Please get this book. Either edition is fine.

Flashcards: Quizlet.com *(Do a search for "Boyev" to find old sets)* *https://quizlet.com/subject/boyev/*
If you make a flashcard set, put "Boyev" in the title so that others can find it.

All information in my lecture handouts is definitely fair game for quizzes and exams, including this page!
At a minimum, be sure you can explain, describe and use all **bold-faced terms**

The web:

Good, *reliable* and easy-to-use sources for pharm & health information:

dailymed.nlm.nih.gov <-(My personal favorite)
mayoclinic.com
fda.gov
I recently discovered **http://tmedweb.tulane.edu/pharmwiki ;** it seems good so far.

Good and *reliably accurate* YouTube channels:

Crash Course Anatomy and Physiology: https://tinyurl.com/okqfcxg
Khan Academy
SciShow
Doctor Mike

Fairly easy-to-use and *usually* reliable websites also include: medlineplus.gov
Other reliable sites can be found at
http://www.nlm.nih.gov/portals/healthcare.html

When purchasing supplements and herbs only buy those with a USP seal:
(This is the U.S. Pharmacopeia, a 3rd party lab that tests drugs to prove that what is inside is actually what is on the label)

Remember that ONLY **"Drug Facts" is a legal document.** "Supplement Facts" is fiction

99% of health-related websites are absolutely unreliable for HEALTH information.
YOU CAN NOT TRUST:

Almost every .com website (sadly)
Almost every .org website (sadly these usually are agenda-based and are free to buy)
ANY AND ALL news websites!
(Remember these stories are almost all written by Journalism Majors, not health or science professionals!)
Blogs
Facebook
Forums (including "ask" websites like yahoo.com)
Be very suspicious of websites that:

- *contain **any** advertising*
- *claim to sell a miracle drug, superfood or supplement*
- *suggest your health providers "don't want you to know the truth"*
- *are endorsed by Dr Oz or other paid celebrities*

And for your own safety:
Always read the **"Drug Facts" Label** - present on all FDA-approved **over-the-counter** (OTC) drugs
Always learn the **generic name** of any drugs you use, OTC or otherwise
Beware of ANY and ALL vitamins or supplements that do not carry the **USP seal of approval**

...I reserve the right to quiz or test you on the above information...

Okay. Let's get started with pharmacology!

Pharmacology: the study of drugs.

Drugs: any substance that interacts with the body in some chemical way, *usually* by binding a receptor and activating or inhibiting a normal body process
organic and/or inorganic
charged (**ionized, polar, hydrophillic**) and/or uncharged (**deionized, nonpolar, lipophillic**)
solids, liquids, gases
differentiated from nutrients or toxins?
What about oxygen, water, garlic, grapefruit, iron or vitamins? Are these drugs?

Dose: the exact amount of a drug given to a **specific** patient to produce a **specific** effect
Recommended Dose: the amount of drug for a given indication for an "average" patient of a certain demographic

Sources of Drugs (examples):
Plants – poppy (opium), nightshade (atropine), foxglove (digoxin)
Animals – horse urine (estrogen replacement)
Genetically engineered/reproduced molecules - human insulin
Manufactured, rational drug design -synthesized chemicals, immunochemistry
Genetically altered viruses: gene therapy *(Luxturna)*

Over-the-counter (**OTC**) drugs like herbal remedies, antacids, supplements and vitamins are drugs too! (**Supplements are not regulated by the FDA** and *frequently* do not contain the drugs or amounts of drugs on the outside label; hence the warning about **USP** above.)

Drug "Classifications": Simply a way to group drugs; helpful to discuss and learn drugs
Chemical Classification: based on the molecular structure (ex. morphine is an opiate)
Physiologic Classification: based on effect on body systems (ex. morphine depresses the CNS)
Therapeutic Classification: based on the use as therapy (ex. morphine used as pain reliever)
Pharmacologic Classification: based on mechanism of action (ex. morphine binds the mu receptor)

Drug Nomenclature:
Chemical name: precisely describes chemical structure. (ex: N-(4-hydroxyphenyl)acetamide)
No one uses these but organic chemists
Generic name: a.k.a. official, nonproprietary name. (ex. acetaminophen)
This is the name least likely to ever change and *usually* help you remember the drug
Suffixes often tell you the drug class: Some common examples:

ON EXAM ONE	ON EXAM TWO	ON EXAM THREE/FOUR
-ol = beta-agonists	**-caine** = local anesthetic	-**sartan** = ARB
-olol = beta-blockers	**-ane** = halogenated hydrocarbon	-**sone** = some kind of steroid
-ilol = weirdo beta-blocker	**-barbital** = barbiturate	-**capone** = COMTI
-zosin = alpha-blockers	-**zepam** = benzodiazepine	-**dipine** = CCB
-**stigmine** = ind. cholinergics	-**pram** = SSRI	-**pril** = ACEI
-chol = dir. cholinergic	-**xetine** = SSRI	-**prazole** =PPI
-curonium = anti-N-cholinergic	-**faxine** = SSNRI	-**afil** = PDE5 ED drug
-**trop**- = anti-M-cholinergic	-**tryptiline** = TCA	-**tidine** = anti-H2-histamine

Trade name: a.k.a. Brand name: marketed by the company that makes the drug (ex. Tylenol)
Easily spotted by the presence of a ® or ™
Eventually you'll need to know major trade names as well, since patients will use these.

Over-the-Counter (**OTC) drugs frequently change** the generic drug enclosed but maintain the same trade name without any warning! It's totally legal. Example: Various versions of Lotrimin antifungal cremes, gels, sprays and powders contain butenafine or clortrimazole or miconazole depending on the product, although all the packages say Lotrimin Athlete's Foot.

Drug Labeling:
Over-the-Counter OTC: "Drug Facts": The most AND ONLY reliable and legally binding part of an OTC label is the box marked **"Drug Facts".** Found **only** on over-the-counter drugs and are written for the general consumer with a **6th-8th grade reading level (age 11-13).**
Reading an OTC drug label:
See Example at FDA: https://tinyurl.com/ybxvfbml

***Do not trust *any* OTC product that does not carry the legally binding "Drug Facts" label.**
(e.g. "**Supplement Facts" is *not* a legal term** and should be *ignored*)

The trade name or packaging is usually misleading:
Ex: Some Robitussin products don't contain dextromethorphan (DM)
Ex: "DayQuil Mucus Control" contains no mucolytic

The "Drug Facts" Label is meant only for the general public and is not detailed enough to be useful to professionals in many situations. Prescription drugs packaged for inpatient and outpatient pharmacies have far more complete information on an insert inside the box that you can read online at rxlist.com or at the DailyMed website.

Some Abbreviations: as patient charts become electronic some are falling out of style...
Do not memorize these now; they are here only for reference.

Common abbreviations found in handwritten prescriptions...		
ABBREVIATION	MEANING	*LATIN TRANSLATION (JUST FOR FUN)*
q am	every morning	*quaque ante meridiem*
qd	every day	*quaque die*
pc	after meals	*post cibum*
qhs	at bedtime	*hora somni*
q1h	every hour	*quaque 1 hora*
bid	twice a day	*bis in die*
tid	three times a day	*ter in die*
qid	four times a day	*quater in die*
prn	as needed	*pro re nata*
Sig or Rx	prescription	*signa (write) or recipe (to take)*

Some abbreviations for route of administration you SHOULD memorize NOW		
PO = by mouth (enteral) **PR** = by rectum	**IM** = intramuscular **IV** = intravenous	**SC** = subcutaneous (sometimes "SQ") **SL** = sublingual

Example: *"Rx: diphenhydramine 50 mg po qhs prn insomnia" means:*
"Prescription: the patient should take a 50 mg dose of diphenhydramine by mouth (and swallow it!) before bedtime as needed for difficulty sleeping."

ROUTES OF ADMINISTRATION: How do we get drugs into the **BLOODSTREAM**?
Route **abbreviations** you must learn: **PO, IM, IV, SQ/SC, SL, PR** (see below)

ENTERAL: Via the **gastrointestinal tract** (from stomach down to superior rectum)
PO: *Orally, "by mouth" *-really means "by mouth **and swallowed**"*
Forms: pill, capsules or sustained-release, EC (enteric coated), pulvules (gelatin pills), powders, syrup, alcohol (elixir, spirit, tincture 5-20% alcohol!)
Other enteral routes: **NG** (nasogastric) tube
PEG tubes (percutaneous endoscopic gastronomy) (G tubes) through the stomach wall
Advantage of PO administration: easy, patients can take pills at home
Disadvantages: slow (30-60) min, nausea
Some patients cannot or will not swallow pills: a serious problem with some pH-sensitive or **extended/ slow-release drugs that can't be crushed or opened** (or else can become toxic or ineffective)
Another disadvantage of enteral administration of some drugs:
First Pass Effect: When food is absorbed from the GI tract (~stomach to large intestine) and into the blood stream it first goes to the liver via the hepatic portal vessels. Since the liver is the main metabolizer of all drugs, some drugs can be significantly inactivated after just one pass through the liver*. (see my video "Muddiest Point: First Pass Metabolism" for more on this!)* (some examples of drugs with high first pass metabolism: nitroglycerin, verapamil). More on this under pharmacokinetics.

TOPICAL : direct absorption through "exterior" surface
Can be placed:
directly on site of action (only tiny dose needed) or
absorbed for systemic use (a systemic dose is used)
Transdermal – patch 30-60 min (Estrogen, lidocaine, clonidine)
Inside the mouth: absorption through a well-vascularized mucosal surface like the inside of the mouth means **very fast action**.
Buccal– lollipops, fast-dissolving strips, oral sprays
Sublingual (SL) tablets (Nitroglycerin)
troches (sore throat lozenges),
chewing gum (nicotine)
Topical ointment: often petroleum-based, creams
Topical sheets - local anesthetics
Vaginal creams
Inhalation to lungs (solution, mist, suspension or gas – anesthetics, asthmatic inhalers)
Nasal spray to surface of sinuses
Eye drops, **ear drops**, and others...

Rectal (PR- per rectum): Variably categorized as enteral or topical (depending on the book you read) because the superior portion of the rectum drains to the portal vein, the inferior doesn't. So whether there will be a first pass effect might depend how far in you decide to shove the suppository!
-often dissolved in cocoa butter (15-30 min)
-good choice for patients who are vomiting or unconscious

"PARENTERAL"

Means: administered anywhere inside the body that isn't part of the gastrointestinal tract

*__Subcutaneous__: **(SC or SQ)**: This type of injection goes under the skin into the loose connective tissues beneath (skin, fat). Onset in minutes. **Can only inject small amounts** (<~1ml) and it has to be non-irritating. Example: Insulin.

*__Intramuscular__ (**IM**) This type of injection is injected into muscle, usually deltoid or leg. Onset in minutes (faster than SQ), still can inject only small volumes.

*__Intravenous (IV__): This is an injection directly into the veins.

Onset is within seconds. Can infuse huge volumes (liters).

IV Push: the drug is injected into the patient directly, usually via a "lock"

This does NOT mean the drug is "pushed in" quickly.

IV Infusion: the drug is diluted in the IV bag and slowly dripped in

Intrarterial Injecting into arteries is usually done to aim right at certain organs Ex. chemotherapy

Intrathecal, Intraspinal (into the spine – epidural for baby delivery)

Intracardiac (into the heart)

Intraocular (into the eye)

Intradermal (into the very outer skin itself) very short thin needle; example: TB test

Pharmacotherapeutics: The study of the use of drugs to treat disease

Indication: The condition for which you use a certain drug

Ex: Headache is an indication to use aspirin

Contraindication: **A situation in which you should NOT use a particular drug**

Ex. A bleeding wound in the brain would be a contraindication for using aspirin (aspirin also inhibits blood's ability to clot)

CATEGORIZATION OF PHARMACOTHERAPEUTIC EFFECTS

Therapeutic Effect: the desired effect of the drug (the effect is usually to treat the indication)

(Tylenol's therapeutic effect: relieves pain)

Adverse Effects Undesirable drug effects (side effects) that occur at recommended doses

Side effects that are extremely harmful or life-threatening are often referred to as **toxic effects**, or we call those effects **toxicity**.

Remember that **ALL substances can be toxic at high enough doses.** Even water!

neurotoxicity = toxicity **to** the nervous system

hepatotoxicity = toxicity **to** the liver

nephrotoxicity = toxicity **to** the kidney

cardiotoxicity = toxicity **to** the heart

ototoxicity = toxicity **to** the ear

*A common student error is to write something like: hepatotoxicity is toxicity **of** the liver... but that would mean that the liver is being toxic, which makes no sense! So don't do that. :-)*

Idiosyncratic Reaction: an unpredictable reaction to a drug; unpredictable in the sense that it may be known to happen, but there is no way to know who will get it.

Example: **Stevens-Johnson Syndrome** with many drugs such as the antiseizure drug. Genetic testing is helping to solve this mystery in many cases (i.e. carbamazepine)

Allergic Reaction: occurs when a patient becomes sensitized to a drug and mounts an immunologic response to that drug involving IgE, mast cells and release of **histamine** binding **H1 receptors**. It can range from mild **itching** to life-threatening anaphylactic shock (bronchospasm, edema, hypotension, tachycardia, convulsions, death).

Black Box Warning: In the old hardcover Physician's Desk Reference book, some warnings were set apart in a **black text box**, often at the beginning of each drug's listing. They are warnings that the FDA or Congress decided should be in a black box, and are not always the worst warning, or even relevant to the drug in question! (example: suicide risk warning on all antidepressants, or mortality risk on all antipsychotics). ALL DRUGS HAVE SIDE EFFECTS, even if they don't have a black box warning. Regardless, **you need to know ALL the warnings for all drugs, not just the "black box warnings"**, if you want to stay out of court.

(also, "black box warning" sounds really scary to patients. "Am I going to be in a black box if I take this drug?!" Don't be surprised if you get calls or emails from patients that hear about these!)

Pharmacodynamics (PD) & Pharmacokinetics (PK)
These are *two totally different processes*. Be sure to know PD from PK!

PD: What **D**oes the **D**rug actually **D**O when it is in the body **to fix the problem** it is used for? What organ does it go to? What proteins does it stick to? What bodily processes does it change? The term for this is **P**harmaco**DYNAMICS (PD).**

PK: **How much** of the **free**, available form of the drug is in your bloodstream? How long does it take to start working (**onset**)? How long does it last? How fast does it leave? The fancy word for this is **P**harmaco**KINETICS (PK).**

Note: Common mnemonics I've seen is: PK is "What the body does to the drug" and for PD: "What the drug does to the body". I think those are incredibly confusing and hard to remember which one is which!

I prefer the slightly misspelled and grammatically incorrect mnemonics:
Pharmaco**D**ynamics: How **D**o **D**rugs **D**o what **D**rugs **D**o? *(Mechanism of Action/Receptors/Enzymes/Direct/Indirect)*
Pharmaco**K**inetics: **Kwantity** *(quantity)* of free drug in the bloodstream *(Absorbed/Distributed/Metabolized/Excreted)*

Let's start with
PHARMACODYNAMICS: The study of the mechanisms of actions of drugs at their site(s) of action. *(See Dr. B's videos on Receptors)*

Mechanism of Action: How a drug produces its intended therapeutic effect
Examples: -by binding a specific **receptor** and activating or blocking it.
-by binding a specific **enzyme** and activating or blocking it.
-by binding a specific **ion channel** and activating or blocking it.

A drug is, as defined on page 1, pretty much any substance that can get into your bloodstream. So a drug is just a molecule with a certain size, shape, molecular charge**.** *Usually* a drug works at its **site of action** through a **protein**, either a **receptor,** an **enzyme** or an **ion channel**.

That makes sense, right? For a drug to work at a specific spot in the body, organ or cell it has to bind a specific molecule that has a **specific shape.** And proteins have primary, secondary, tertiary, quaternary structure (that's why you had to learn that in Biology class!) so that **every protein sequence has a unique distinct shape**. So for a drug to find its perfect mate, it has to bind its specific protein.

The **site of action** is the location in the body where a drug works. For instance, aspirin helps to lower a fever by acting at a temperature-regulating area in the hypothalamus in the brain. Therefore, we would say that the site of anti-fever action of aspirin is the hypothalamus.
*Note: Since almost all drugs end up in the general blood circulation, the drug molecule will be dispersed throughout the body. But the "site of action" is where you **want** the drug to work!*

Direct-acting drugs are those that act directly at a **receptor**. Let's focus on those for now.
At the site of action, a direct-acting drug will momentarily bind a receptor that will in turn trigger (or block) some event *(noted as "**Yay!**" in my video).*
The *Yay* usually represents opening of an ion channel, activation of a G-protein or enzyme, etc.

Drugs developed to be **"direct-acting" can target specific organs or areas of the body** based on **which receptor subtypes** are in those organs (see below).

A receptor is a specific protein where the drug binds. This receptor has a specific receptor **binding site** that is conformationally specific for this drug. Normally in the body, this receptor is the binding site of a hormone or chemical (either is called the **natural ligand** of the receptor) that the body makes.

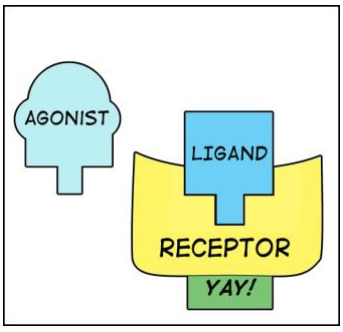
*This is why drugs can only affect natural processes; they have to interact with receptors already in your body!

PHARMACODYNAMICS TERMINOLOGY:

RECEPTOR NAMING:
*A receptor is usually named for the normal ligand it binds. For **hormones**:*
*Ex: **estrogen** binds **estrogen (Eα, Eβ)** receptors*
***aldosterone** binds **aldosterone** receptors,*
insulin** binds **insulin (IR) receptors
***angiotensin** binds **angiotensin (AT1)** receptors.*

*When you talk about receptors for **neurotransmitters**, the suffix **"-nergic"** is added.*
*ex: **adrenaline** (epinephrine) binds **adren**ergic **(ADR) (alpha & beta)** receptors*
***acetylcholine** binds **choli**nergic **(CHO) (M & N)** receptors,*
***dopamine** binds a **dopami**nergic **(D1-D5)** receptors,*
***serotonin** binds **seroto**nergic **(5HT$_1$-5HT$_7$)** receptors...and so forth.*

Please watch my video: Receptors: Agonists and Antagonists (15:56 long)



PROTEINS HAVE SPECIFIC SHAPES: RECEPTORS vs ENZYMES

*Quick review from A & P: Don't get **receptors** confused with **enzymes**. They are both proteins but are defined by their natural action in the body:*

A **ligand** binds a **receptor**, changes the structure of the receptor, and this causes an effect in/on the target process. Example: When the neurotransmitter Acetylcholine binds an Cholinergic N receptor on a skeletal muscle, an ion channel opens and sodium and potassium pass through. In this situation, Acetylcholine is the ligand.

*In contrast, when a **substrate** binds an **enzyme**, and the enzyme changes the substrate.*
*Enzyme names almost always end with **the suffix -ase.***
*Example: **Acetylcholinesterase** binds acetylcholine and turns it into acetate and choline. In this situation Acetylcholine is the substrate.*

A bit confusingly, notice that the same molecule (in this case acetylcholine) can be a ligand or a substrate, depending on what it is binding. If it binds a receptor, it is called a ligand. If it binds an enzyme, it is called a substrate.

SUBTYPES: The development of drugs has led us to discover that there are **subtypes** of receptors for almost every ligand. This becomes important when learning the mechanism of action of various drugs.

Please watch my video: Receptor Subtypes and Selectivity (7:23 long)

*For example: **Acetylcholine binds "cholinergic receptors".** But scientists have discovered that some of these receptors bind the drug nicotine, and others bind the chemical muscarine. These subtypes were renamed as nicotinic (N) and muscarinic (M) **receptor subtypes**. Within these subtypes are more subtypes: Nn, Nm, M1, M2, M3, M4, M5, etc:*

Acetylcholine binds all **Cholinergic Receptors**						
Cholinergic **Nicotinic (N) Receptors** *(Site of action: in ganglia and skeletal muscle)*		Cholinergic **Muscarinic (M) Receptors** *(Site of action: in CNS and autonomic organs)*				
Nn Receptors *in autonomic ganglia*	**Nm Receptors** *in skeletal muscle*	M1 **Receptors** *CNS salivary glands pupils*	**M2 Receptors** *heart*	M3 **Receptors** *GI & lung smooth muscle, bladder, pupil*	M4 **Receptors** *CNS?*	M5 **Receptors** *CNS?*

By knowing where these receptor subtypes occur in the body, chemists can design drugs that will have specific actions. For example, if I design a cholinergic agonist drug that will only activate an M2 receptor, and no other subtypes of the cholinergic receptor, then it will have the same actions as acetylcholine in the heart (to slow it), but it will not have any **side effects** in other organs!

(Hint: The only CHOlinergic subtypes you need to know in 2020 are Nn, Nm and M2)

Here's a common question I get: *If all those receptors subtypes bind acetylcholine just at the spot between the nerve releasing acetylcholine and the receptor on the receiving muscle or nerve, then why are there different subtypes? Acetylcholine doesn't travel through the bloodstream, it makes no sense! :(*

Answer: Probably the variation is due to genetic mutations that accidentally happened over evolutionary time millions of years ago. The good news for us health professionals is that this subtype variation in receptors is fantastically useful when it comes to developing drugs! YAY!

Extremely cool side note: There are acetylcholine receptors found in some parts of the body *where acetylcholine isn't even released,* like on blood vessels. So they don't DO anything in a healthy, non-medicated person. They're just evolutionary leftovers that serve no purpose in a healthy person, but they're very useful when you give a cholinergic-receptor-binding drug to a patient! YAY!

Anyway, a drug with a high **selectivity** to a particular receptor subtype will prefer it rather than other receptors because the drug's shape fits into the receptor's binding site, like a key in a lock.

Poor selectivity is a problem when drugs are developed that have a weak affinity for some other receptor than the one they were designed for, usually because they accidentally have a shape that fits into that unwanted receptor's binding site.

Example: The diuretic spironolactone is designed for and has a high affinity for the aldosterone receptor, and it is good at causing a patient to produce more urine. However, it also binds and blocks androgen (testosterone) receptor. So it can be used for androgen-caused acne...and can also make patients, even male ones, grow significant breast tissue. (Say whaaat??? See Diuretics lecture for more on this.)

Agonist v. Antagonist: If the drug we design **mimics** the natural process, it is an **Agonist** to that process:

•**Agonist** – drug that binds to a specific receptor to produce an **effect that mimics the natural ligand.**

•**Antagonist** ("Blocker")– drug that binds to a specific receptor to **block the action of a natural ligand** or agonist drug from receptor binding

Example: In the body, the natural hormone epinephrine (also called adrenaline) causes the passages in the lungs to expand to let more air pass in breathing. Epinephrine does this by binding a special **adrenergic receptor subtype** (see below) called a beta-2 receptor in the lungs that triggers a reaction to expand the breathing passages. In this case we say epinephrine is the **natural ligand** of the beta-2 receptor.

A drug called albuterol is a **agonist** of epinephrine. So if a patient has an asthma attack, and he can't breathe, he can inhale albuterol, and it will bind the beta-2 receptor and trigger the same effect. Namely, the passages will expand and more air will flow.

In contrast, a drug called propranolol is an **antagonist** of epinephrine. When it binds the beta-2 receptor, it prevents breathing passages from widening. Of course, propranolol would be a dangerous drug to give to an asthmatic patient.

(Hint: the only ADRenergic receptor subtypes you need to know in 2019 are alpha-1, beta-1 and beta-2)

<u>Antagonists (Blockers) are Classified two ways:</u>

***Competitive** antagonists: they bind at the receptor binding site and merely block the normal hormones ability to bind by taking its space (most drugs bind competitively).

vs.

Non-Competitive antagonist: binds somewhere else on the receptor but ruins the receptor binding site for the normal ligand. There are few non-competitive drugs.

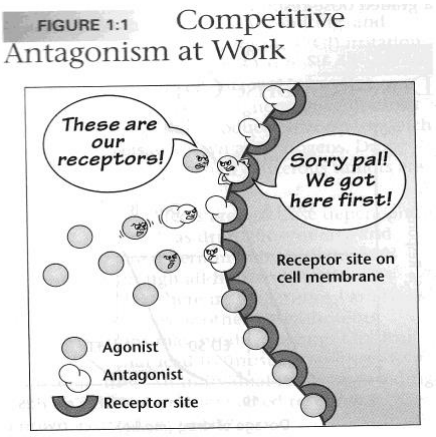
OR

***Reversible antagonists**: Most drugs are reversible antagonists… they bind the receptor for a while and then drift off. (Most drugs are reversible.)

vs.

Irreversible antagonists: They bind and won't move out of the way. Once they do the damage it is all over. There are few irreversible drugs.

Examples: aspirin, clopidogrel, MAOIs, organophosphates/nerve gas

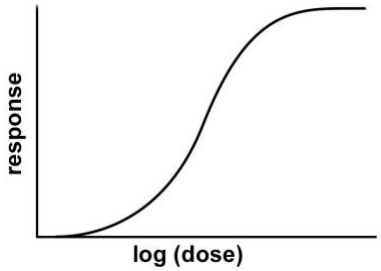


Now, say we have a drug and we know what organ system it will work on (site of action) and what it will do (mechanism of action) and what protein it will bind to (receptor). *But will the amount we give be directly proportional to the effect we get? That is, if we give higher doses will we **always** get more effect?*

No! ...because the effect we get will be related to:

1. the amount of drug we give,
2. the **affinity** (stickiness) of the drug to a receptor AND
3. the number of receptors present that can be bound!

Once every receptor is bound, or every cellular process is activated, or the maximum possible output of the biologic machinery is achieved, you can add more drug but you won't have any more drug effect. The number and type of receptors, the processes those receptors trigger, the selectivity of the drug and the actions of the agonists and antagonists determine the relationship between the dose and effect.



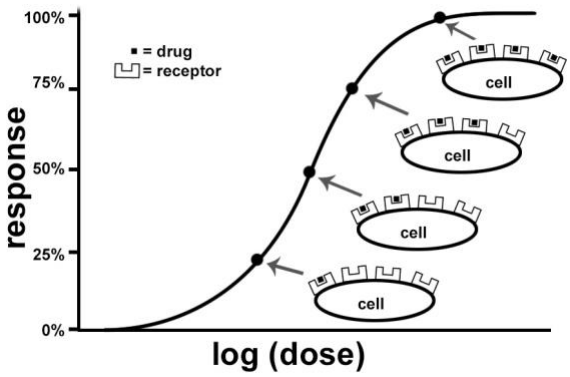
The dose-response curve:

The LOG of the dose (X-Axis) vs the response to the drug (Y-axis)

Note that using the logarithmic scale is so common that many graphs in textbooks just have "Dose" as the X-Axis. But they mean "Log of the Dose" if the graph looks like this →

All drugs are chemicals, and for most of them to have any effect they *have* to bind some sort of binding site: a receptor, an enzyme, an ion channel, whatever. This explains why we get the same shaped curve every time. *But how?*

So, let's imagine a drug called *TinyBlackSquare*® that binds a particular receptor on a cell. Binding each receptor causes a certain amount of effect. Imagine every cell has only four receptors. Simplistically we can therefore explain the graph by the little diagrams shown on the right.
Once all four of the *TinyBlackSquare*® receptors are bound you can't get any more effect by increasing the dose. This 100% effect is called the "**ceiling**" of the effect, or "**ceiling effect**".

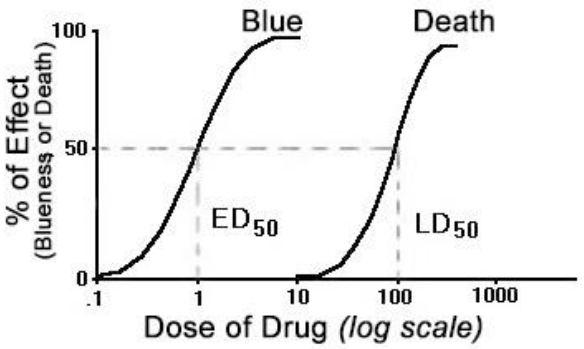


This is why **MORE IS NOT ALWAYS BETTER.** In fact, taking more than the recommended dose is frequently toxic or fatal.

Since we've shown the effect of a drug is related to the number of receptor sites that are bound, it should also make sense that drugs with **high affinity** to a receptor (high affinity drugs easily bind and activate receptors) will therefore have more **intrinsic activity** (defined as the ability of the drug-receptor complex to cause the effect).

Okay. Let's concentrate on dose-response curves for **agonists only**:

Imagine we have identical numbers of cells in several dishes and we've invented a drug that turns cells light blue. Let's give different doses of the drug to each dish (to get a concentration of drug in the dish) and see how blue the dish turns. Look at the left-hand curve on the graph shown to the right.



It works! (Why does the blue effect max out again?)

Imagine we want to tell our investors what dose will turn 100% of the cells blue. However, we can't figure out the dose exactly at 100% "blueness" because the curve there is curvy and it's hard to tell exactly where it is. But the middle of the curve is nice and straight. So we report the dose at 50% effect, and now other labs can try to duplicate our results. This is actually how various research labs communicate the most accurate information and why the ED is ED50 and not ED100 like you, or any reasonable person would think it should be. ED50 is also related to a pharmacologic constant called Kd and can tell you about drug potency. *The more you know!*

ED50 (**Effective Dose 50)** dose is the dose of drug that will produce **half** (50%) of the maximal drug response, determined from a dose-response curve.
But... *oh no!...* if you too much of the drug, it will be toxic and the cells start to die. (All drugs are toxic at high enough doses.) This gives rise to:
LD50 – Lethal Dose 50: the dose that will kill half of your cells.

Now, let's do this same trial, but with two groups of 100 cute squeaky *mice* instead of cells. We'll give increasing doses of drug (to get increasing concentrations of drug in the bloodstream). Now you'll find you get a different **ED50** (where 50% of the mice turn blue) because mice have more cells than a dish. But... *oh no!...* if you too much of the drug, it will be toxic and the mice start to die. (All drugs are toxic at high enough doses.) This gives rise to:

LD50 – Lethal Dose 50: the dose that will kill half of a group of test animals, determined from a lethal dose-response curve (for most studies researchers use **TD50**, **T**oxic **D**ose for 50% of patients suffering toxicity, rather than pumping up the dose to lethal effect)

This all leads to the term most relevant to your future practice:

(Note: Similarly, ED10 = 10% maximal effect, ED90 = dose for 90% effect, etc...)

TI : Therapeutic index, the ratio of the LD50 to the ED50 (or TD50 to ED50).

$$TI = \frac{LD_{50}}{ED_{50}} \quad \text{or} \quad \frac{TD_{50}}{ED_{50}}$$

So: **High** Therapeutic Index means it is a **safer** drug (i.e. penicillin)
Low Therapeutic Index (close to 1) means the chances of accidental, harmful overdose is very possible. (i.e. digoxin, acetaminophen)

Example: Imagine I invent a new beta-blocker drug called "boyevolol". **During Phase I testing** of boyevolol the ED50 is found to be 100mg. At a dose of 1000mg, half of the volunteer patients begin to show signs of liver toxicity. So we would say the TD50 is 1000mg.

Therefore, the TI = 1000mg/100mg = 10. This tells us that if a patient takes ten times the recommended dose of this drug they will be at high risk of liver damage.

Therefore, after approval, if a patient calls me to say they accidentally took twice the normal dose, they'll *probably* be okay, as long as they delay their next dose.
If the patient accidentally takes 10 times the dose, they are in huge trouble.

Thinking question: What if I invent a new drug called boyevicillin where the effective dose is 1mg and I give volunteers 20,000 mg and they still feel fine? Then what is the TI? What does this mean when I work at Poison Control and a patient calls in to tell me they think they took too much boyevicillin?

Note! A low TI does NOT mean the drug should not be used. It simply means that the drug must not be taken at a dose higher than the recommended dose. With some drugs the

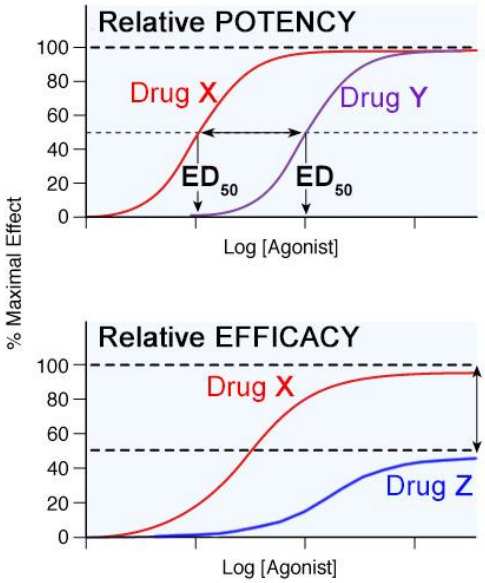
toxicity is so dangerous that the patient's blood levels will have to be monitored with blood tests.

Some example drugs with low TIs: digoxin, lithium, warfarin, acetaminophen, aspirin, TCAs like nortryptiline, theophylline, some chemo drugs, some antibiotics, and more.

Remember: **ALL drugs are toxic at high enough doses**, even water and oxygen!

Other pharmacodynamic terms:

Potency: A measure of the amount of drug needed to produce a certain effect. (i.e.: Morphine and Codeine might both help after a certain surgical procedure, but you need less morphine. So morphine is more potent.)
In the graph to the right, X is more potent than Y.
Another way to look at it: A lower ED50 drug is more potent.
A high potency drug will be useful when a small amount is needed, as in when injecting into a very small space, like the eye or the spinal cord.



Efficacy: A measure of the degree to which a drug can induce maximal **effect**.
(i.e.: Tylenol has a lower efficacy in reducing pain than morphine does. Higher doses of Tylenol won't get you the same effect, so it has less efficacy.)
In the graph to the right, X has more efficacy than Z.
A high efficacy drug will be needed when a higher effect is needed. In this example, Tylenol is a wonderful drug for most pain, but for severe immediate post-surgical pain, an opioid like morphine is likely the drug of choice.

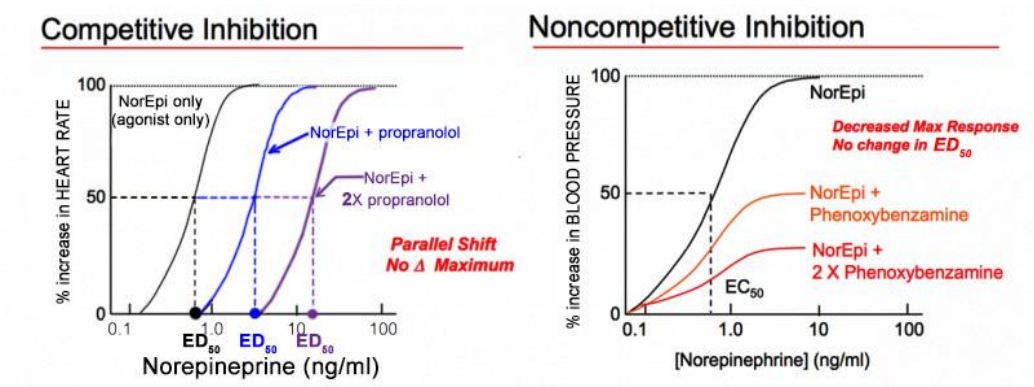
Receptor Down-Regulation: Sometimes repeated stimulation of a receptor will cause the cell to reduce the total number of receptors present in that cell. This reduces the ability of the cell to respond to that ligand or drug. This is one mechanism by which drug **tolerance** may occur. It is also the mechanism by which Type 2 Diabetes occurs (type 2 diabetics have reduced numbers and sensitivity of receptors to the hormone insulin due to chronic overstimulation due to obesity).

Another mechanism by which **tolerance** occurs is **enzyme induction** (see "metabolism" below under PharmacoKinetics).

Critical Thinking: Let's think now about **antagonists**. If you compare dose-response curves of agonists where you've also added antagonists, you get something like the graphs below. The ligand Norepinephrine (NorEpi) has a **competitive** antagonist drug called **propranolol**.

It has a **noncompetitive** antagonist called phenoxybenzamine used in labs.

Here's some **Advanced Stuff:** Can you explain the results on the charts below?
They represent the dose of NorEpinephrine on the x-axis and the labeled effect on the y-axis.



Answer:

Explanation: In the LEFT diagram, the NorEpinephrine (NorEpi) is injected and after binding adrenergic-β1 receptors the heart rate increases. The ceiling effect (100% increase in rate) occurs when all the β1 receptors are occupied.

*If I instead inject **propranolol** and **then** NorEpi (blue line), the propranolol is an antagonist and competitively competes with NorEpi to block the β1 receptors.*

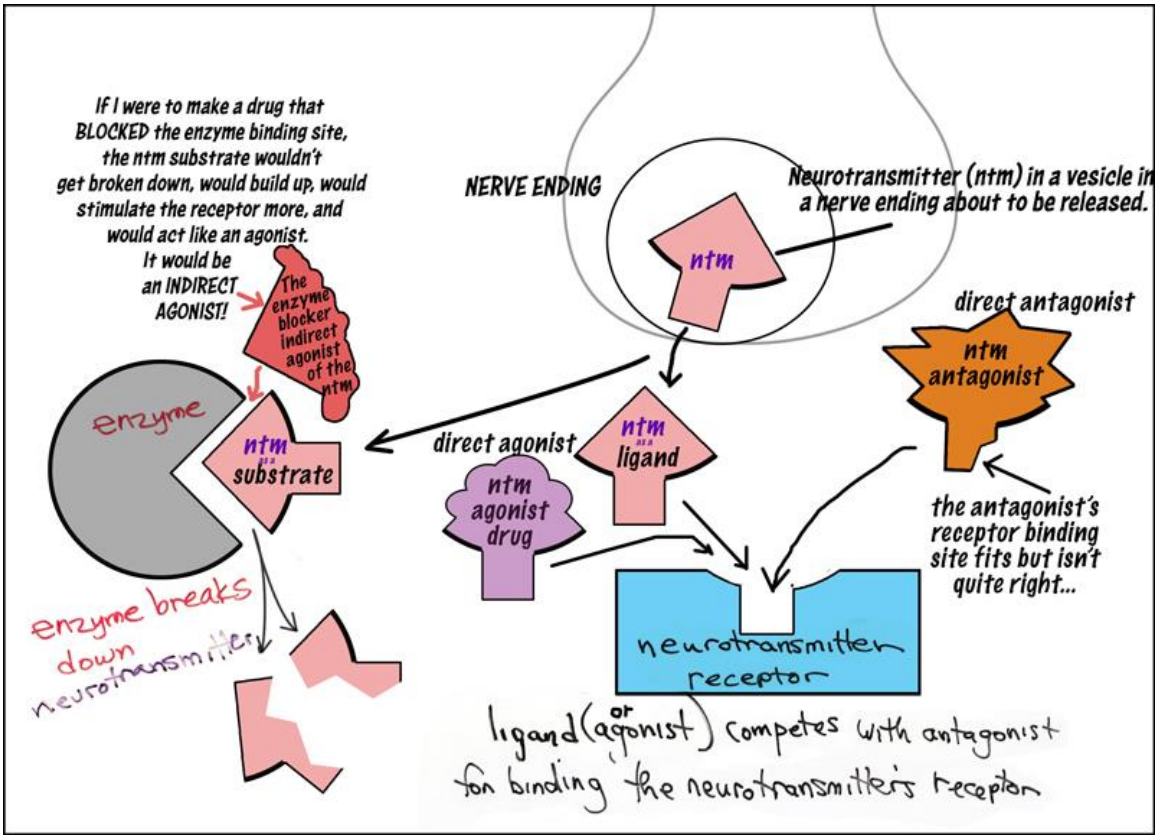
So now I need to inject MORE NorEpi to outnumber the propranolol molecules.

In the next experiment (purple line), doubling the propranolol dose means I need even more NorEpi to get the effect I want.

*In the RIGHT diagram, Nor-Epi binds adrenergic-α**1** receptors to increase blood pressure. Phenoxybenzamine is an **irreversible** noncompetitive alpha inhibitor. Injecting this effectively **destroys** adrenergic-α1 receptors. If I inject phenoxybenzamine before the Nor-Epi (orange line), there are less α1 receptors, so there is less effect on blood pressure, no matter how much Nor-Epi I inject. Doubling the dose of phenoxybenzamine (red line) destroys even more receptors, so NorEpi has an even lower ceiling effect.*

Phew! I want to bring this all together now with a picture we will see in the next handout on Autonomic Drugs. Take a quick look at it and make sure you can explain everything that is going on here.

Hint: There is a very high chance I'll ask you to draw something very similar to this on an exam or three...



Try drawing this yourself. Then try drawing it without looking at the original. If you can draw this out AND explain it to another person, then you've got pharmacodynamics of the nervous system 90% down! Seriously!

So... all of the above talked about **Direct-acting (**drugs that bind receptors) and target-specific organs. Which organs are targeted is based on which receptor subtypes are in which organs.

EXAMPLE hormone or neurotransmitter	EXAMPLE RECEPTOR SUBTYPE	DRUGS	example subtype specific agonist	example subtype specific antagonist (blocker)
Adrenaline/epinephrine binds at least 2 major subtypes of ADRenergic alpha and beta receptors in blood vessels, kidney, fat, liver, brain and autonomic organs	**ADR**energic **beta-1** receptor subtypes are found only in the **heart** and kidney	**beta-1 ADR** receptor-binding drugs work in the **heart** and kidney and not other adrenergic organs	**beta-1 agonist: dobutamine** makes heart beat faster and stronger	**beta-1 antagonist: atenolol:** makes heart beat slower and weaker
Serotonin binds more than 7 major subtypes of serotonergic **5HT** receptors in the brain and all over the body	Serotonergic **5HT3 receptors** are found in the intestine and chemoreceptor trigger **vomit zone (CTZ) in the brain**	5HT3 receptor binding drugs work in the intestine and chemoreceptor trigger zone	5HT3-specific agonist: research only	**5HT3 antagonist:** ondansetron *(Zofran):* blocks 5HT3 receptors and **prevents nausea** and vomiting
The hormone **vasopressin/ADH** binds 3 major subtypes of vasopressin **V** receptors in the kidney, blood vessels, brain, anterior pituitary	**Vasopressin V2 receptors** are only in the distal and **collecting ducts of the kidneys** where they stimulate aquaporins	V2 binding drugs will work in kidney only (not in blood vessels or anterior pituitary)	V-2 agonist: research only	**V2-antagonist:** tolvaptan *(Samsca)* blocking V2 receptors reduces water reabsorption by blocking aquaporins: **causes urination** (diuresis)

Indirect-acting drugs are those that act ANYWHERE OTHER than at a receptor. They might bind enzymes, reuptake proteins, packaging machinery, etc. They **act to <u>increase or decrease the natural hormone or neurotransmitter all over the entire body</u>** and are not specific to any given organ or physiologic system. This means there will be more side effects because you can't target the drug to a specific receptor subtype. We'll get back to this in the next unit.

An Example of an indirect-acting drug:
Anticholinesterases (like the -**stigmine** drugs or in organophosphate pesticides and nerve gas):
Block the enzyme that breaks down acetylcholine.
Increase the neurotransmitter acetylcholine everywhere in the entire body, including:
at the neuromuscular junction in muscles
between nerves in the brain
between nerves in peripheral ganglia
in the autonomic nervous system.

PHARMACOKINETICS: The study of the **QUANTITY** of drug in your bloodstream: the processes of drug **absorption**, **distribution**, **metabolism** and **excretion**.

Remember: A drug is just a molecule with a certain size, shape, and molecular charge and the body looks at all molecules with similar such characteristics as the same. (Your liver and kidneys don't care if it's an asthma drug or a diarrhea drug!)

ABSORPTION: entry of the drug into the bloodstream depends on**:**

1. **Ionization** and Water- and Lipid-solubility:

See my ionization and absorption video/handout for a chemistry review...

Ionized (charged, polar) drugs are water soluble
De-ionized (uncharged, nonpolar) drugs are lipid soluble

T**he more lipid soluble a drug is, the faster the drug can be absorbed** through fatty cell membranes (through GI tract walls, tissues, skin, etc.) and into the bloodstream.

The **more water soluble,** the easier it is **excreted by kidneys in urine.**

Weakly acidic drugs are perfect for PO administration, because they get de-ionized (uncharged) in the low pH of the stomach. The de-ionized form easily passes through the cell membranes of the stomach/intestinal walls.

Note that weakly acidic drugs that never see a low pH environment will be poorly absorbed. This can happen if a patient takes antacids constantly, or long-term.

If we want to administer a basic drug PO we have a few options:

1. Wait: Weak bases will have a delayed onset of action because they won't get easily absorbed until they reach the intestine.
2. Do something else to make the drug absorbed faster like crush it up or take it on an empty stomach. It will still be absorbed poorly, but it will be absorbed a *little* faster
3. Just administer the drug parenterally or topically, (e.g. I.V. or inhaled) and bypass the whole business in the stomach.

2. **Form** of the drug:

Pills vs. Powders: A large coated pill will take longer to dissolve than a powder, so absorption of a powder dissolved in water will be faster.

What would be the effect of food in the stomach on absorption of PO drugs?

3. **Surface area or contact time** at the absorption surface.

Enteral: intestinal transit/gastric emptying needs to be slow enough for a drug to be absorbed; if too fast, then most drugs are absorbed through intestines

Topical: Too much lidocaine on your skin for too long is toxic!)

4. **Route** of Administration: How fast is drug absorbed when it is given PO vs IM? vs IV?

5. **Size** of the drug: A drug with higher molecular weight/size will diffuse more slowly through tissues as it moves toward the bloodstream

6. **Solubility** of the drug: this can be changed somewhat by making the drug a salt (why some generic names have "chloride" or "sodium" in the name), or changing what solution the drug is in if it is given by injection. *(Example: basic drugs like lidocaine can be dissolved at higher pH) so they are more lipophillic when injected- but not too high pH because if they are too lipophillic they will precipitate out of solution in water. ...right?)*

7. Other things affect absorption like specific molecular transporters and water channels.

DISTRIBUTION throughout the tissues of the body:

1. Blood flow to tissues: varies. Ex: blood flow higher to brain/kidneys than muscles/skin/fat
   Also: drug may have difficulty getting to abscesses or solid tumors

2. Pooling in tissues: example: Fat-soluble drugs can hide out in fatty tissues of the body and have a prolonged effect. Example: Inhaled anesthetics.

3. **Binding to blood proteins** (i.e. Albumin)
   Many drugs stick onto proteins in the bloodstream and that portion that is stuck onto random proteins is not available as a drug because it can't go and bind to receptor
   Would a drug's action be shortened or prolonged in a person with reduced blood protein levels (malnourishment, burn victims, anorexics)?

4. **Centrally-Acting** vs Peripherally Acting:
   In medicine, the word "**centrally-acting**" means that the drug has an effect on the **Central Nervous System (CNS).** A centrally-acting drug must enter the peripheral blood stream and then cross the **Blood-Brain Barrier (BBB).**
   There are certain areas of the body (brain, eye, testes) that are impermeable to many molecules. This presents a special challenge when delivering drugs to these areas.
   Ex: antibiotic delivery in meningitis patients
   Drugs that cannot cross the BBB would be only peripherally-acting.

Advanced Stuff: **Volume of Distribution" (Vd)** is mathematical estimate of the fluid volume that would be required to contain the drug dose given at the same concentration in the plasma. So, if you have a certain blood concentration of drug, what size tank of water would you need to get the same concentration with the same dose? Yes, it's a weird concept, but it gives you an idea of how the drug distributes. (*See Chapter 1 in Whalen)*

METABOLISM: (a.k.a. biotransformation)
(Note: "metabolism" in pharmacology means something very different than "metabolism" in nutrition!)
Inactivation of most drugs is done in the liver.

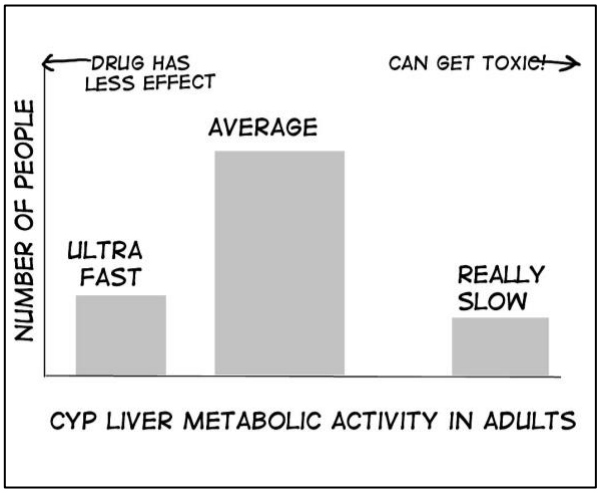
*[EXCEPT: most neurotransmitters are metabolized in the synaptic cleft where they were secreted: in the brain, tissues or even bloodstream. Some direct-acting neurotransmitter **drugs** are also metabolized in the tissues. More on that later.)*

Drugs are usually transformed into an inactive metabolite that the kidney can easily excrete.
Usually this means making the molecule more ionized/water soluble
(since urine is mostly water ..right?)

Two main types of drug metabolism in liver
1. PHASE 1. Oxidation/Reduction
   Cytochrome P450 Enzymes a.k.a. CYP, C450, or Mixed Function Oxidase enzymes
   ~30 enzymes, but 90% of drugs are metabolized this way
   The heavy-hitter P450 enzymes have boring names like 1A2, 2C9,2C19, 2D6, 2E1, 3A4/5

2. PHASE 2: Conjugation/ hydrolysis. Second set of enzymes also increase polarity (charge/ionization) of drugs by sticking on extra molecules to improve excretion by the kidney (since the drug will be dissolved in urine, the drug should be charged/ionized/polar to be water soluble ...right? ...right?! This is important!)

How well an individual metabolizes a given drug is dependent on age, weight, gender, genetics, and… other drugs!

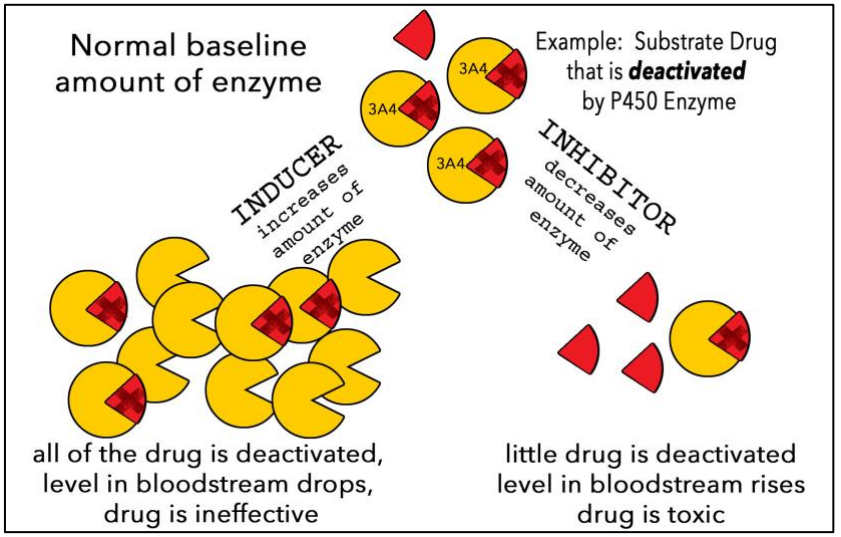


<u>P450 Enzyme Induction & Inhibition</u>

Enzyme Induction by drugs means that a drug will increase the amount and/or speed of an **<u>enzyme</u>**, which in turn means all substrates of that enzyme will be metabolized faster. (If the enzyme *deactivates* the substrate, *inducing* the enzyme means the substrate drug will be *less* effective).

Enzyme Inhibition also occurs by some drugs (and strangely grapefruit juice) meaning that the **<u>enzyme</u>** amount or function is inhibited, which in turn means all substrates of that enzyme will be metabolized slower (so you can build up toxic levels).

*Example: St. John's Wort is a "natural drug" that **induces** CYP3A4. CYP3A4 metabolizes the anticancer drug tamoxifen. Does St. John's Wort make tamoxifen more or less effective?*



Example: If a patient is taking the anti-seizure drug phenytoin, and you add the anti-ulcer drug cimetidine, and you know they are both metabolized by the enzyme CYP2C9, but that cimetidine inhibits that enzyme, is it likely the effective daily dose of phenytoin will stay the same, go up or go down?

ENZYME	**CYP2C9**	**CYP3A4**
SUBSTRATES	ibuprofen phenytoin warfarin	alprazolam progesterone tamoxifen
INDUCERS	carbamazepine phenobarbital	St. John's Wort phenobarbital phenytoin
INHIBITORS	cimetidine fluconazole	ketoconazole grapefruit juice

*Tables of P450 Enzyme Induction and Inhibition are constantly updated. An example is given above. The most common mistake students make is thinking the **substrate** is induced or inhibited. It isn't. **It is the ENZYME that is affected!***

First Pass Metabolism can make a HUGE difference in dose:

The veins of the GI system from the bottom third of the esophagus to the top third of the rectum all drain to the portal vein, then to the liver, and then to the vena cava and back into circulation.

This allows the liver to have a crack at breaking up poisons that you might have accidentally eaten!

Question: If drugs absorbed via the GI system ***always*** go ***first*** to the liver and ***then*** the systemic circulation, why is it that for drugs that have a high degree of *"first-pass"* metabolism, the oral dose will be far higher than the IV dose?

See my video "First Pass Metabolism" if this isn't clear to you.

i.e. Verapamil IV dose is 1-5 mg, PO is 40-120 mg.

Nitroglycerin is almost completely metabolized in first pass so it is given sublingually

(Aha! Remember here that sublingual (SL) is different from oral (PO) SL absorption goes directly into the veins under the tongue and never passes through the liver!)

Some drugs are actually **prodrugs**… they *have* to be metabolized into an **active metabolite** to work: (*example: codeine to morphine)* So, if the enzyme in question **activates** the substrate, as in the case of a **prodrug**, the effects of inducers or inhibitors will be reversed.

EXCRETION: elimination from the body (Mostly kidneys, also bile, feces, sweat, milk, etc)

How do kidneys excrete drugs? To simplify:

Kidneys strain out everything from your blood and then selectively take back all the good stuff, leaving all the dirty filtrate to be flushed away with the urine. So what gets passed out of the body and into urine is water and water-soluble molecules. So, molecules that are charged (ionized), or are not reabsorbed to the bloodstream for some other reason, are preferentially urinated away. ...right?

> Advanced Stuff: The rate of blood filtration by the kidney is estimated by lab test called "creatinine clearance" where **clearance** is the amount of drug cleared out of the body per minute. From creatiine you can calculate an estimate of the GFR (glomerular filtration rate). This number can give you an idea of how well the kidney is doing its job.
> *(See Whalen Ch 1 for more detailed explanations)*

If you remember that for a drug to be easily excreted, that drug molecule should be ionized/water soluble, you're 90% of the way to understanding how the kidneys get rid of drugs and metabolites! It's important because in cases of overdoses, you can encourage drug to leave the body by changing the urine/body pH slightly so that more of the molecule is in ionized form.

(example sodium **bicarbonate** can be given to increase excretion if a patient takes an overdose of a weakly acidic drug like aspirin)

There are also acid and base **transporters** (one for acidic molecules and one for basic molecules) to help get rid of unwanted substances. These work for only a select number of drugs.

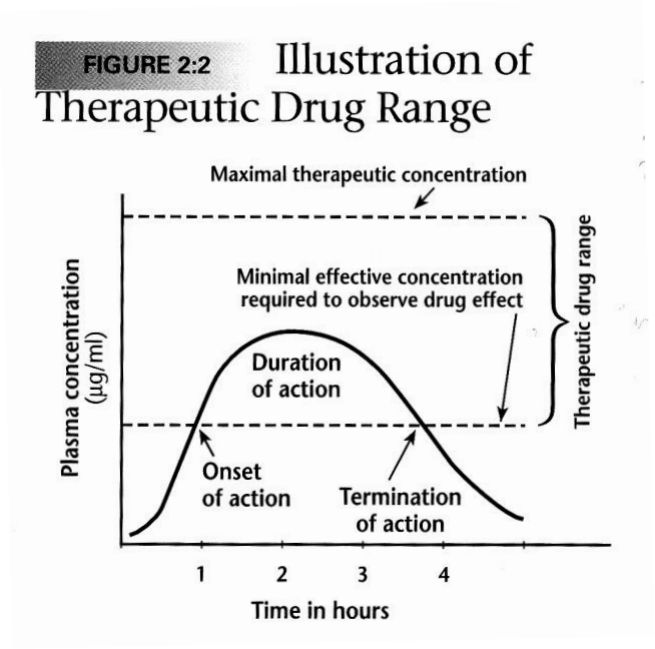
Excretion by means other than **renal** (by the kidney).

GI: some drugs are excreted into cholesterol-rich **bile** and then into feces, also important is the so-called "**enterohepatic**" circulation

Lungs: a great example is alcohol! Alcohol in the bloodstream is exhaled from the lungs and can be measured in the alcohol breath test.
Secretions: sweat, milk, saliva

Absorption, Distribution, Metabolism & Excretion together will determine the **bioavailability** of the drug.

BIOAVAILABILITY: the **percentage** of the **administered dose** that reaches the systemic circulation and **is unbound in the blood stream** and **available to work in target tissues.**



For example: If you give a person 200mg PO of drug X, and you absorb 140 mg from the stomach (the other 60 mg gets flushed away with poop), and 10 mg is destroyed in first-pass metabolism, and 35 mg is bound to albumin and another 15 mg distributes to fat, then that leaves only:

140 mg **absorbed** through the stomach wall and into the bloodstream
-10 mg **destroyed by first-pass metabolism**
-35 mg **bound to plasma proteins** (like albumin)
-15 mg **distributed** to fat
= 80 mg **free** in your bloodstream to actually work and bind its target protein binding site (on a receptor or enzyme or ion channel, etc.)

So drug X has:

$$\frac{80\text{mg available dose}}{200\text{mg original dose}} = \frac{40}{100} = 40\% \text{ bioavailability}$$

Thinking question: If I take **two** tablets of the 200mg drug described above, what is the most likely bioavailability? Answer: 40% ***Why?***

Answer: Because bioavailability is a **percentage.** *For example, imagine the drug is the painkiller ibuprofen. In your relatively giant stomach, the difference between 200mg and two tablets, or 400 mg, is not much! So if normally you can absorb 140/200=70% of a 200mg ibuprofen pill, you will also likely absorb 70% of 400 mg, or 280mg.*
And if 10 mg/140 mg= 7% is destroyed by 1st pass, then 7% of 280 will be destroyed, which is 20mg
Similarly, if you do the calculations, you'll find 70mg will be bound to proteins and 30 mg will be distributed to fat, ending up with 160 mg free in the blood. 160/400= 40% bioavailability

Remember, the % sign is just shorthand for "This number over 100", just like when you see a "Sale: 30% off!" sign at a store it means that the price will be 30 cents off of every 100cents (dollar) of the price.
Come see me if you have questions about this. ☺

Loading Dose: This is a high dose, often given IV, that is given as the first dose to get the blood levels high as quickly as possible. You can't always use loading doses, esp. if the drug has a low TI.

Maintenance doses to keep blood levels in therapeutic range

Onset of action: The onset of action is dependent on when the blood concentration is high enough to observe a clinical, practical effect. When blood level drops below the minimal effective concentration the patient will lose the benefit of the drug. The rate at which this happens will determine how often the drug has to be given.

Half-Life: time required for the blood concentration to fall to half of its original level after the drug is discontinued.

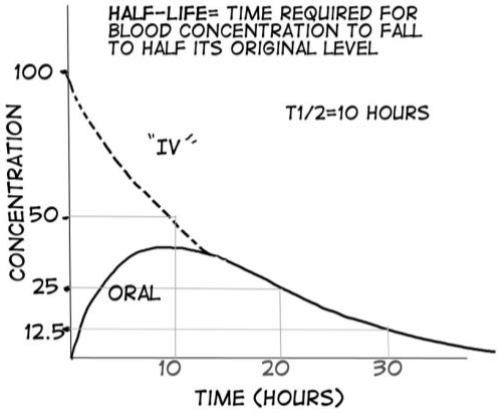
Pearl of knowledge: It takes 3-4 (3.3 to be exact) half-lives for drugs to reach their steady state blood concentration after the first dose, and the same amount of time to be about 90% gone from the body once the patient has their last dose.

Let's do an example:

If the first dose is 100mg at noon, and the half-life is 10 hours, how long does it take for the drug to leave the body?

…the answer is NOT 20 hours.
(Note: there are further examples of this type of problem in your Unit ONE Extras)

Because half-life is a unit of time and dictates the halving of whatever dose you began with, you can predict that 90% of the drug will be gone after about 3-4 half-lives, and 99% will be gone after about 7 half-lives. *If you choose to memorize those facts, and accidentally forget them later, you can always re-work the problem... which is easier than memorizing...*



Day	Time	Hrs	# of half-lives	Total Drug Remaining in the Body (rounded)	(%)
Monday	*Noon*	*0*	*0*	*100mg*	*100%*
	10PM	*10*	*1*	*50mg*	*50%*
Tuesday	*8AM*	*20*	*2*	*25mg*	*25%*
	6PM	*30*	*3*	*12.5mg*	*12.5%*
Wednesday	*4AM*	*40*	*4*	*6.25mg*	*6.3%*
	2PM	*50*	*5*	*3.13mg*	*3.1%*
Thursday	*12AM*	*60*	*6*	*1.56mg*	*1.6%*
	10AM	*70*	*7*	*0.78mg*	*0.8%*

THE REAL WORLD

Polypharmacy (taking many drugs): this includes taking OTC drugs and "supplements".

Drug-Drug Interactions:
Altered Absorption:
i.e. Antacids and Tetracycline
i.e. drugs taken with or without food
Altered metabolism:
i.e. changes in Cytochrome P450 enzymes
(induction and inhibition as above in the Pharmacokinetics section)

Formulation: The drug + carrier substances that make up a given pill/solution/mist/etc.. Differences in formulation account for why some generic drugs work differently than the brand name version.

Strength: The amount of drug in a given formulation.
Ex: Extra-Strength Tylenol® contains 500mg of acetaminophen in each single tablet.

Incompatibility: **NOTE!!!** This word has a ***very specific meaning*** in pharmacology!
Drugs react with each other in the bottle, IV tubing or syringe (e.g. they precipitate, deactivate and/or form a gas).
This term means the drugs **cannot be physically given together** in the same syringe or tube.

COMBINATION THERAPIES: There's a lot of confusion and drama about definitions of these terms between scientific fields. Ultimately the name is less important than the effect and cause

1. You combine two drugs and you get MORE **effect:**

Additive Effects 1 + 1 = 2 the action of two drugs is the sum of their effects
(Ex. Tylenol + Codeine: Tylenol is good for dull pain, Codeine is good for sharp pain, so taken together.)
(Ex. Two drugs that bind the same receptor might have the same effect as double the dose of one of the drugs.

Synergism/Potentiation: Combined effect is **greater than the sum** 1 + 1 = 3
(Ex. alcohol + benzodiazepine: A double dose of either one might make you sick, but taken together you might die because of respiratory depression)

Enzyme Induction/Inhibition or other pharmacokinetic factors

2. You combine two drugs and get **LESS effect**

Antagonism 1 - 1 = 0 Antagonism usually refers specifically to drugs that work on the same receptor or binding site.
Ex. **agonist + antagonist**
(i.e. morphine (opioid mu receptor agonist) + naloxone (opioid mu partial blocker)

Enzyme Induction/Inhibition or other pharmacokinetic factors

TOLERANCE/ CROSS-TOLERANCE/ DEPENDENCE/ ADDICTION/ WITHDRAWAL

Tolerance: decreased drug effects after chronic administration (usually reversible)
e.g. drug addicts who need more and more to get "high", morphine
Tolerance is usually due to:

1. **enzyme induction/inhibition**
2. **homeostatic mechanisms and/or**
3. **receptor up- or down-regulation.**

Cross-tolerance: drugs that act via the same mechanism and therefore tolerance to one causes tolerance to the other:
e.g. heroin & morphine (both bind opiate receptors), or
barbiturates & benzodiazepines (both open chloride channels)

Dependence: Patient requires drug to function, abruptly stopping the drug causes withdrawal
This does NOT only refer to illicit drugs! (i.e. propranolol, benzodiazepines, **caffeine**)

Addiction: A drug that takes over all aspects of a patient's life **including social aspects**
The term "addiction" suggests that desire for the drug is **destroying the patient's life.**

Withdrawal: Symptoms that are caused by stopping a drug and the **blood levels drop.**
Seen with ***many*** common drugs and happens when the body has adjusted to the constant presence of the drug. This is especially true with CNS drugs. In fact, it's probably safest to assume that ALL drugs cause withdrawal; it's just that usually the withdrawal isn't bad or noticeable.

For example, some **amphetamines** taken for ADD or ADHD speed up brain activity, so after taking the drug for a long time, the brain has slowed down its internal activity level to compensate (**homeostasis**!). Then if you take away that amphetamine abruptly, the patient will be so sedated they'll barely be able to function until their brain compensates This is a type of withdrawal.

EVEN MORE things affecting how varying doses drug will affect a given patient:

Babies: Slower absorption from IM injections. Thinner skin means better absorption of topical drugs or creams. Less acidic pH in stomach changes profile of absorption. babies are more easily dehydrated. They have less protein in blood & so have higher bioavailability of protein bound drugs. **Babies are not just little adults; they're like a totally different species!**

Geriatrics: Slower GI motility slows absorption. Decreased blood-brain barrier and lower body mass changes distribution. Slower liver metabolism and kidney function means slower clearance. Decrease in blood protein levels (sometimes due to poor diet) can mean more free drug. Polypharmacy is common. **The elderly are not just wrinkly adults; they're we're like a totally different species!**

Other variables between patients: Genetics, weight/height, race, gender, socioeconomic and cultural Issues, and understanding by patient of the proper use and side effects of their medications will all affect how various patients will respond to the same dose of a given drug.

DRUG COMPLIANCE:

Some studies suggest 2/3 of patients don't take prescriptions as written, half of those patients never even get the prescription filled.
10% of hospital admissions due to non-compliance
In combination with overprescribing, antibiotic noncompliance is significantly contributing to development of antibiotic-resistant bacteria**.**

Things that increase non-compliance:

expense of the medication or supplement
lack of symptoms (hypertension) or resolution of symptoms (infection)
bad symptoms not completely fixed by medications
side effects (real or perceived)
inconvenient dosing/ bad packaging
misunderstanding or poor communication from prescriber
the internet (a LOT of misinformation out there!)

Do not blame the patient. Find out *why* they are non-compliant to help fix the problem.

"PLACEBO EFFECT": *Not the placebo effect you are thinking of!*

It's true that some patients will feel relief or side effects simply by believing the medication will cause them, especially in cases of nausea or pain. This "placebo effect" is the layperson's understanding of the term.

*Disclaimer: It is **illegal** to give a patient a placebo without their express written consent and is always done in within a controlled clinical trial.*

In the world of research, "placebo effect" means something else**.** When drugs are tested, some patients are given the new drug, and some are given a **placebo**, a fake pill that has no medication in it. So in pharmacology when we talk about a "placebo effect" we actually mean, **"an effect not caused by the drug",** not that the patient has been tricked into thinking they have a particular symptom by taking a pill with nothing but starch or paste in it.

Example: Your patient Sue says, "I won't use a Nitro-Dur patch, I tried it for a day once and I had nausea later that week."
You reply: That was a placebo effect."
Sue says: I didn't take a placebo!
You reply: What I mean is that your nausea was not caused by the Nitro-Dur. Let's try to figure out what really caused the nausea.
Sue: You're so understanding and helpful! You're the best medical provider I've ever had!
You reply: Thanks! That will be a $20 co-pay.

Explanation: Imagine the nitroglycerin patch (NitroDur®) was used in a drug trial. All study subjects (the placebo AND the NitroDur groups) are given surveys and checklists to report any of a long list of possible symptoms. At the end of the trial, the following numbers are reported in the standard format:

Adverse Reaction	NitroDur (n=307) (%)	Placebo (n=307) (%)
lightheadedness	4	4
nausea	2	5
headache	63	18

The numbers listed under "**placebo**" are the **percentage** of patients that were given the placebo that reported the listed side effect. **These patients would have had those symptoms even without taking the drug.**

The numbers listed under "NitroDur "are the **percentage** of patients that reported the listed side effect.

So: Headache is very definitely a true side effect of the drug because it was more common with the drug than with the placebo. 18% of the patients who took the drug would have had a headache no matter what, but the remaining 63-18= 45% had a headache because of the drug.

Lightheadedness is a placebo effect. 4% of patients feel lightheaded regardless of whether or not the patient takes NitroDur.

Nausea is definitely a "placebo effect" in this case. You expect 5% of patients to be nauseated anyway, but 3% LESS patients had nausea if they took the drug. (It may even be the case that NitroDur reduces nausea in some patients!)

So: Any time the effect in the placebo group **is equal to or greater than the treatment group,** that side effect is a placebo effect.

Remember, the numbers in the placebo group are the numbers of people that would have those symptoms anyway over the time spent in the trial even if they weren't in a medical trial. Almost everyone has a headache or nausea or a rash every now and then...

This is why testimonials are completely useless. Your patient Sue above said that the drug caused her nausea. But there was a 5% chance that she would have been nauseated that week anyway, regardless of whether she took the pill. If anything, the pill may have fixed her coincidental nausea!

You will definitely see problems on quizzes and exams about "Placebo Effect" in the form of "determine a placebo effect from a table or research study" Hopefully you'll never again be swayed by someone telling you that some outlandish thing worked for them or someone they know, or some well-established thing didn't work. One patient's experience is interesting, but not scientific! ☺

CONTROLLED SUBSTANCES

Many Controlled substances cannot be easily refilled; a problem for chronic pain patients. The Controlled Substances Act requires prescribers to register with the Drug Enforcement Agency (DEA), pay a fee, keep records, etc. A DEA number must be written on all controlled drug prescriptions. In Illinois you also need a CSR registration to write prescriptions for controlled substances.

Drug Schedules I – V (Drugs with Abuse Potential)

Schedule	Definition	Examples
I	**Definitely Illegal**	**Heroin, LSD, Pink**
II	Medically useful but high abuse potential (no refills)	morphine, cocaine, amphetamines
III	Moderate abuse potential	low dose narcotics, ketamine
IV	Low abuse potential	diazepam, phenobarbital
V	**Limited abuse potential**	**Some of these are over-the-counter**

Different states have different laws about how many days worth of the controlled substance drug can be given, whether refills can be phoned in or given at all, etc.

Currently **marijuana** is listed as different schedules by state depending on that state's laws. In Illinois as of Jan 1, 2020, marijuana is no longer schedule I. (Side note: If I needed to use marijuana for medical reasons, I would grow my own plants; I don't trust anyone peddling a drug that is so completely unregulated in this state. As of Jan 18, 2020, it is legal in Illinois to own up to five plants *with a prescription*. It is ***not*** legal to grow marijuana for recreational use. Article 10 Section 10.5 Public Act 0027 http://www.ilga.gov/legislation/publicacts/101/101-0027.htm

PREGNANCY CATEGORIES: THEY WON'T GO AWAY!

Always be cautious when prescribing to a patient with a working uterus and ovaries; you don't want to cause birth defects!

FDA Pregnancy Categories A-D, X, NR were *supposedly* being phased out as of 2014, and replaced with long explanations of data on the likelihood of birth defects. Alas, most sources still list the categories below as a sort of shorthand. Note: **Pregnancy Categories B & C do NOT define whether a drug is safe for pregnancy.** They only report whether they are known to cause **birth defects in animals** or have been reported to possibly cause defects in humans.

Pregnancy Category	Description	*Dr B's mnemonic*
A	No risk (The only drug I know that is Category A is Diclegis®)	***A-Okay!***
B	No studies in humans, animals okay but might be toxic	*Be wary*
C	No studies in humans but causes **birth defects in animal** testing	***C****areful - you don't know for sure about humans*
D	**Reports suggest causes birth defects in humans**, weigh benefits/risks to mother/baby	***D****on't use this!*
X	Definitely causes defects (mutant) human babies, contraindicated in pregnancy	***X-Men are mutants***

Note that **when drugs are first approved, the danger to human women is not known**, since drugs are tested on breeding animals, but usually ***not*** on pregnant women. So **pregnant women probably should avoid any drug until it has been on the market for a long time.**

GENERIC DRUGS: These are drugs that are not packaged under a brand name, usually by a different company for less money. **Generic drugs are totally absolutely okay to use and are bioequivalent.**

> Sometimes the carrier substance in which the drug is embedded may be slightly different with different manufacturers. (This is called a **change in formulation**.) This may change the **absorption profile** of the drug a TINY BIT (~±3%), and so a specific brand name, or a particular generic brand might be preferred in extraordinarily rare situations**.**

The FDA will publish notices when the generic is significantly different from the trade name drug. (You can get on the FDA mailing list by signing up at drugs.com)

Thought experiment: If two formulations of the same strength of the same drug differ significantly in the rate of absorption, how might the patient perceive the difference?

The "Orange Book" (*Approved Drug Products with Therapeutic Equivalence Equations)* lists all the different generics and which are equivalent (most are). The Orange Book can be found

online via the FDA website. Nowadays the generics are listed with the proprietary drugs at the DailyMed website, so the Orange Book is most useful for pharmacy personnel.

Supplements, Vitamins and "Natural" Cures:

These are **NOT** regulated by the FDA and are notorious for claiming to contain some wholesome item but actually contain prescription drugs. The worst offenders are **"natural diet aids"** which are actually full of **amphetamines, laxatives and diuretics,** and **"natural drugs for erectile dysfunction" which contain high doses of Viagra.** The FDA generally *only* investigates products that do not have the Drug Facts label when they get reports of people dying from the product due to lack of manpower.

(Note also that "natural" has no legal meaning in food or supplement advertising.)

Even "trusted" stores such as GNC, Target, Wal-Mart and Walgreens are guilty of scams. In 2015 the State of New York sued them in a class action suit, as many of their brand supplements contained nothing but rice or houseplant fiber. 22 other states have brought similar charges against these and other retailers. (I was surprised and disappointed that even GNC was using fake fillers!) See the reading *"Supplements are filled with nothing"* in the Unit One handouts and readings.

Additionally, common over-the-counter **vitamins rarely have the dose claimed** on the packaging. (See the article posted on my website called: "Variable potency of vitamin D pills" for an example if you are interested.)

If you want to take a supplement or vitamin, you **should only buy them from companies that are USP-certified.** USP stands for United States Pharmacopeia. The symbol to look for is on page 1 of this handout. This is the same organization that certifies hospital drugs actually contain what they claim. Go to the USP website www.usp.org for more information.

Unless you have been **documented** to be deficient in a micronutrient, you should not be taking supplements at doses greater than the RDA.

This is also why **prenatal vitamins have been advised to be taken only by prescription**, because prescription products ARE regulated and are monitored that they contain what they claim. **Some prenatal vitamins are now available OTC that are USP labeled**. (We'll look at some the first day of class). Note that except for folate, all the micronutrients are listed at 100% or less than the RDA.

Prescribing errors: Nurses are often the final line of defense for inpatients against a prescribing error. The final line of defense for an outpatient is the patient themself.

Recent changes in the law make some nurses in Illinois liable for malpractice.

Watch out for: Contraindications (disease, patient, age)
Drug Interactions (alcohol is a drug too!)
Bad handwriting (hopefully phasing out as more hospitals go paperless)
Omissions
Dosing errors

A few common abbreviations Dr B would like you to memorize

ABBREVIATION	MEANING
BP	arterial blood pressure (systolic/diastolic)
HR	ventricular heart rate ("pulse")
RR	respiratory rate (breaths per minute)
HTN	hypertension (“pressure”)
N/V	"nausea and/or vomiting"
SOB	shortness of breath (yes, it’s not a joke, it’s real)
MI	myocardial infarction ("heart attack")
CVA	cerebrovascular accident ("stroke")
TIA	transient ischemic attack ("ministroke")
Na_+	sodium (usually what people mean when they talk about “salt” in the diet.)
Ca_+	calcium
K_+	potassium (**do not confuse this with *vitamin* K**, the blood clotting vitamin made begun bacteria that neonates get as a shot when they’re born)

Addendum: regarding other outside pharm resources. I haven’t found a good reliable open resource on the internet yet other than dailymed, so I think the best thing is still a paper book with an index in the back to help look up things quickly. **Other pharm books** that I have read and like:

Introductory:
1. Hitner Pharmacology An Introduction 6th or 7th Edition
2. Adams et al. Pharmacology for Nurses 5th Edition
3. Aschenbrenner & Venable Drug Therapy in Nursing 3rd or 4th Ed

Advanced:
1. Lehne's Pharmacology for Nursing Care 9th or 10th Ed
2. Golan et al. Principles of Pharmacology 4th Edition