DISCLAIMER

Prof. Archambault has confirmed that some content has been updated since the last course offering of NUR1 300 in Fall 2019.

Students enrolled in NUR1 300 in Fall 2020 are still responsible for covering everything that is being expected (i.e., the course material as posted in MyCourses during the Fall 2020 semester).

These NTCs are intended to complement your current lecture notes, not to replace them altogether.

INTRO TO PHARMACOLOGY

History Capsule

- Paracelsus is considered the father of pharmacology. He said “all things are poison, and nothing is without poison, the dosage alone makes it so a thing is not a poison”
- Any substance can kill you in high concentrations.

Defining drugs

- Recreational drugs
- Therapeutic drugs
- Other chemicals
- Food & drinks

From drugs to therapeutics

- Pharmacology is the study of all drugs
    - Ex: effects, interactions, biochemical properties; research & development; therapeutic usage
- Clinical pharmacology is the study of drugs in humans
    - Ex: patients & healthy volunteers during R&D
- Therapeutics is the study of the medical use of drugs
    - Ex: why forbid grapefruit juice when someone is on anti-cholesterol medications?

What is the ideal drug?

1. **Effectiveness** - does it do the job?
2. **Safety** - is it harmful?
3. **Selectivity** - does it only do what we want it to do?

* No single drug has all of the qualities. The best drugs have most of these qualities.

More ideal drug properties

- Reversible
    - Ex: anesthesia & contraceptives; exception: Abx
- Predictability - can we predict the outcome?
    - Ex: personalized medicine
- Ease of administration - convenient route + minimum # of daily doses
- Minimal drug interaction - increased effectiveness & safety
- Low cost - increased adherence & decreased stress
- Chemical stability - decreased drug decay & allergic reactions
- Simple generic name
    - Ex: acetaminophen; simvastatin, etc.

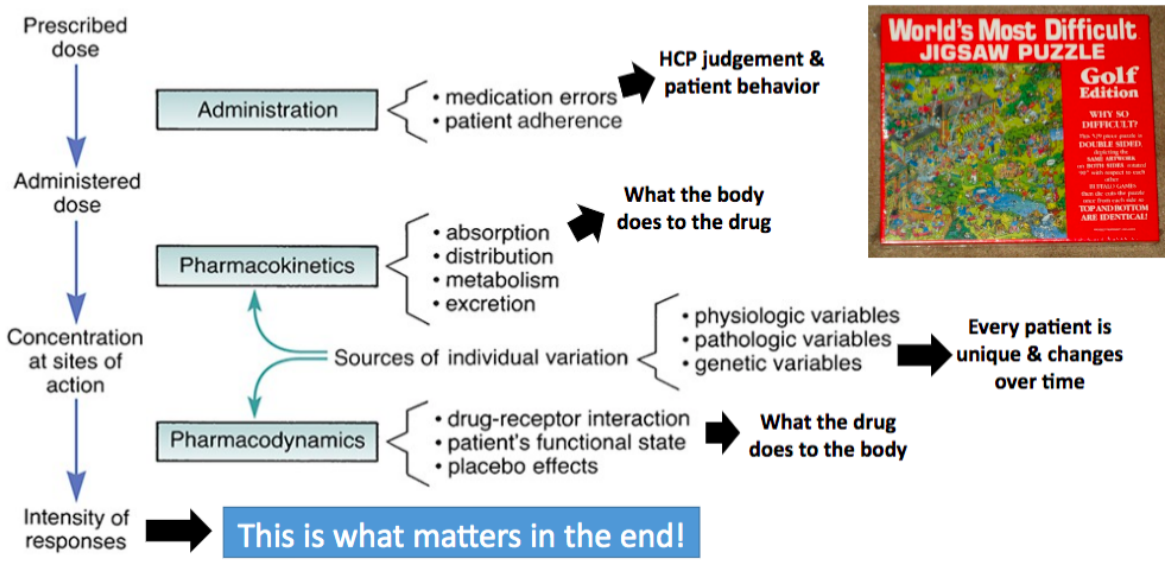
Therapeutic commandments & objective

Pharmacology commandments:

1. **Effectiveness** is the most important property a drug can have
2. There is no such thing as a drug without side effects
3. There is no such thing as a ‘perfect drug’

Primary goal of drug therapy: maximize benefits while minimizing harm (optimize risk-benefit ratio)

The drug response puzzle



Why teach pharmacology to nursing student?

- Anticipate potential drug responses
- Intervene promptly and effectively
- Defense against medication errors
- Improve patient care & education

Patient Care

Aspects	Goals	Examples
1) Pre-administration Assessment	Collecting Baseline Data	*Blood Pressure; Liver Function*
	Identifying High-Risk Patients	*Allergies; Liver/Renal Pathologies*
2) Dosage & Administration	Understand Rationale	*Larger Morphine doses per Os vs. IV*
	Avoid Admin Errors	*Verify patient identity & dosage calculation*
3) Maximize Therapeutic Effects	Therapeutic Response Evaluation	*Pain decrease following Morphine admin*
	Promoting Adherence	*For Self-Admin Drugs for out-patients*
	Implement Nondrug Measures	*Exercises; Nutrition; Social Support*
4) Minimize Adverse Effects	Know potential adverse events & how to intervene	*Glucose Admin ↓ Brain damage from insulin-induced hypoglycemia*
5) Minimize Adverse Interactions	Know your patients' regimen & known interactions	*Oral contraceptives efficacy ↓ when on Carbamazepine → Propose condom use*
6) Managing Toxicity	Know early sign & management of possible severe toxicity	*Penicillin may cause severe allergic reactions → Switch to different antibiotic*
7) Making PRN Decisions	PRN = *As needed*; Nurse controls administration	*Pain relief medications*

Patient education

Aspects	Goals	Examples
1) Dosage & Administration	Provide both Trade & Generic Names	*Acetaminophen & Tylenol*
	Teach proper dosage, schedule, administration & storage	*PRN vs. Fixed-schedule* *What to do if missed a dose?* *When to discontinue Tx* *How to store & expirary dates*
2) Maximize Therapeutic Effects	Teach expected therapeutic effects	*Pain decrease following Morphine Admin*
	Inform on Potential Delays	*Antidepressants & Antipsychotics Tx*
	Teach Nondrug Measures	*Exercises; Nutrition; Social Support*
3) Minimize Adverse Effects	Inform patients of potential adverse effects, early detection signs & interventions	*Early signs of hypoglycemia = sweating & ↑ HR* *If injected insulin and feel those Sx, take fast-acting carbohydrate-rich food* *Tx affecting physical appearance or urine color*
4) Minimize Adverse Interactions	Inform patient of potential drug-drug & drug-food interactions	*Phenelzine (antidepressant) interacts with most cheeses & avocado → ↑ BP*

Pharmacological nursing process

1. Pre-administration assessment:
    a. Evaluation of therapeutic & adverse effects
    b. High risk patient identification
    c. Patient self-care capacity assessment
2. Analysis & detection:
    a. Verify appropriateness of Rx
    b. Identify potential adverse reaction/interactions
    c. Characterize patient's self care capacity
3. Planning:
    a. Define therapeutic goal & priorities
    b. Establish criteria for goal evaluation
4. Evaluation
    a. Therapeutic effects
    b. Adverse reactions & interactions
    c. Patient adherence
    d. Patient satisfaction & quality of life

Landmark Drug Legislation

- Creation of FDA + Mandatory safety testing
    - Food drug & cosmetic Act of 1938
    - Diethylene glycol (car antifreeze) was found in Abx and killed 100 individuals. This was the turning point where the law was created to regulate.
- Mandatory proof of efficacy
    - Harris-Kefauver Amendments of 1962
    - Thalidomide tragedy: thalidomide was given to pregnant women, and later found out that it was creating child deformities. Today, there needs to be mandatory proof of efficacy.
- Controlled substance Act of 1970
    - Drugs classified by abuse potential within schedule I through V

- FDA Amendments Act of 2007
    - Mandatory post-marketing safety studies - continuous monitoring even after being put on the market
    - FDA can withdraw market approval

Canadian Legislations appendix

- Food and Drug Act (1927)
    - Safety and efficacy testing for all new drugs
    - Safety testing for all foods and natural health products (NHPs)
- Controlled drugs and substance act (1997, Federal Law)
    - All prescriptions drugs (except narcotics & controlled substances) = Schedule F
    - Schedules I through VII for drugs of abuse (ex. Opioids; cocaine; LSD; cannabis; precursors..)
    - Provincial harmonization schedules:
        - Schedule I = prescription & controlled
        - Schedule II-IV = OTC
- Canadian New Drug R&D process
    - Therapeutic product directorate (TPD) section of health Canada = FDA
    - Canada vigilance program = post marketing surveillance for all drugs & NHPS
    - Bill C-91 (1993): extension of new brand-name drug patent to 20 years from time of filling
    - Advertising: providing name drugs only (ex. Viagra ads)

New drug R&D Stages

TABLE 3.2
Steps in New Drug Development

Preclinical Testing (in animals)
Toxicity
Pharmacokinetics
Possible Useful Effects
↓
Investigational New Drug (IND) Status
↓
Clinical Testing (in humans)
Phase I
↓ *Subjects:* Healthy volunteers
↓ *Tests:* Metabolism, pharmacokinetics, and biologic effects
Phase II
↓ *Subjects:* Patients
↓ *Tests:* Therapeutic utility and dosage range
Phase III
↓ *Subjects:* Patients
↓ *Tests:* Safety and effectiveness
Conditional Approval of New Drug Application (NDA)
↓
Phase IV: Postmarketing Surveillance

Phases	# of Compounds	# of Participants	Question Answered
Drug Discovery	5-10 Thousands	N/A	Optimize target affinity Cytotoxicity Tests
Preclinical	250	Min. 2 animal species (1 non-rodent)	Organismal Toxicity Kinetic Parameters
I	5	20-100	Is it safe?
II		100-500	Does it work?
III		Few Thousands	Better than what we have?
IV	1	Infinite	Rare & Long-Term Adverse Effects

From discovery to market:
10-25 years + Billions of $$$ + Several Failures

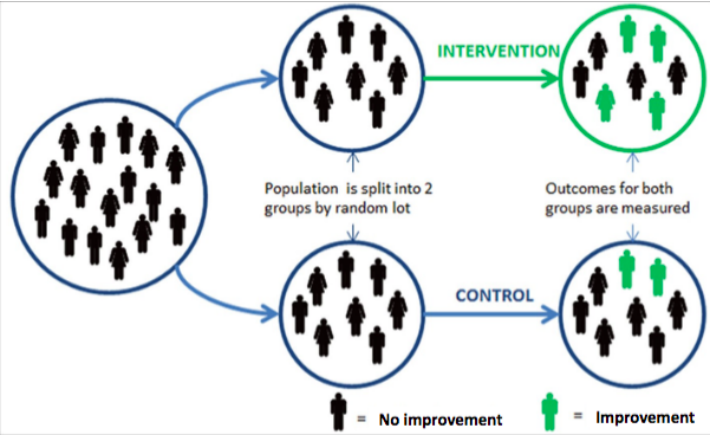
- Preclinical phase is where they test the drugs on animals. Usually a minimum of 2 animal species. If deemed safe, it will then be tested in humans: clinical testing.
- Phase 1: the drug will be tested in healthy volunteers. We want to see if the drug is safe in this phase.

- Phase 2: the drug will be used in patients in the population you want to treat. Now we want to see if the drug works.
- Phase 3: now we are comparing the drug to the other thing that is the current best drug at the moment. They need it to be better/improved to be approved.
- Phase 4: now that the drug is on the market, you need to continue surveillance.

Randomized Control Trials (RCTs)

3 key RCT features:

- **Randomization** to prevent bias.
- **Use of controls** helps you compare one group to the control group, to be able to compare if it is actually functioning.
    - New drug vs. gold standard vs. placebo
- Blinding
    - Single vs. Double-blind



R&D limitations

Results of new drug R&D are averages of conveniently selected (ie. non-representative) 18-55 cis white males, over a relatively short timeline.

3 key knowledge gaps:

- **Individuals variations**
    - Polymorphisms; allergic reactions; polypharmacy
- **Special populations**
    - Women; children; elderly; minorities
- **Long-term & rare adverse effects**
    - Pre vs. post marketing

When using a new drug:

- Be alert for unknown adverse effects/interactions
- Expect potential differences in efficacy

Which drug name to use?

- Unique vs. multiple trade names
- OTC with same name but different active agents
- International differences

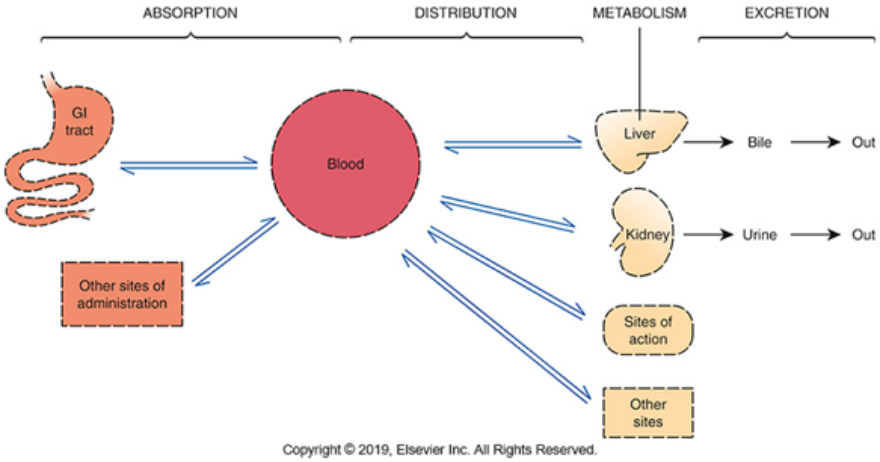
OTC drugs

- Available without Rx
- OTC status determined by FDA/health canada
- Common complaints treated by OTCs:
    - Mild pain
    - Constipation
    - Allergies
    - Motion sickness/nausea
- Save time, $$ & resources for healthcare system and patients
    - Redirect patients toward OTC whenever possible & effective

Pharmacokinetics (Ch. 4)

By definition it is what our body does to the drug

- Absorption
- Distribution
- Metabolism
- Excretion
- Response timeline



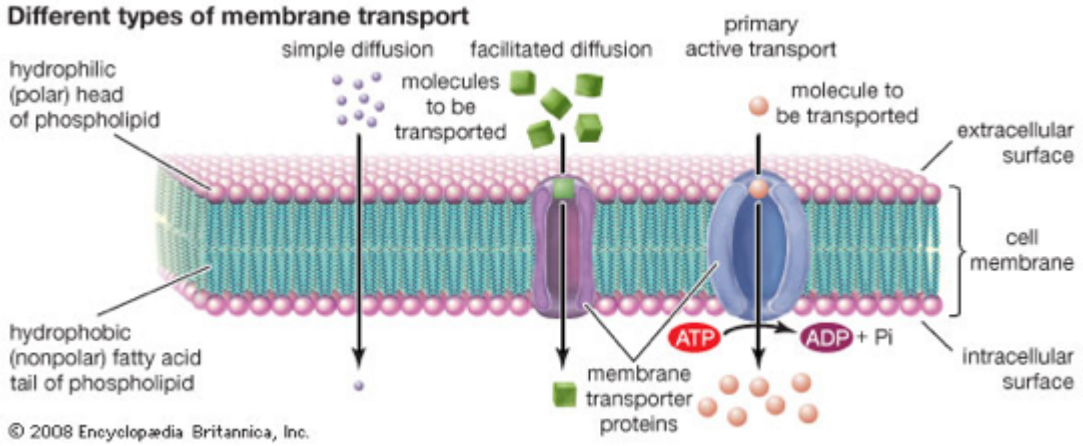
Absorption

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

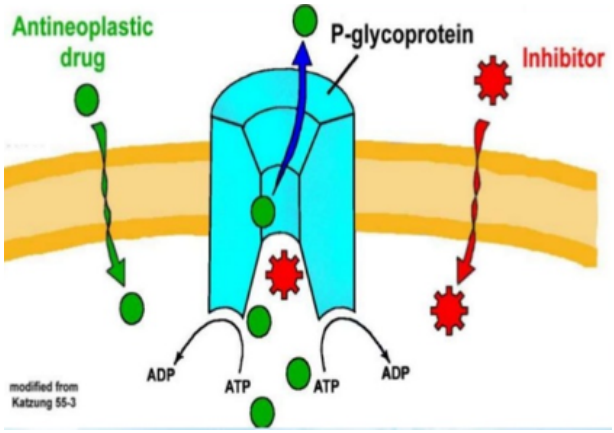
Drug membrane transport

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:

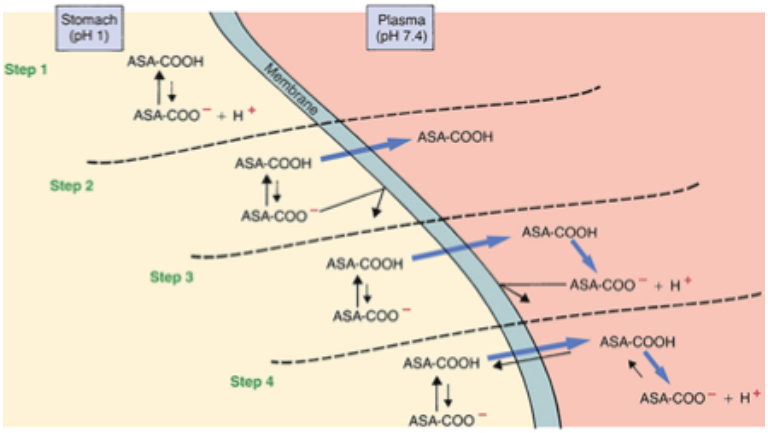
- Intestines
- Kidneys
- BBB
- Placenta

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.

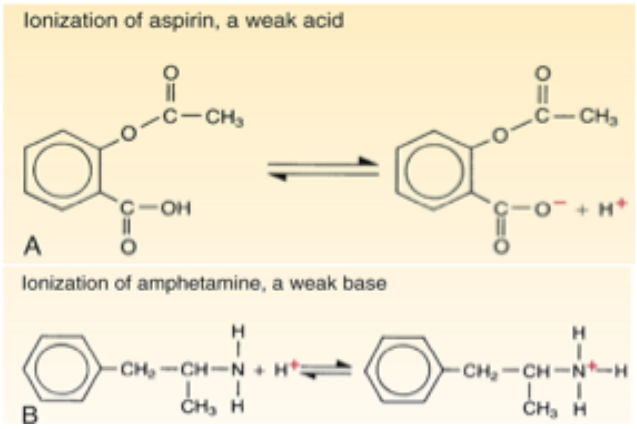
- Ex: a weak acid in an acidic environment becomes non polar: in an acidic environment, do you want to make this environment even more acidic? No. Therefore a weak acid will become non –polar, and therefore won't add to the acidity. If the environment is alkaline, the acid says i can neutralize this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



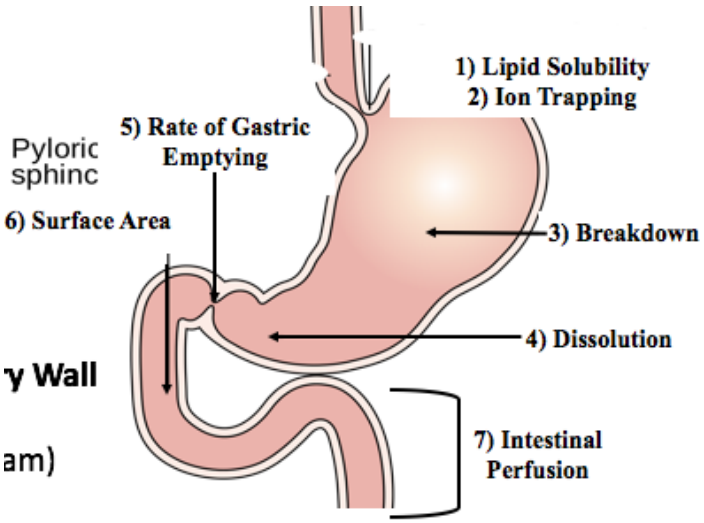
When we want to save someone from a drug overdose, changing the pH of the urine will help excrete more of the drug.

<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

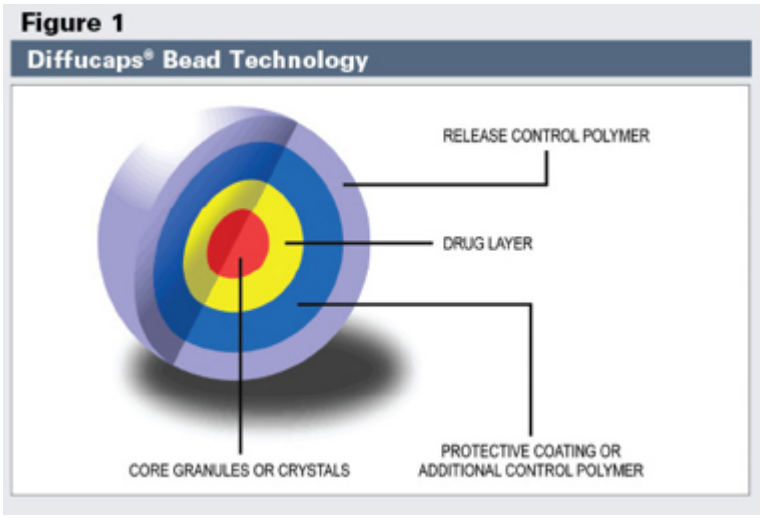
*Example of exam question: would this factor affect absorption?

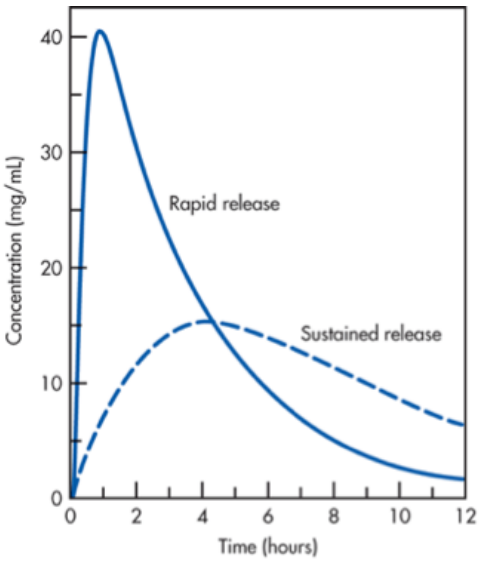


1. **Lipid solubility**: lipid-soluble drugs are absorbed more rapidly because they can readily cross the membranes.
2. **Ion trapping** (pH partitioning): absorption will be enhanced when the difference between the pH of plasma and the pH at the site of administration is such that drug molecules will 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

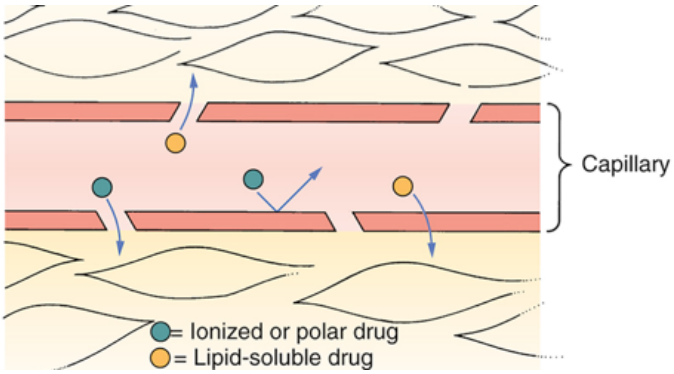
Is the movement of drug to cells & tissues

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

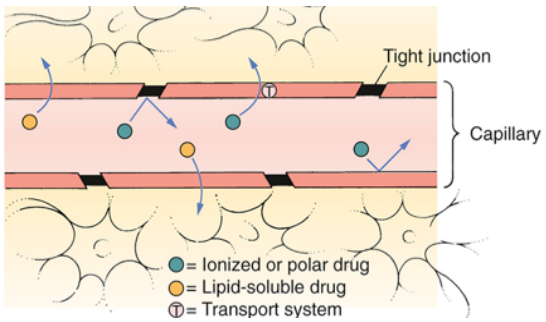
<u>Distribution barriers & factors</u>

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.

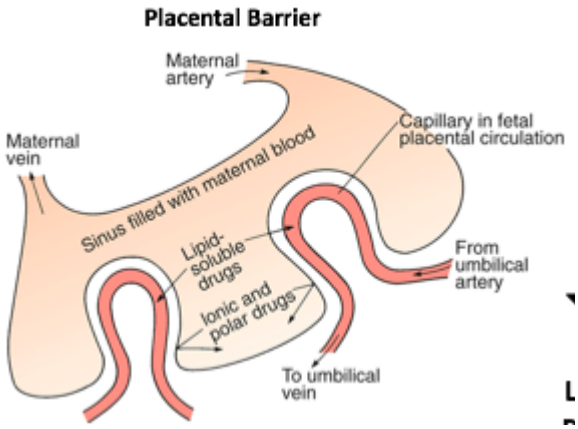


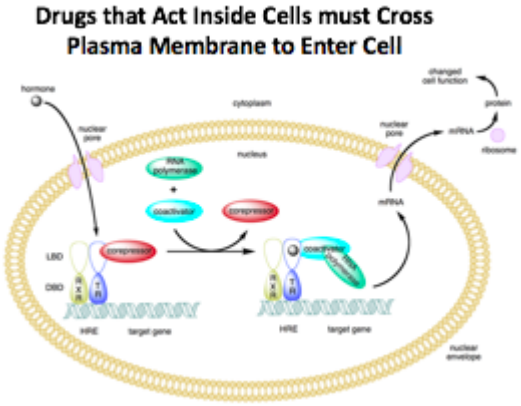
    b. you do not want a drug that binds to plasma protein. It will just attach to the PP and travel aimlessly throughout your bloodstream. It won't have an effect
3. Cross optional barriers (ex: BBB, placenta; plasma membrane)
    a. Capillary beds: because of the slits, polar drugs cross through those 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.



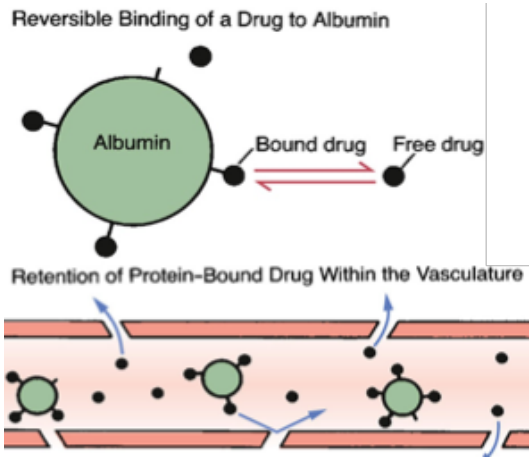


Drugs that are lipid soluble/non-polar have more ease crossing the placenta, but if they cross, they stay there (ion trapping).

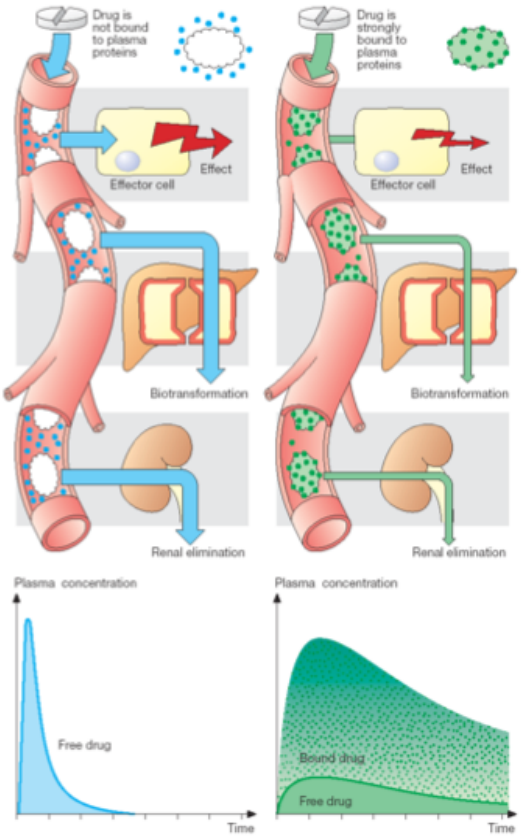
Hormones have easy access through barriers.

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

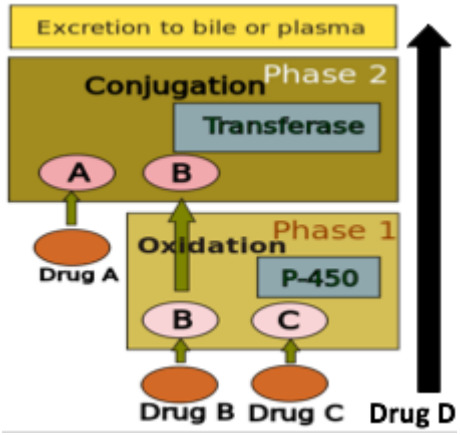
Alteration of the drug's chemical structure

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

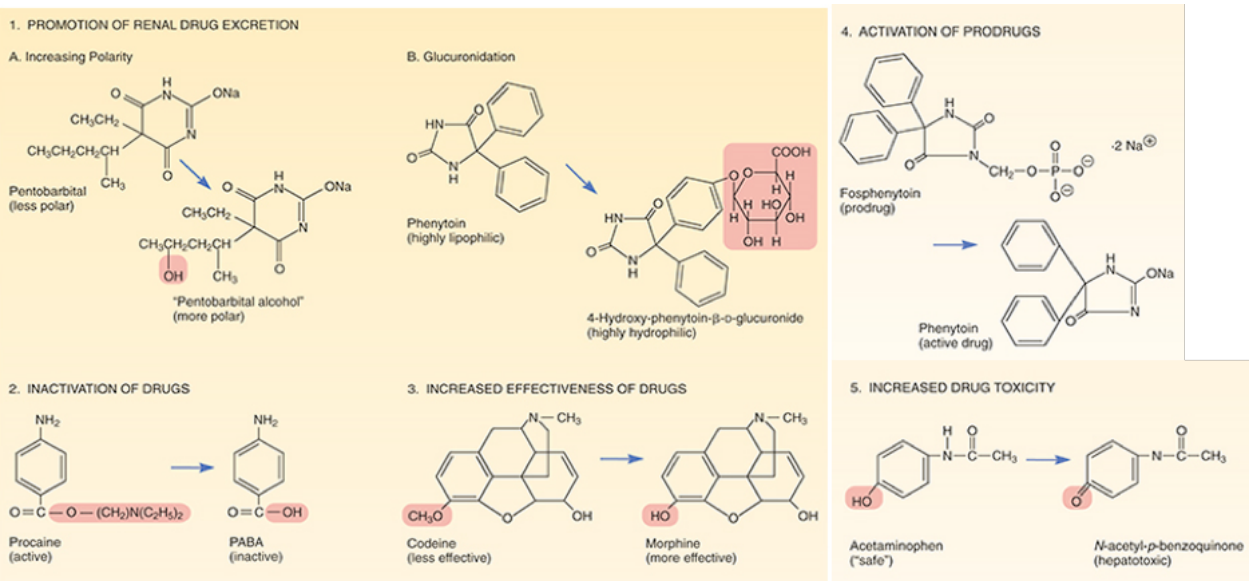


- Phase 1 enzymes: job of the phase 1 enzymes, is to perform redox reactions (turn off the drugs/inactivate).
- Phase 2 enzymes: conjugation reaction with transferase - they transfer a particular chemical group onto the drug. The goal of phase 2 is to promote excretion (making the drug more water soluble,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

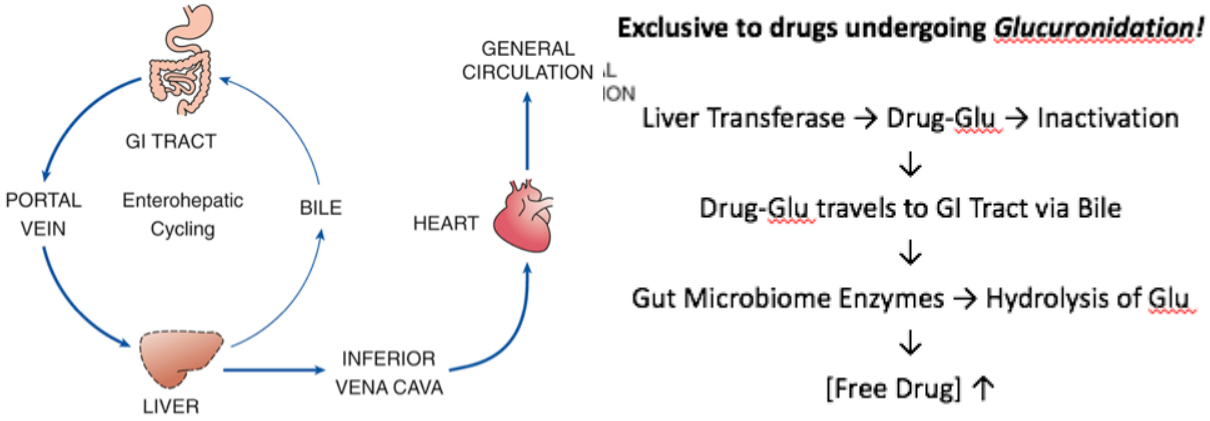
Special metabolic considerations

- **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

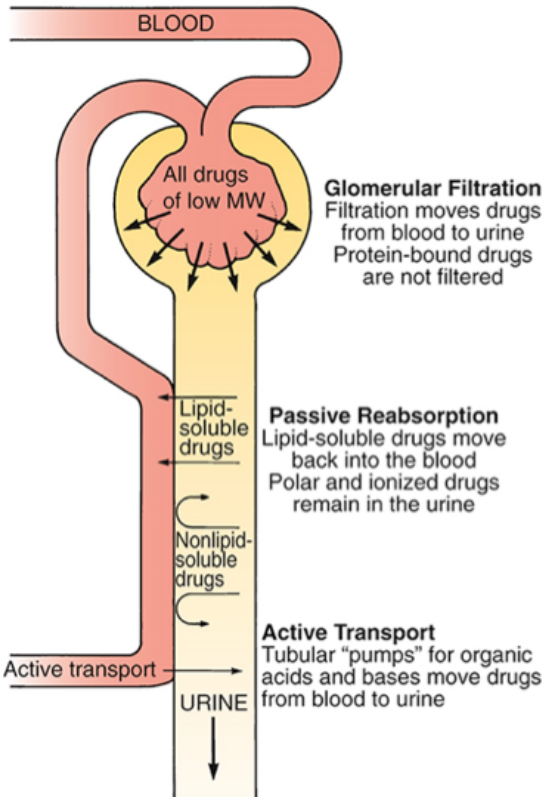
Metabolism + Excretion =

<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.



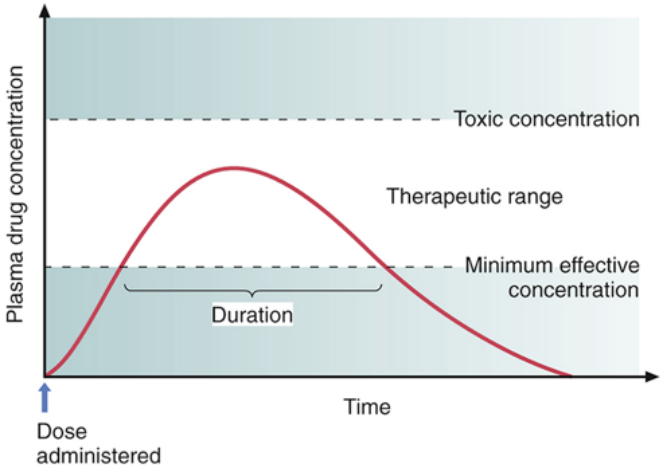
- Tubular transporter competition:
    - If you have 2 drugs, and they both need to be secreted in the tubules by the same protein, they'll have to compete. This causes accumulation of one of the 2 drugs, leading to toxicity.

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

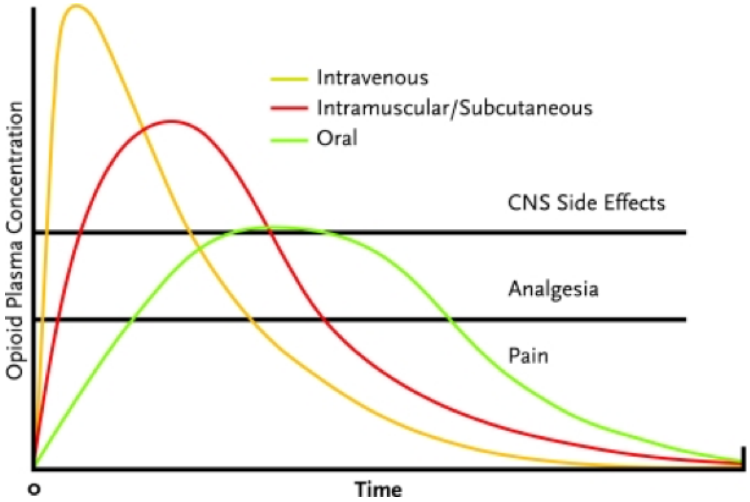
Plasma Drug Concentration



- 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

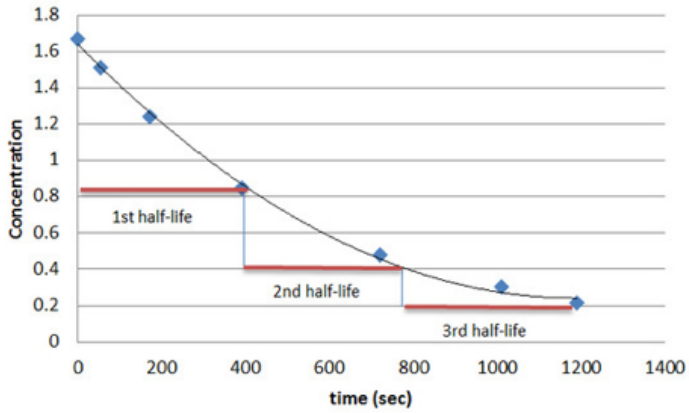
- Minimum effective concentration: the plasma drug level below which therapeutic effects will not occur.
- Toxic concentration: toxicity occurs when plasma drug levels climb too high
- Therapeutic range: is the range where there is enough drug present to produce therapeutic responses but not so much 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

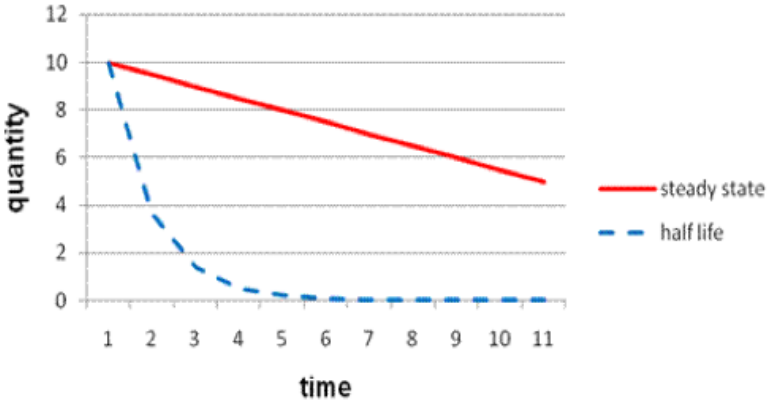
Half life



$T_{1/2}$ 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

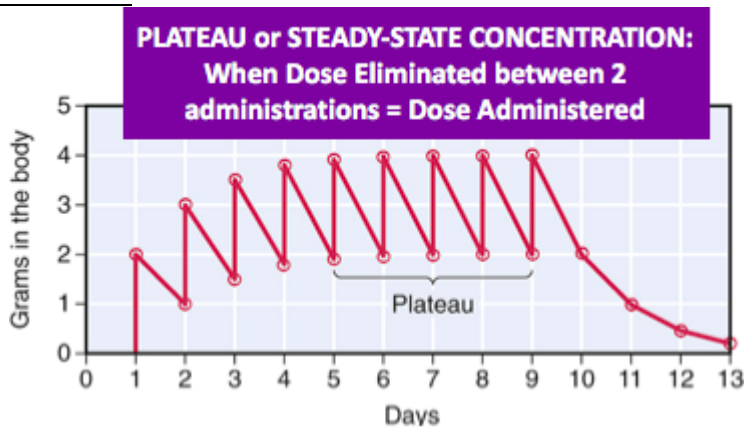
Hours ($T_{1/2}$)	1st-Order (mg)	1st-Order (mg)	Zero-Order (mg)
0 (0)	10	50	50
3 (1)	5	25	44
6 (2)	2.5	12.5	38
9 (3)	1.25	6.25	32
12 (4)	0.62	3.12	26
15 (5)	0.31	1.06	20

- 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)

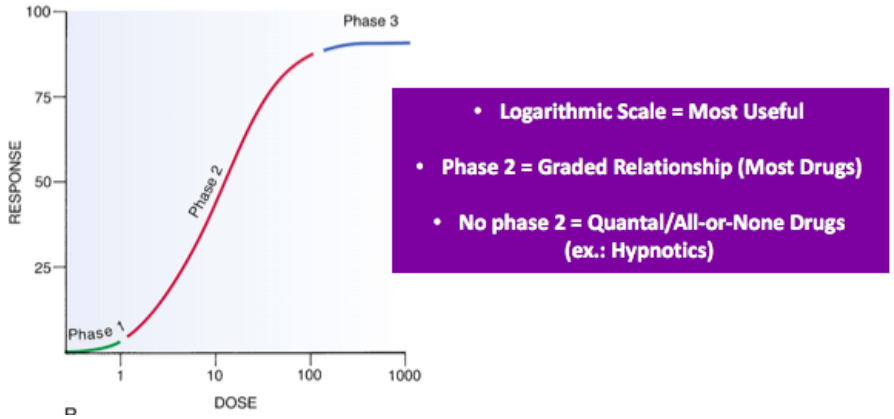
- Maintenance dose = regular dose at regular intervals to maintain plateau phase (ex: 2g/day afterward
- Most useful for drugs with long half-lives

- 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)

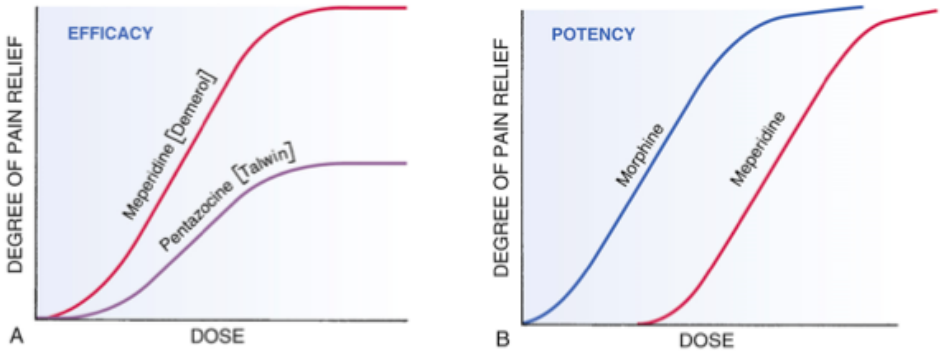
DRC: What is the response of the drug at different doses? Dose response relationships determine the minimum amount of drug needed to elicit a response, the maximum response a drug can elicit, and how much to increase the dosage to produce the desired increase in response.



- 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.



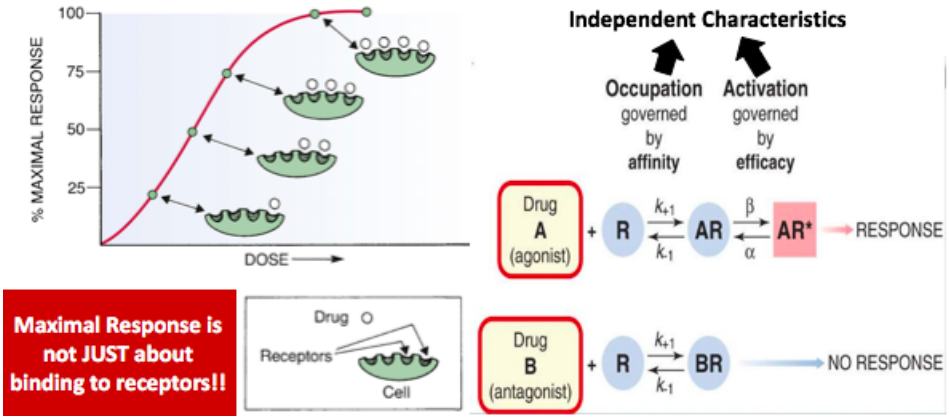
- Efficacy: the largest effect that a drug can produce → height of the curve
  - Mepiridine is more effective than Pentazocine, because the response is much greater than Penta (higher curve).
- Potency: the amount of drug we must give to elicit an effect → relative position of the curve along the x-axis
  - 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)

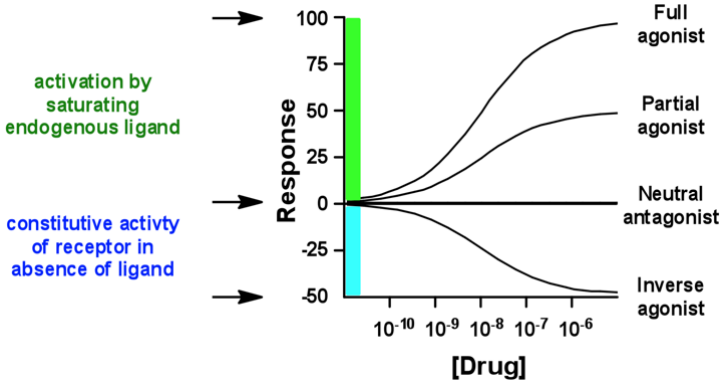
- Efficacy: maximum dose response you can get. When the drug binds to the receptor, does it activate it?
- Affinity: physical binding of the drug
  - Ex: Morphine interacts on opioid receptors. But heroine, also an opioid, is more potent because it has a much higher affinity for the opioid receptor than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

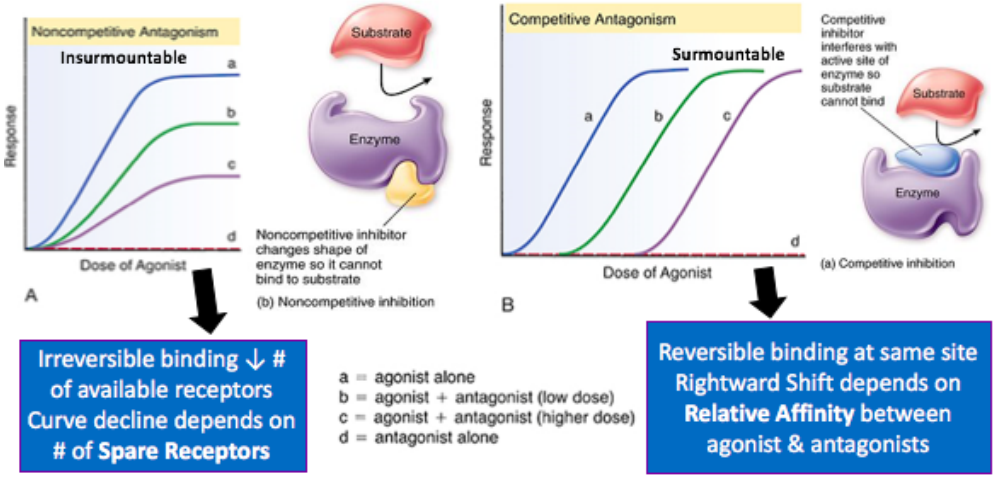
- This has to do with efficacy



- 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)

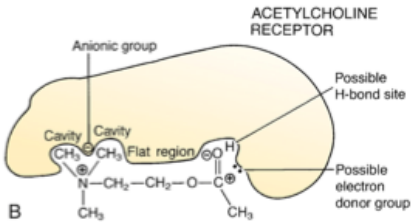
- Two types of antagonists:
  - **Insurmountable (non competitive) antagonist**: the antagonist binds to a receptor/enzyme (target) at a different site than the drug (substrate). They are not fighting for the same site/spot. When they bind to the receptor, it causes the enzyme to change its shape, preventing 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

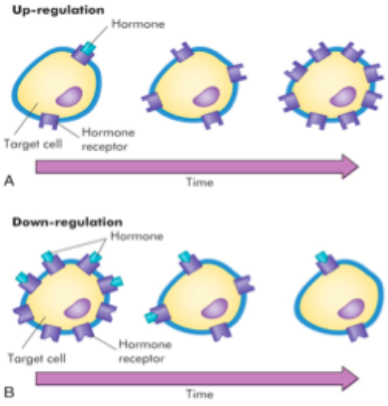
<u>Receptor Selectivity vs. Sensitivity</u>

- 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

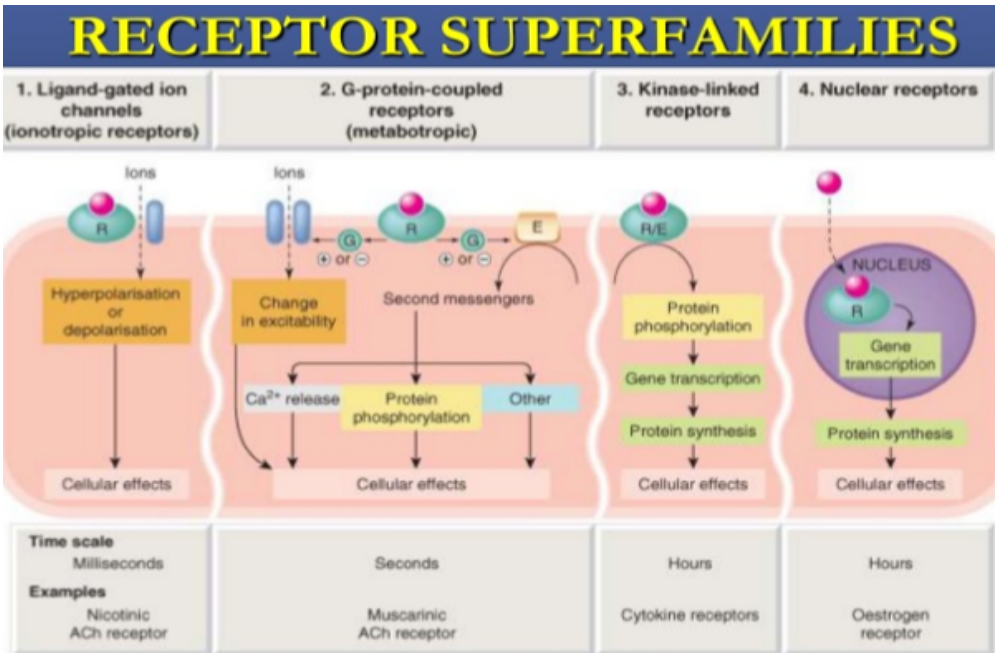


- Red box example: opioid receptors are not only found just for pain, they also regulate respiration (found in the medulla), bowels, etc.
- Sensitivity: what's the impact of the drug on the # of the receptors overall. How sensitive are you to a certain drug? Your sensitivity level can fluctuate over 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.

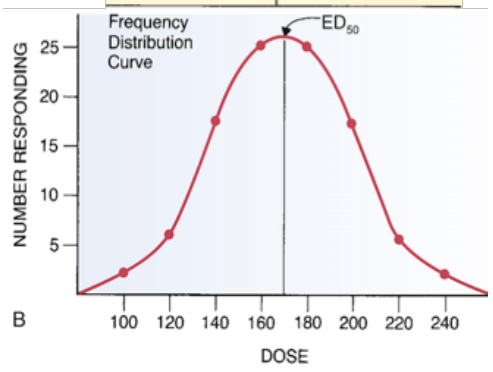
Non-Receptor Targets

- 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).

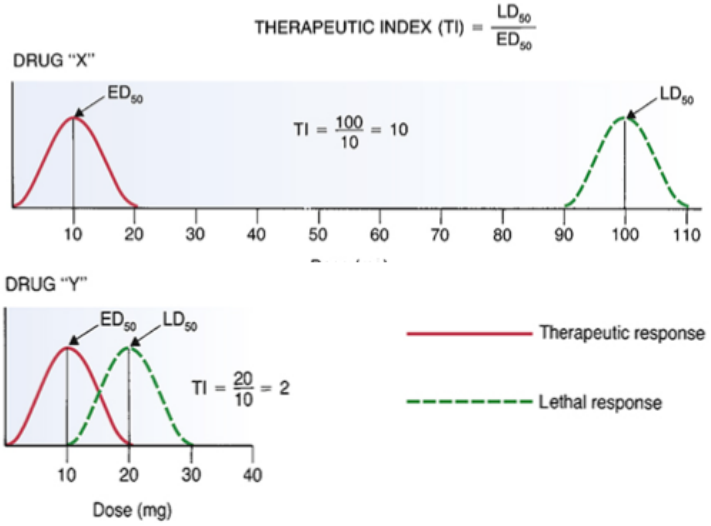
Nursing clinical implications:

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.



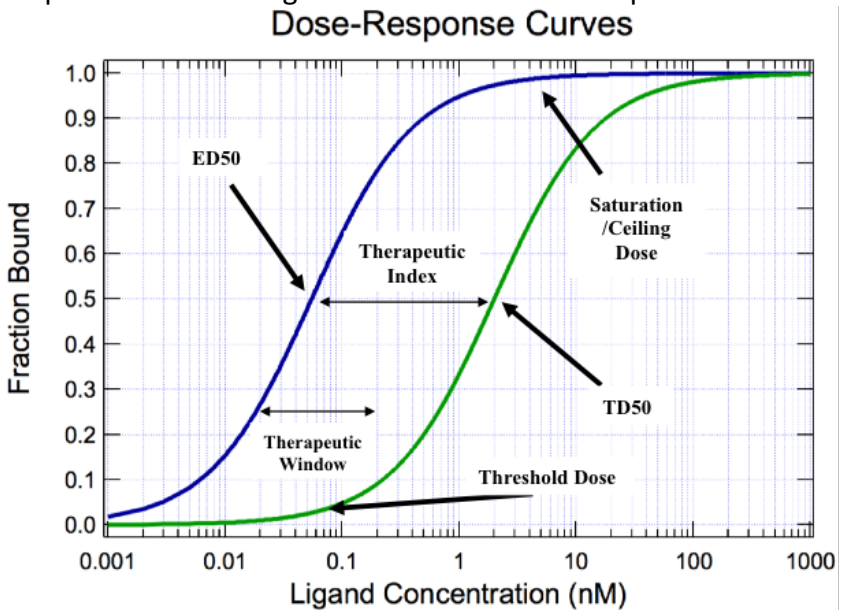
The larger the distance between those two curves, safer the drug. (ie. Drug X)
The smaller the distance between the curves, the more risky it is to give a lethal dose. (ie. Drug Y).

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

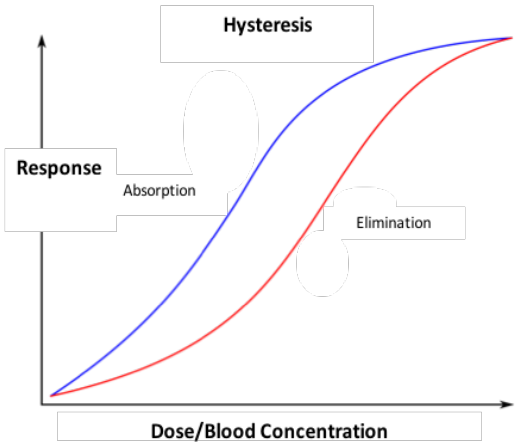
Pathophysiology

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

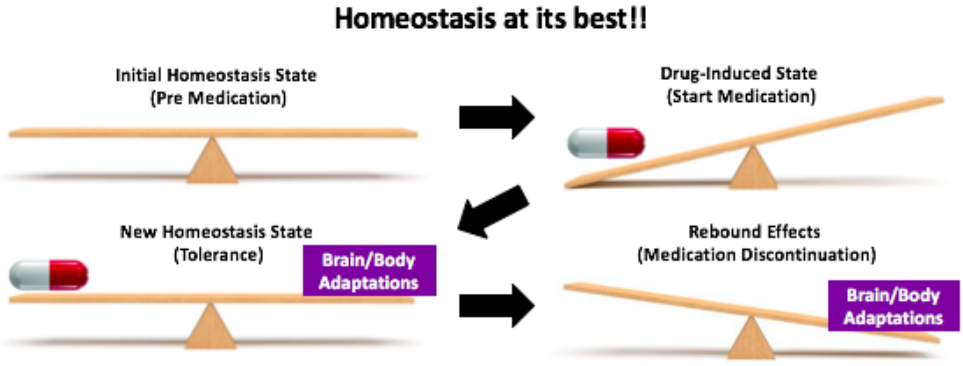
Metabolic (kinetic) tolerance:

- 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:

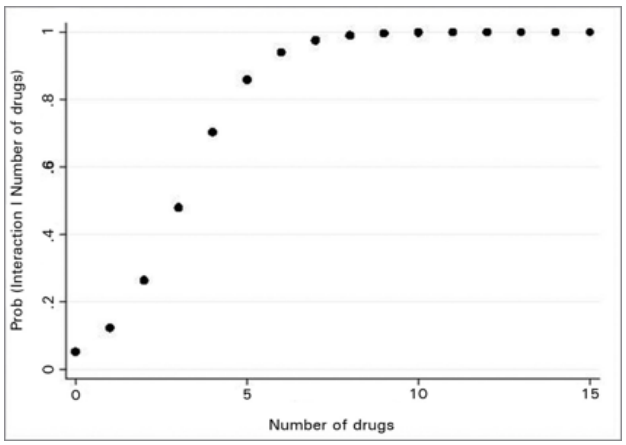
- Digoxin increases mortality of women only
- Women alcohol metabolism is lower
- Opioid pain relief efficacy in women > men

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

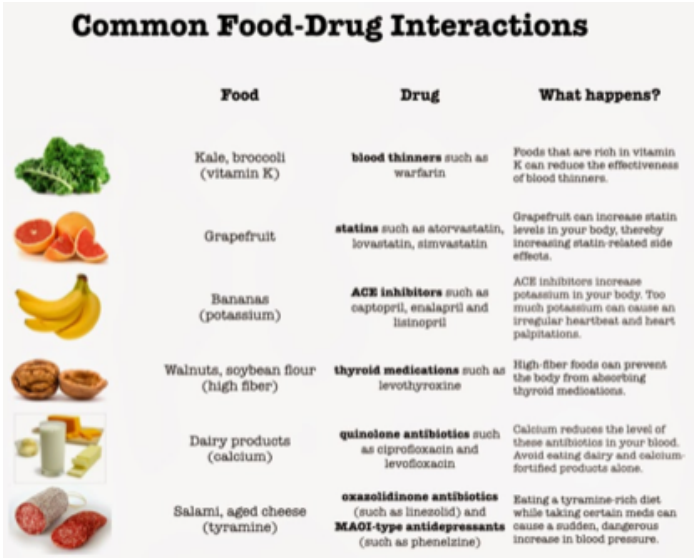
- Comorbidities: patient with 2+ conditions requiring Tx
    - Ex: patient with asthma & hypertension → if you give beta-blocker for HTN, it could cause bronchoconstriction and worsen asthma
- Polypharmacy:
    - associated with comorbidities
    - Frequent in elderly
    - Significant increased risk 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

DRUG INTERACTIONS (Ch. 6)

A drug can interact with:

- Drugs: occurs when a patient is taking 2+ drugs. They can be both intended or undesired.
- Foods
- Supplement
- Medical conditions

Possible effects:

- Decrease action of drug(s)
- Increase action of drug(s)
- Cause adverse effects

Drug Interaction Consequences

- Consequences depend on patient-related & drug administration-related factors
- Patient-related = diet, genetics, comorbidities
- Administration-related = route, dosage, order of administration

Consequences	Definition	Example
Potentiation	Drug B ↑ Drug A	β-lactamase inhibitors ↑ Ampicillin **(Beneficial)**
Additive	Total effect = Drugs A +B	Alcohol & Anxiolytics **(Harmful)**
Synergistic	Total effect > Drugs A + B	Codeine + NSAIDs for Pain **(Beneficial)** Aspirin + Warfarin for Anticoagulation **(Harmful)**
Antagonistic	Drug B ↓ Drug A	Naloxone ↓ Morphine/Heroin **(Beneficial)** Propranolol ↓ Albuterol **(Harmful)**
Unique	Effect unrelated to A or B	Disulfiram + Alcohol **(Harmful & Beneficial)**

*Beneficial = increased therapeutic effects or decrease in toxicity or cost ($) of therapy
*Harmful = decreased therapeutic effects or increased toxicity or cost ($)

The table lists the possible consequences of the different drug interactions:

- Potentiation (beneficial): when administered alone, ampicillin undergoes rapid inactivation by bacterial enzymes. Beta-lactamase inhibits those enzymes, and thereby prolongs and intensifies ampicillin's therapeutic effects.
- Potentiation (harmful): interaction between aspirin and warfarin represents detrimental potentiative interaction. Aspirin and warfarin both suppress the formation of blood clots. When given concurrently, the risk of bleeding is significantly increased.
- Additive: usually happens when two drugs do the same thing (ie. 2 CNS depressants)
- Synergistic: the total effect is greater than the sum of its parts. The effect is greater than A + B.
- Antagonistic: Drug B decreases the efficacy of Drug A.

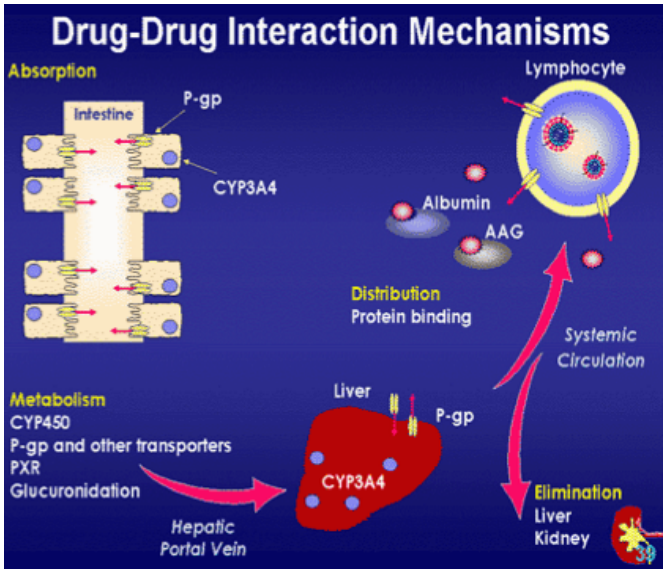
Chemical or Physical Interactions

- Most likely antagonistic consequences
- Most common when drugs combined in IV solution → frequently form precipitate
- Risks of chemical/physical interaction in body decreases thanks to body water dilution

Never combine 2+ drugs in a container unless you know for sure there are no interactions. Absence of precipitate DOES NOT mean no interactions.

Kinetic Interactions

Kinetic vs Dynamic: Kinetic has to be related to ADME.
Horizontal DRC shift: kinetic interaction usually slides the curve to the right or left (horizontally), because it changes your concentration (concentration is on the x-axis).



- Absorption:
  - Gastric pH alterations
  - Anything altering transit time
    - ex. Laxatives can reduce absorption of other oral drugs by accelerating their passage through to the intestine.
    - Drugs that depress peristalsis (ie. morphine, atropine) prolong drug transit time in the intestine, thereby increasing the time for absorption.
  - P-Glycoprotein affinity/concentration
- Distribution
  - Extracellular pH alterations → a drug with the ability to change extracellular pH can alter the distribution of other drugs. If a drug were to increase extracellular pH, that drug would increase the ionization of acidic drugs in extracellular fluids.

As a result, acidic drugs would be drawn from within cells (where the pH was below that of the extracellular fluid) into the extracellular space.

- Ex: aspirin toxicity → symptoms of aspirin toxicity can be reduced with sodium bicarbonate, a drug that elevates extracellular pH. By increasing the pH outside cells, bicab causes aspirin to move from intracellular sites into the interstitial fluid and plasma, thereby minimizing injury to cells.

- Plasma competition for protein binding: when two drugs bind to the same site on plasma albumin, coadministration of those drugs produces competition for binding. As a result, binding of one or both agents is reduced, causing plasma levels of free drug to rise. In theory, the increase in free drug can intensify effects.

- Metabolism
  - Hepatic enzyme induction: some drugs increase metabolism by inducing synthesis of hepatic drug-metabolizing enzymes
  - Hepatic enzyme inhibition: some drugs decrease the metabolism of other drugs by inhibiting those enzymes.
- Excretion
  - Anything altering glomerular filtration (ex. BP) - drugs that reduce cardiac output, which decreases renal perfusion, which decrease drug filtration at the glomerulus, which in turn decreases excretion.
  - Urinary pH alterations: one drug can alter the ionization of another and thereby increase or decrease the extent to which that drug undergoes passive tubular reabsorption
  - Tubular secretion transporters competition: competition between two drugs for active tubular secretion can decrease the renal excretion of both agents.
  - P-Glycoprotein: drugs can induce or inhibit PGP. Drugs that induce PGP have the following impact:
    - Reduced absorption: by increasing drug export from cells of the intestinal epithelium into the intestinal lumen.
    - Reduced fetal drug exposure: by increasing drug export from placental cells into the maternal blood
    - Reduced brain drug exposure: by increasing drug export from cells of brain capillaries into the blood.
    - Increased drug elimination: by increasing drug export from liver into the bile and from renal tubular cells into the urine

    drugs that inhibit have the opposite effect

P450 interactions

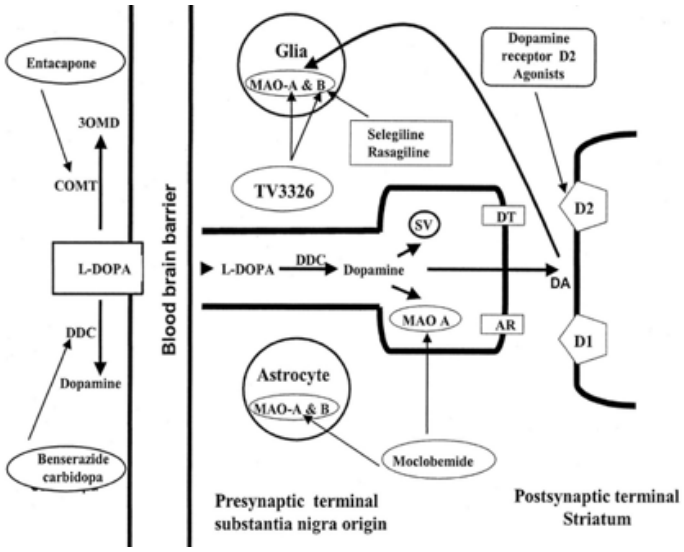
Top 5 P450 Enzymes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4

The P450 enzymes have a 7 day induction onset & offset

- some drugs might increase the amount of a specific enzyme. It takes about a week to get the full effect.
    - Ex: increases the amount of CYP3A4 from 100 to 150. So all the other drugs that are metabolized by CYP3A4 are not being metabolized more quickly. We have more enzymes to do the work.
- The dosage needs to be adjusted every time a new drug is added or discontinued.

Dynamic Interactions

- Dynamic has to do with efficacy (found on the y-axis).
- Usually causes Vertical DRC Shifts (response alterations)
- The effect of the drug changes without any significant changes in drug concentration!



Example in the picture: L-Dopa doesn't cross the BBB very fast, therefore a lot gets metabolized by the 2 enzymes COMT and DDC. These enzymes are usually located on the outside of the brain, and therefore not a lot of L-Dopa reaches the brain in the end. However, we found out that carbidopa is able to inhibit the DDC enzyme. So, if you combine L-Dopa and carbidopa, DDC metabolism is blocked, and allows L-Dopa to cross the BBB at its slow rate, and more of it reaches the brain. So L-Dopa is much more efficient when combined with Carbidopa.

- Shift is vertical

Receptor Interactions

- Mostly antagonism: occurs when an antagonist drug blocks access of an agonist drug to its receptor
    - Ex: naloxone and morphine

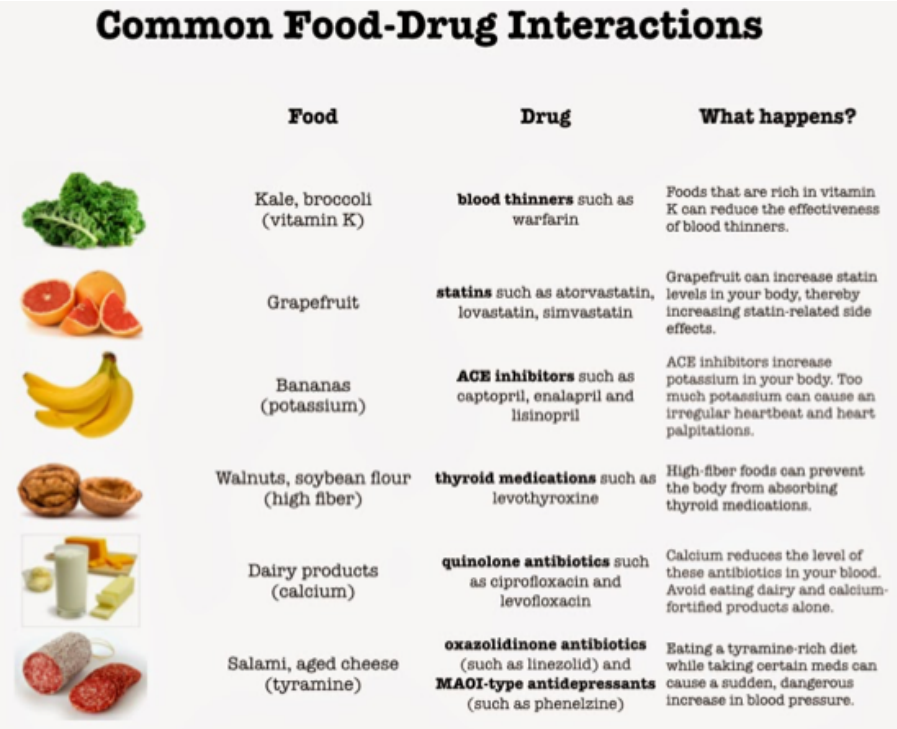
- Receptor regulation/tolerance
    - Ex: alcoholics have decreased GABA receptors

Physiologic Interactions

- Same physiologic effects via different mechanisms
- Ex:
    - Morphine & Diazepam = CNS depression synergy
        - These drugs act at different receptor sites but together act as a potentiation
    - L-DOPA + Carbidopa = increase efficacy (potentiation)
    - Proton Pump Inhibitors + Aspirin = decreases toxicity

Food-Drug Interactions

- Includes Dietary supplements/Natural Products



- Kale, broccoli: decreased drug response
- Grapefruit: metabolism interactions
- Walnuts, Dairy products, etc: absorption interactions
- Salami, aged cheese, etc: increased toxicity (ex: MAO inhibitors - can lead to life-threatening BP levels)

The Grapefruit Juice Effect

Grapefruit has 2 molecules that have a big interaction with CYP3A4 enzyme, found in the liver and intestinal wall. Any drug that is supposed to be metabolized by CYP3A4, mixed with grapefruit, will now be less metabolized.

- Grapefruit inhibits intestinal CYP3A4, decreasing the intestinal metabolism of many drugs, and thereby increasing the amount available for absorption (drug bioavailability). As a result, blood levels of these drugs rise, causing peak effects to be more intense.
- Because inhibition of CYP3A4 in the liver is minimal, grapefruit juice does not usually affect the metabolism of drugs after they have been absorbed.
- Grapefruit juice effect has little or no effect on drugs administered IV. Why? Because with IV administration, intestinal metabolism is not involved.
- Inhibition of CYP3A4 is dose dependent - the more grapefruit juice, the greater the inhibition
- Inhibition can persist up to 3 days.
- Avoid completely during course of Tx

Clinical considerations of Interactions

- High risk drug interaction cases
    - Polypharmacy → increases risk exponentially
    - Narrow therapeutic range drugs → therapeutic failure or toxicity
    - New/recent drugs → undocumented interactions
- Minimizing adverse reactions
    - Avoid polypharmacy whenever possible
    - Obtain a complete history of drugs taken by patients → undisclosed OTCs or illicit drugs
- Timing of meal and drug intake
    - Reduce stomach irritation or avoid interactions
    - "Empty stomach" indication = 1 hour before meals OR 2 hours after

ADVERSE REACTIONS & MEDICATION ERRORS (Ch. 7)

Definitions

- Adverse drug reaction (ADR): noxious, unintended and undesired effect occurring at normal dosage (only bad)
- Side effects (SE): Nearly unavoidable secondary drug effect at therapeutic dosage, can be good or bad
    - Often predictable & dose-dependent
    - Ex: gastric irritation from Aspirin; constipation from opioid painkillers
- Toxicity: Detrimental physiologic effects caused by excessive drug dosage

    - Clinical usage: any severe ADR regardless of dosage
    - Ex: coma from morphine overdose; neutropenia from anticancer therapeutic dose
- Allergic reactions (AR): Aberrant and harmful immune response triggered by a drug
    - AR intensity = dosage-independent, but patient-dependent
    - Most severe AR caused by Penicillins
- Idiosyncratic effect = uncommon DR resulting from genetic variation
    - Ex: G6PD Deficiency + Aspirin → RBC hemolysis
- Paradoxical effect: opposite effect than intended/expected
    - Ex: excitation following diazepam for sedation
- Iatrogenic disease = disease produced by a drug
    - Ex: antipsychotics → Parkinson-like symptoms
- Physical dependence = body adaptation to long-term physiologic drug effects
    - Ex: nasal sprays for airway openings; sedating effects of sleeping pills
- Psychological dependence = intense motivational cravings to consume a drug
    - Ex: opioids; nicotine dependence
- Carcinogenic effect = ability of a drug to induce cancer development
    - Usually undocumented until many years post-marketing
- Teratogenic effect = ability of a drug to induce birth defects (thalidomide!!!)
    - Scrutinized and tested during new drug development

<u>Hepatoxicity</u>

- Liver enzymes convert drugs into toxic metabolites
- Frequent cause of Acute Liver Failure
- Super hepatotoxic drugs = withdrawn from market
- Patients taking hepatotoxic drugs:
    - Frequent LFT → look for increased AST or ALT
    - Monitor liver injury symptoms (ie. jaundice, dark urine, light-colored stool, N/V)
    - Educate patients for liver symptom recognition

<u>QT interval Drugs</u>

- Q is the beginning of ventricular contraction and T is the ventricular repolarization. So if you start prolonging the QT interval → prolonging the duration of a heart beat. If this continues to happen over time, you're likely to cause arrhythmias.
- Prolonged QT interval time (FDA mandatory QT interval testing for all new drugs)
- QT > 470 msec → increased dysrhythmias (torsade de pointe) → increased V. fibrillation
- Women are at a higher risk of a prolonged QT interval compared to men, because women already have a longer QT interval normally.

- Avoid QT drugs whenever possible
- See page 66 of book for drug examples

Clinical considerations of ADR

- Identifying ADRs
  - Temporal relationship: ADR starts shortly after drug administration & ceases when discontinued
  - ADR cannot be explained by the illness or other drugs in the regimen
  - High vigilance with new drugs → report suspected ADRs
- Minimizing ADR
  - Know the major ADRs associated to drugs you administer/taken by patients under your care
  - Monitor organ functions if known specific toxicity (ex: liver, QT interval; kidneys; bone marrow)
  - Individualize therapy considering patient history (ex: allergies, pregnancy, etc)
- Guides & Box warnings
  - Medication guides = excellent patient education tool
  - Black box warning = serious life-threatening ADR risk

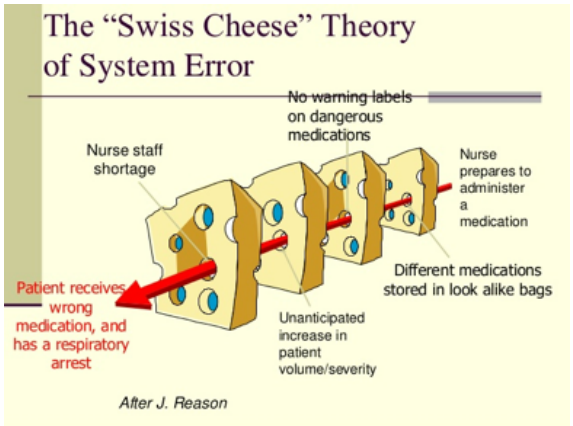
Medication Errors

Any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the HCP, patient or consumer.

- Major cause of morbidity & mortality → injure ~ 1.5M & kill ~ 7000/year
- Huge financial burden → 3.5 billions/year

Types of Medication Errors

Wrong patient
Wrong drug
Wrong route
Wrong time
Wrong dose
Omitted dose
Wrong dosage form
Wrong diluent
Wrong strength/concentration
Wrong infusion rate
Wrong technique (includes inappropriate crushing of tablets)
Deteriorated drug error (dispensing a drug after its expiration date)
Wrong duration of treatment (continuing too long or stopping too soon)



Major causes:

- Human factors
- Communication mistakes - written or oral
- Name confusion
- Packaging, formulations, and delivery devices
- Labeling and reference materials

Clinical Considerations of Medication Errors

Who makes them?

- HCP makes the order → pharmacist verifies and prepares order → nurse practitioner administers order
- Nurses = last line of defense: last one to catch mistakes by others but no one can catch a nurse's mistake!

Minimizing medical errors

- Institution-wide processes = best /most effective
- Ex: computer order vs. hand-written; bar-code matching systems for drugs & patients' armbands.

How to report

- Report via MER program (not to blame) - is a nationwide system run by the ISMP. All reporting is confidential and done via phone or internet.

Medication Reconciliation (box 7-1)

- Compare list of medications currently taken with new medications that are about to be provided
- Done whenever a patient undergoes a transition in care
- Decrease medication errors during transition in care by 70% + ADRs by 15%
- Provide a list of all medications to be taken following discharge

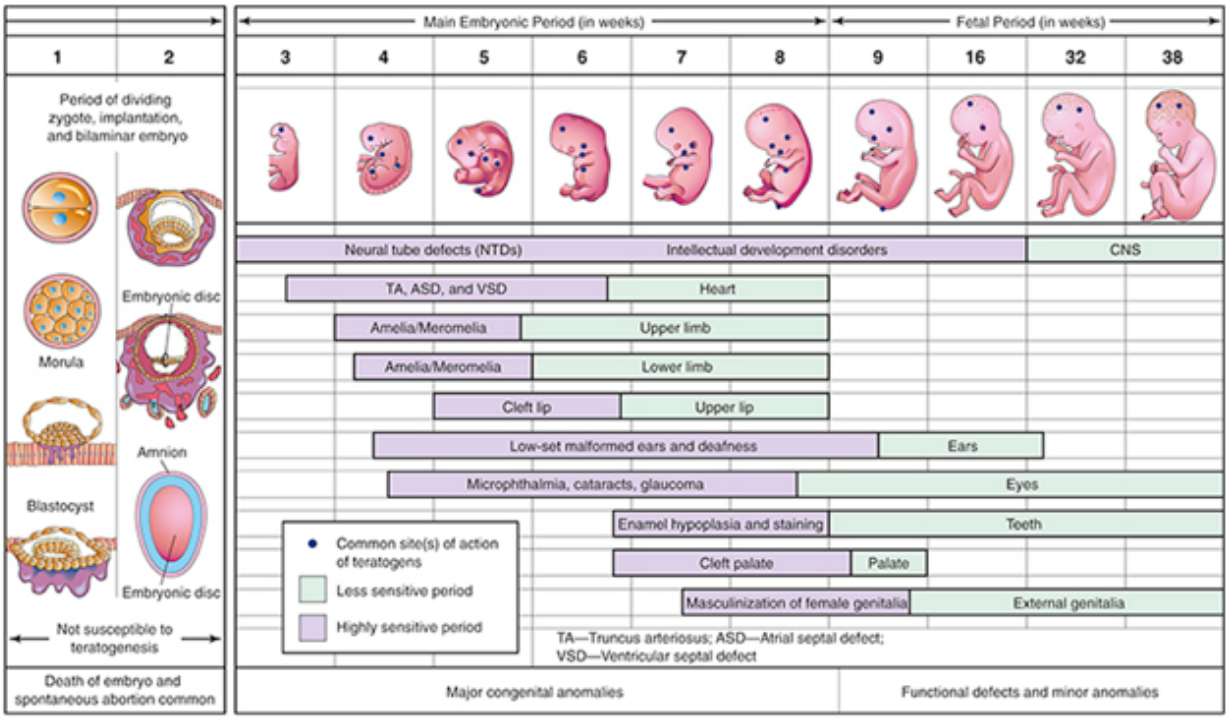
PREGNANCY & BREAST-FEEDING (Ch.9)

Basic Considerations

- ⅔ pregnant patients take at least 1 medication; majority takes more
- Reliable data on drug toxicity during pregnancy = very limited
- Risk-benefit analysis without knowing most of the risks..
- Health of the mother = crucial to fetus health → MUST treat!
- Pregnancy physiologic changes → dosage adjustments!
    - Ex: increased BP → increased GFR → increased excretion
    - Increased GI transit time (slowed) → more time for drugs to get reabsorbed → increased absorption
- Assume that drug taken during pregnancy reaches the fetus
    - Although polarity affects placental barrier crossing

Teratogenesis

Teratogenesis is the development of birth defects.



From Moore K, Persaud TVN, Torchia M: *The developing human: clinically oriented embryology*, ed 9, Philadelphia, 2012, Elsevier, with permission.

During the 1st two weeks, from fertilization until day 14, drugs cannot reach the fetus because the blood supply of the fetus is not fully attached to the mother yet. First it needs to implant, then the blood supply will become attached..

Starting from week 3, when the fetus is attached to the mother, the organs begin to develop. The fetus is especially vulnerable during the embryonic period.

- Major congenital anomalies typically occur in the first trimester

Window of vulnerability: different organs develop at different time frames in the pregnancy. It varies per organ/drug/defect/fetus

- For example, if the mother is taking a drug that affects the fetus at week 16, there's a very very low chance that the development of the limbs will be affected.

Teratogen exposure during the fetal period (2nd and 3rd trimester) usually disrupts function rather than gross anatomy.

Drug exposure = minor cause (<1%)

Teratogens

- Proof of teratogenecity = difficult → almost no direct human studies
- Animal safety = FDA requirement does not equal human safety (ex. thalidomide)

- Fast-acting: a single dose can cause malformations. Can be easily detected in the fetus or at birth.
- Slow-acting: needs repeated doses to cause malformations. The effects can only be detected later in life
    - for example, fertility problems only show up later and not at birth of the baby
- Behavioural teratogens = almost impossible to detect because this would occur much much later in life, and a correlation cannot be made to a medication taken during birth

Breast-feeding

Patient education advice:

- Avoid drugs from table 9-4 - favor those from table 9-5 (p.88)
- Administer immediately after (or even during) breast-feeding to minimize drug concentrations in milk at the next feeding
- Avoid Rx with long half-life or sustained-release formulations

Pregnancy Risks

- FDA categories → pregnancy & lactation labelling rules (PLLR)
    - Categories phased out by 2020 → replaced by PLLR (see table 9-3, p.85)
    - Drug-specific infos on exposure/risk/clinical considerations/scientific data
- Minimize teratogenesis
    - Discontinue unnecessary drugs for pregnant patients (including all recreational drugs)
    - Substitute teratogenic drug to less harmful option if applicable
    - Educate reproductive-age patients taking proven teratogen Rx to use contraceptives
- Responding to teratogen exposure
    - Reassure about the absolute low risk of birth malformation + most birth defects being drug-independent
    - Consult literature for anticipated malformations
    - Ultrasound to assess injury →
        - Severe = possible termination
        - Minor = possible surgical correction
- Food for thought: what do you do in the case of an epileptic patient where the anti-seizure drug is a teratogen but seizure attacks are also a known teratogen?
    - Treat the patient, give one epileptic drug at its smallest possible dose. Seizures are teratogenic for the fetus, and therefore still want to treat the seizures.

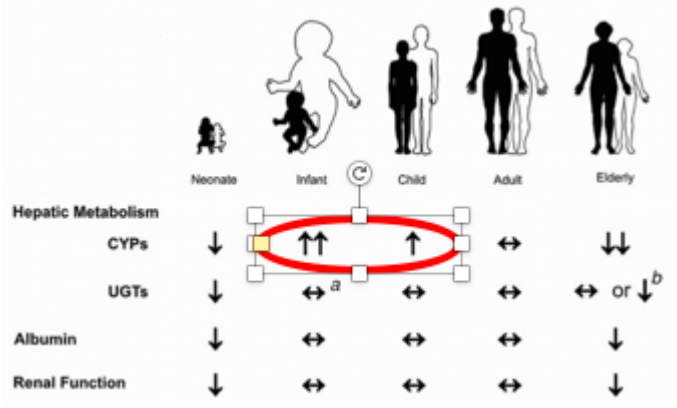
PEDIATRIC & GERIATRIC PATIENTS (Ch. 10 & 11)

Pediatric patients - basic considerations

- Organ immaturity → infant drug sensitivity > adults
- Very limited pediatric drug research
- New FDA Acts in 2000s' forced to increase pediatric research
    - Early results:
        - 20% of effective Rx in adults = ineffective in kids
        - 20% required different dosage than extrapolated
        - 30% of drugs had new serious ADR in kids
- Kids DO NOT EQUAL miniature adults

Pharmacokinetics

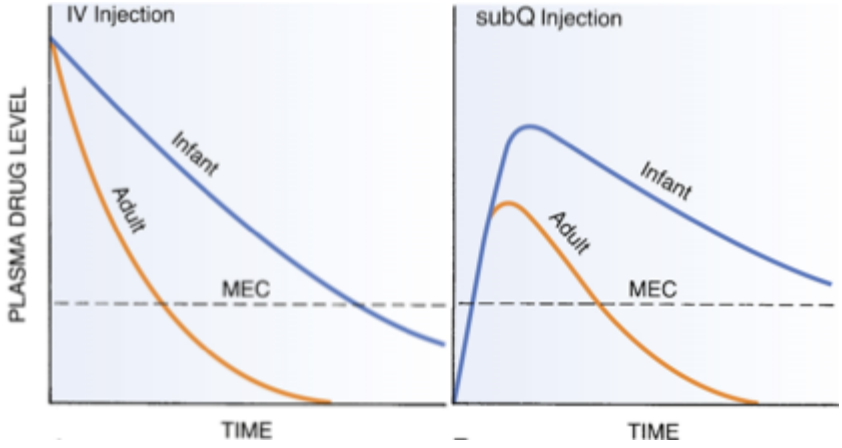
- One of the biggest differences in kids and adults isin the kinetics (see red circle)



- Everything is reduced because organs are immature.
- Neonates & infants immaturity in 5 major PK processes:
    - Absorption - gastric emptying is both prolonged and irregular in early infancy
    - Protein binding (distribution)
        - The amount of serum albumin is relatively low and endogenous compounds (fatty acids, bilirubin) compete with drugs for available binding site. As a result, the concentration of free levels of such drugs is relatively high in the infant, thereby intensifying effects. Dose will need to be decreased.
    - Permeable BBB (distribution)
        - BBB is more permeable in children than in adults, drugs can reach the brain more easily. They will need a smaller dose.
    - Hepatic metabolism
        - Drug-metabolizing capacity is low. Dosages must be reduced.
    - Renal excretion

- Renal blood flow, glomerular filtration, and active tubular secretion are all low during infancy. Therefore, dose will need to be reduced.

- CYP enzymes are working better in kids than in adults. One hypothesis is that kids and babies are always putting bacteria and harmful things in there mouth, therefore the CYP enzymes are thought to be increased.



Pediatric considerations

- ADRs
  - Altered kinetics increases intensity & prolonged drug effects
  - Avoid Rx from table 10-1 (p.92) whenever possible
- Dosage
  - Look for pediatric dosage whenever available
  - When unavailable use body surface area (BSA) approximation
    - (Child BSA x Adult dosage)/1.73m^2 = pediatric dosage
  - Adjust dosage accordingly following initial dose
- Adherence promotion (see table 10-2,p.92)
  - Child caregiver and child education = crucial!!
  - Select most advantageous route of administration + provide demonstration
  - Written instructions + conscientious participation of parents

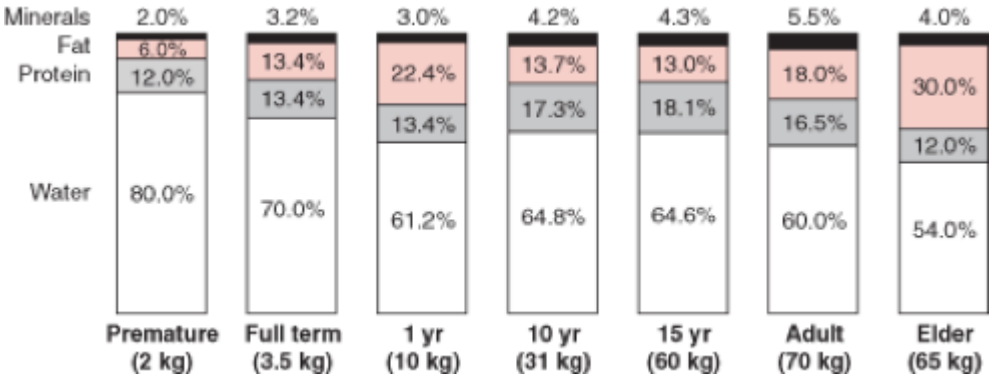
Geriatric Population

Kinetic Changes (p.95 Table 11.1)

- The kinetics of the elderly are very similar to babies/children.
- High individual variation depending on:
  - Physical fitness
  - Pathologies (organ degeneration)
  - Polypharmacy
- The excretion changes are the most important. Key factor: loss of kidney function.

- Decreased renal blood flow
- Decreased glomerular filtration rate
- Decreased tubular secretion
- Decreased number of nephrons

- Body water:Fat ratio changes with Age



Geriatric considerations

- Minimize ADRs
  - High risk population (7x more common!!) due to polypharmacy, comorbidities, poor adherence, etc.
  - Avoid drugs on Beers' list
  - Watch out for few dynamic alterations
    - Ex. Beta blockers decrease efficacy
    - Ex. warfarin increase efficacy
- Adherence promotion
  - Counter the most common adherence hurdles
  - Simplify dosage & administration
  - Recruit friends & family assistance
  - Intensive education → intentional nonadherence
- Factors decreasing adherence in elderly
  - Multiple disorders
  - Multiple prescriptions & prescribers
  - Multiple doses per day for each medication
  - Drug packaging difficult to open
  - Regimen changes
  - Low SES (literacy, $$, social support)
  - Personal conviction that a drug is unnecessary or the dosage too high
  - Cognitive or physical impairment (memory, vision, hearing, etc)
  - Presence of side effects
  - Recent discharge from hospital

ANTISEPTICS & DISINFECTANTS (Ch. 96)

General considerations

- Action antimicrobial agents → toxicity too large for internal use
- Definitions:
  - Antiseptics: living tissue (ex: hands, patient skin prior to intervention)
  - Disinfectants = non-living objects (ex: surgical instruments)
  - Sterilization = destruction of all microorganisms
  - Sanitization = contamination meeting public health standards
  - Germicide = kills microorganisms vs. germistatic drugs = inhibit growth
- Important characteristics
  - No perfect agent
    - Ex: safe + selective + effective + no odor + kills all germs + …
  - Variable time course of action
    - Ex: alcohol = 36 secs vs. 7 minutes of benzalkonium chloride
  - Effective prophylaxis → best usage = application on medical personnel & instruments
  - Infective vs. local (topical) infections

Individual properties of antiseptics & disinfectants

Antiseptics and Disinfectants: Chemical Category and Application

Chemical Category	Drug	Application	
		Antisepsis	Disinfection
Alcohols	Ethanol	✓	
	Isopropanol	✓	
Aldehydes	Glutaraldehyde		✓
	Formaldehyde		✓
Iodine Compounds	Iodine tincture	✓	
	Iodine solution	✓	
Iodophors	Povidone-iodine	✓	✓
Chlorine Compounds	Oxychlorosene	✓	
	Sodium hypochlorite	✓	✓
Phenolic Compound	Hexachlorophene	✓	
Miscellaneous Agents	Chlorhexidine	✓	
	Hydrogen peroxide	✓	✓
	Benzalkonium chloride	✓	✓

Focus on those that are used in the clinical section

Alcohols

	Characteristics
Prototype	Ethyl Alcohol
Main Usage	**Fast-Acting Antisepsis only** (ex.: Staff hand washing)
Antimicrobial Spectrum	Most Pathogenic Viruses & Bacteria Dissolve membranes + Protein precipitation
Weakness	Bacterial spores & Fungi **Thus poor Disinfectants**
Optimal Concentration	70% Solution (Higher % ↓ Efficacy)
Contraindications	**Do not use on open wounds!** Tissue damage + Coagulation Mass
Miscellaneous	↑ Efficacy of other Antiseptics (Ex.: Chlorhexidine & Benzal Chloride)

Iodine Compounds

	Characteristics
Prototype	Iodine
Main Usage	**Antiseptic only** Best for skin of patients prior to IV injections or blood sampling
Antimicrobial Spectrum	All microorganisms & spores
Optimal Concentration	Solution = 2% Iodine + 2.4% Sodium Iodide Tincture = Solution + 47% Ethanol (↑ Efficacy)
Contraindications	**Avoid tincture on open wounds** (Alcohol = Irritant)
Miscellaneous	Oldest Antiseptics (160 years old!!) Very cheap + Very low toxicity Only Free Elemental Iodine kills (≈ 0.15% of solution) Sodium Iodide works as a reservoir for sustained-release

- Tincture increases the efficacy because of iodine combined with ethanol, but cannot be used on open wounds

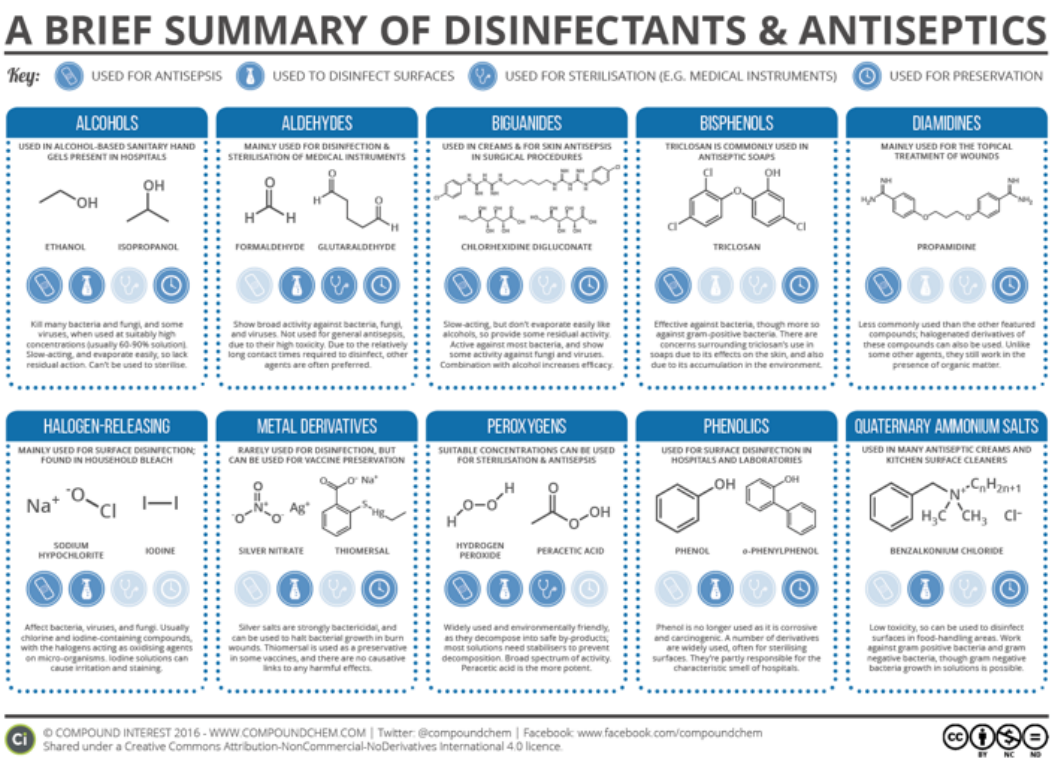
Chlorhexidine

	Characteristics
Main Usage	**Fast-Acting Antiseptic** (ex.: Preoperative preparation of skin & hand-wash)
Antimicrobial Spectrum	Most Pathogenic Viruses & Bacteria Low concentrations: Cell membrane leaks High Concentrations: Protein + Nucleic Acid Precipitation
Weakness	Bacterial spores
Miscellaneous	Preferred agent against central venous catheter infections Oral-rinse in gingivitis patients Very Safe!

September 19, 2019
William Archambault

Summary

*focus only on those discussed in class



Hand hygiene

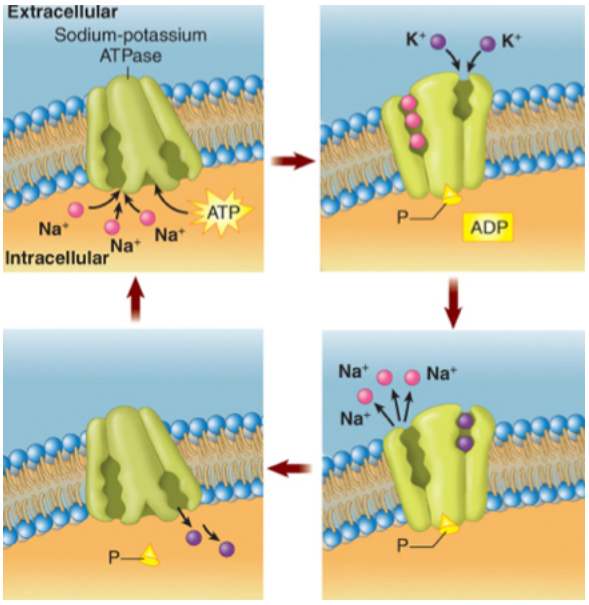
Specific CDC recommendations with highest evidence-based support (category 1A)

- Used antimicrobial soap + water when hands are visibly dirty
- Use alcohol-based hand rub when hands are not visibly dirty
- Decontaminate hands following body fluids or mucous membranes or wound dressing contact
- No artificial fingernails or extenders in ICU or OR
- Administration should provide healthcare workers with readily accessible alcohol-based products
- Alcohol-based products located at convenient locations (ex. Entrance of patients' rooms)

Antimicrobial Spectrum and Characteristics of Hand-Hygiene Antiseptic Agents

Group	Gram-Positive Bacteria	Gram-Negative Bacteria	Mycobacteria	Fungi	Viruses	Speed of Action	Comments
Alcohols	+++	+++	+++	+++	+++	Fast	Optimum concentration 60%–95%; no persistent activity; not lethal to bacterial spores, including those of *C. difficile*
Chlorhexidine (2% and 4% aqueous)	+++	++	+	+	+++	Intermediate	Persistent activity; rare allergic reactions
Iodine compounds	+++	+++	+++	++	+++	Intermediate	Causes skin burns; usually too irritating for hand hygiene
Iodophors	+++	+++	+	++	++	Intermediate	Less irritating than iodine; acceptance varies
Phenol derivatives	+++	+	+	+	+	Intermediate	Activity neutralized by nonionic surfactants

BODY FLUID & ION CONTENT AGENTS (Ch. 42)

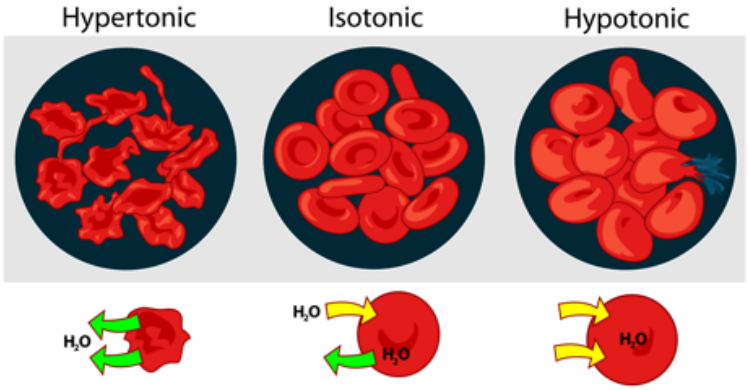


Patho Review - Active Transport

- Pump against concentration gradient
- Requires ATP
- Sodium-potassium pump
  - Generates electrical gradient
  - Essential for life!

Osmosis

- Depends on:
  - Hydrostatic pressure & solute concentration
  - Independent of size or weight
- Osmolarity = mOsm/L
- Tonicity = effective osmolarity/osmolality

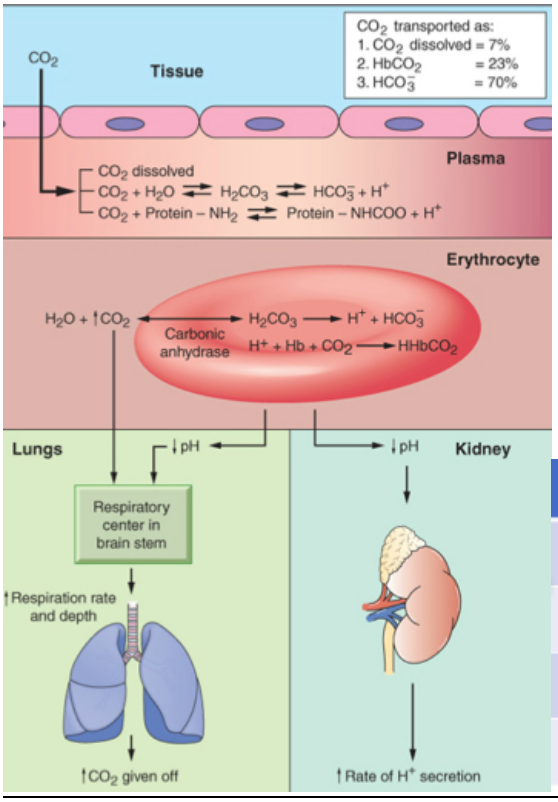


Fluid alterations

- Isotonic alterations
  - hypo/hypervolemia
- Hypertonic alterations
  - hypernatremia/dehydration
  - Leads to coma, fever, cognitive deficits
- Hypotonic alterations
  - hyponatremia/excessive water intake
  - Leads to coma, fever, cognitive deficits
- Many others… potassium, calcium, etc.

Acid-Base Regulation

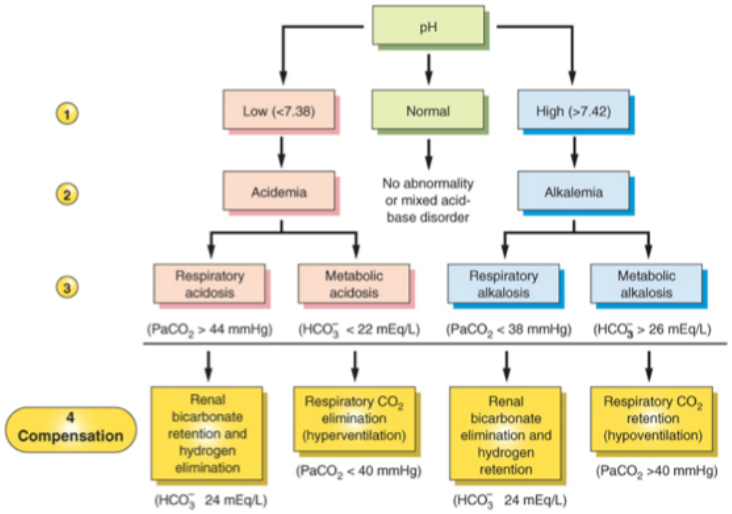
$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$



Fluid	pH
Gastric	1.0-3.0
Urine	5.0-6.0
Blood	7.35-7.45
CSF	7.28-7.32

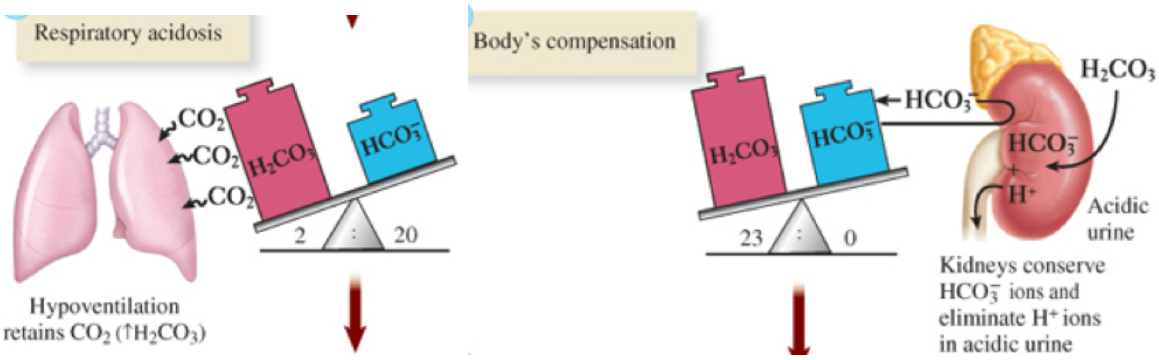
Acid-Base Disorders

To Understand you need: "H_20"+$CO_2 \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$ *& Le Chatelier'sPrinciple*



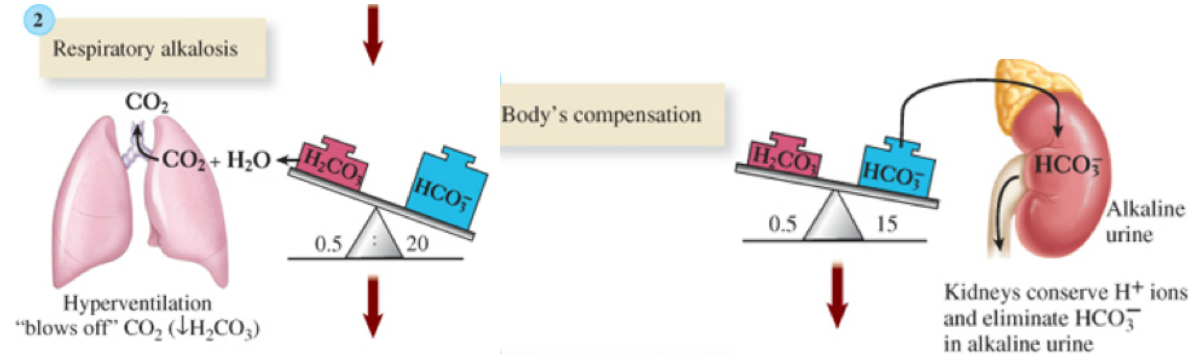
Respiratory Acidosis Scenario

Increase CO2 (ex. Hypoventilation) → increased H+ (acidosis!) → kidney compensation: increased bicarb retention & H+ excretion



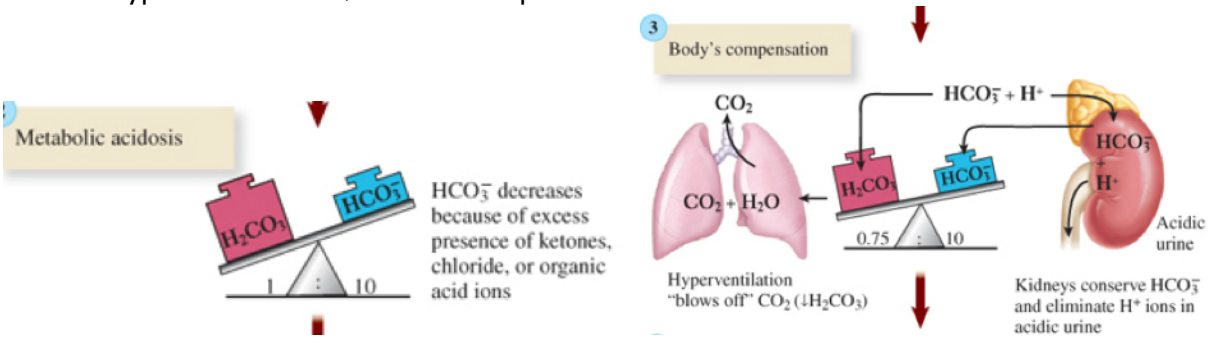
Respiratory Alkalosis Scenario

Decreased CO2 (ex: hyperventilation) → decreased H+ (alkalosis) → kidney compensation: increased bicarb excretion & H+ retention



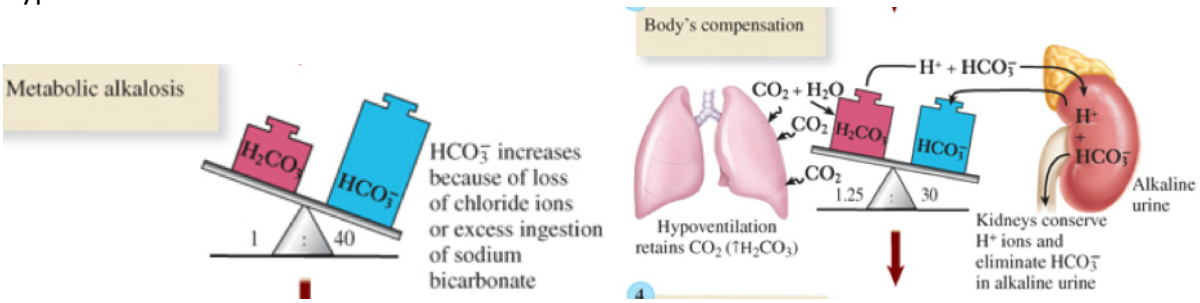
Metabolic Acidosis Scenario

Decreased bicarb (ex: renal failure) → increased H+ (acidosis) → lung compensation: decreased CO2 via hyperventilation → kussmal respirations



Metabolic Alkalosis Scenario

Increased bicarb (ex. vomiting) → decreased H+ (alkalosis) → lung compensation: hypoventilation to increase CO2



Acid-Base Disorders Summary

Disorder	pH	H^+	CO_2	HCO_3^-
Respiratory Acidosis	↓	↑	↑	↑
Respiratory Alkalosis	↑	↓	↓	↓
Metabolic Acidosis	↓	↑	↓	↓
Metabolic Alkalosis	↑	↓	↑	↑

Initial Event!!

BACK TO PHARM

Osmolarity Disorders

- Healthy [total plasma Osm] = 280-300 mEq/L
- Clinical setting:
  - Osmolarity in terms of [plasma Na+]
  - Healthy = 135-145 mEq/L ~ 50% TPO
- Isotonic contraction: equal loss of salt and water
  - Ex: hemorrhage
  - Slow administration - you need to give the body time to readapt and not overload it, because your body is actively adapting to the situation. You don't want to do the work for the body.
  - If administered rapidly, can cause pulmonary edema

- Volume expansion: when you have a water gain or a large sodium gain (significant enough to have a volume expansion)

Volume Expansion	H_2O Gain < or > or = Na^+ Gain
Causes	Therapeutic Fluid Overdose Heart Failure Liver Cirrhosis Ascites
Treatments	Diuretics Anti-Heart Failure Agents

Isotonic Contraction	Na^+ Loss = H_2O Loss
Causes	Cholera infection (Diarrhea; Vomiting) Diuretics ADR Kidney Disease
Treatments	Slow admin of Saline (0.9%) solution
Hypertonic Contraction	**Na^+ Loss < H_2O Loss**
Causes	↑↑↑ Sweating Burn Shock
Treatments	Hypotonic Saline (0.45%) solution Simply drinking tap water
Hypotonic Contraction	**Na^+ Loss > H_2O Loss**
Causes	↑↑↑ Kidney Na^+ Excretion Ex.: Low aldosterone Chronic Kidney Disease
Treatments	Hypertonic Saline (3%) solution until [Plasma Na^+] = 130 mEq/L Aldosterone replacement therapy

Acid-Base Alterations

- Treat only when compensation mechanisms FAIL/INSUFFICIENT

Respiratory Acidosis	↑ CO_2 → ↑ H^+
Causes	Hypoventilation Ex.: COPD; CNS (Medulla) Depression
Treatments	Treat Respiratory Impairment Severe : Sodium Bicarbonate infusion
Respiratory Alkalosis	**↓ CO_2 → ↓ H^+**
Causes	Hyperventilation Ex.: Hypoxia, Aspirin, Hysteria
Treatments	Mild: No need to treat Severe: Paper bag; sedative for hysteria

Metabolic Acidosis	↓ HCO_3^- → ↑ H^+
Causes	Renal failure; Severe diarrhea Ketoacidosis; Aspirin Poisoning
Treatments	Treat the cause Severe: Sodium Bicarbonate infusion
Metabolic Alkalosis	**↑ HCO_3^- → ↓ H^+**
Causes	Sodium Bicarbonate overdose Excessive vomiting
Treatments	NaCl + KCl infusions → ↓ HCO_3^- Severe: 0.1 N HCl infusion

Hyperkalemia

Healthy Concentrations	Regulation	Key Cellular Functions
• **Major Intracellular Ion** • Intracellular ≈ 150 mEq/L • Extracellular ≈ 4-5 mEq/L	• Insulin ↓ [Plasma K^+] (↑ Cell Uptake) • Alkalosis ↓ [Plasma K^+] • Acidosis ↑ [Plasma K^+] • Aldosterone & Diuretics ↑ Renal K^+ Excretion	1) Action Potential Conduction 2) Muscular Excitability 3) Acid-Base Regulation

Hyperkalemia = [Plasma K^+] > 5mEq/L	
Causes	Addison's Disease; Acidosis/Renal Failure; K^+-Sparring Diuretics or IV KCl Overdose
Symptoms	**Cardiac Electrical Dysfunctions → Dysrhythmias (see in 2 slides)** Mild: [Plasma K^+] ≈ 5-7mEq/L → Peak T-waves + Prolonged PR Interval Severe: [Plasma K^+] ≈ 8-9 mEq/L → Ventricular Tachycardia/Fibrillation & Arrest Non-Cardiac Sx: Confusion; Anxiety; Muscle Weakness/Tingling/Numbness
Treatment	1) Discontinue any potassium in food or drugs that ↑ [Plasma K^+] 2) Calcium Gluconate → Cancel Cardiac Effects of Potassium 3) Glucose or Insulin or Sodium Bicarb Infusions →↑ Cell Uptake of K^+ 4) If still insufficient: ***Sodium Polysterne Sulfonate (Kionex)*** → K^+ chelating agent

* In alkalosis, potassium moves into the cells, causing a reduction in extracellular K+

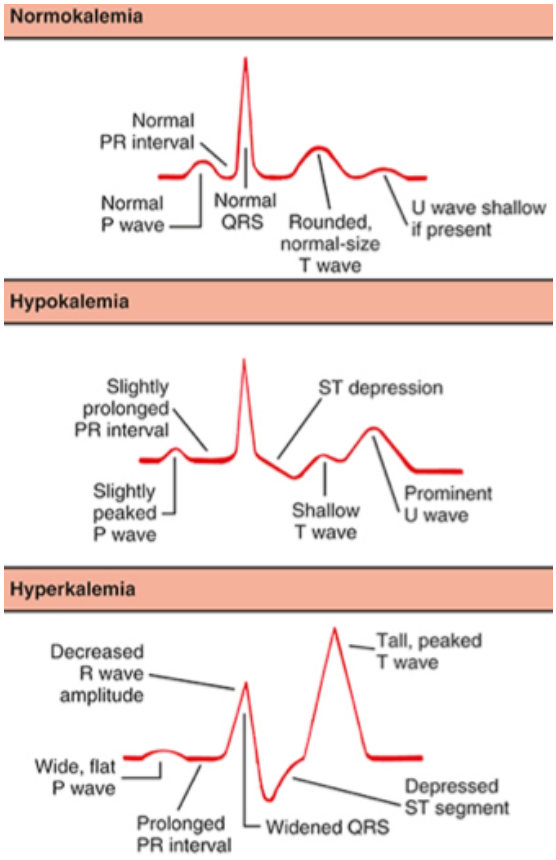
*In acidosis, potassium moves out of the cells, causing extracellular hyperkalemia.

Hypokalemia

Hypokalemia = [Plasma K^+] < 3.5 mEq/L	
Causes	Diuretics Therapy; Insulin poisoning; Alkalosis, etc.
Symptoms	↑ risk of HT, Strokes, fatal Dysrhythmias Muscle weakness & paralysis
Frequent Comorbidities	Loss of Cl^- → ***Hypokalemic Alkalosis***
Prevention & Treatment	***Potassium Chloride (preferred)*** or bicarbonate or phosphate
Oral KCl	Prevention (16-24 mEq/day) or Mild (40-100 mEq/day) Sustained-release = ↑ Patient Adherence (convenient + safer) **ADR**: GI Irritations (ex.: nausea; vomiting; diarrhea) **Rare ADRs**: GI Ulcers & Bleeding; Hyperkalemia
IV KCl	≤ 40 mEq/L solutions for Prevention (*PO* impossible) or Severe cases **ADR**: Hyperkalemia ***Nursing Tip***: monitoring of [Plasma K^+], renal functions & ECG for early toxicity ***SLOW Infusion ONLY** (< 10mEq/h) or else → Cardiac Arrest (ex.: lethal injections!!)**

Potassium Imbalances: ECG Alterations

- If you have less potassium, it takes longer for it to depolarize
- If you have too much potassium, the depolarization is overdone (high peak on the EKG)
    - The T wave heightens and the PR interval becomes prolonged



Magnesium Imbalances

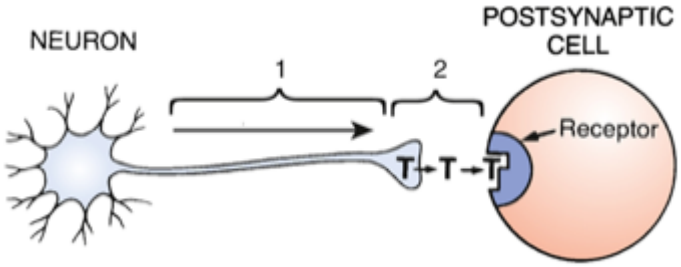
- Healthy Concentrations
  - Intracellular = 40 mEq/L
  - Extracellular = 2 mEq/L
- Key cellular functions
  - Enzymatic cofactor
  - Ribosome-mRNA binding
  - Long-term potentiation
  - Muscle excitability

Hypomagnesemia	
Causes	Diarrhea; Kidney Disease
Symptoms	↑ Muscle & Neural Excitation Ex.: Tetany; Psychoses; Seizures ↑ Kidney stones formation
Frequent Comorbidities	Hypocalcemia Hypokalemia
Prevention	Magnesium Oxide Supplements >800mg/daily → Diarrhea
Treatment	**Magnesium Sulfate (IM or IV)**
Adverse Effects	Hypermagnesemia Sx (Resp. & Cardiac) Calcium Antidote should be pre-prepared!!

Hypermagnesemia	
Causes	Renal Insufficiency
Symptoms	Muscle Weakness; Sedation; Hypotension Respiratory Arrest ≈ 12-15 mEq/L; Cardiac Arrest > 25 mEq/L
Treatment	**IV Calcium Gluconate Antidote**

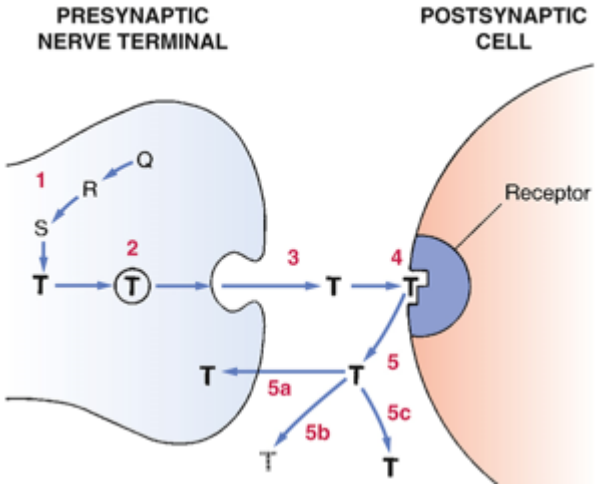
NeuroPharmacology (Ch. 12 & 20)

Neuropharmacologic Drug Action



2 main mechanisms that all drugs acting on the CNS/PNS share:

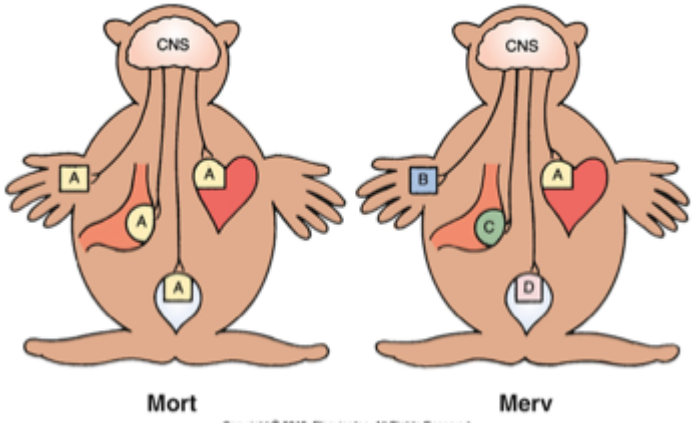
- They can either interact on the **axonal conduction (1)**: when the action potential is travelling from the cell body to the axon terminal.
- Or it can interact or interfere with the **synaptic transmission (2)** which is the process by which information is carried across the gap between the neuron and the post-synaptic cell
    - Most agents that we use today affect the synaptic transmission, either by increasing or decreasing the amount of NT, binding to the receptors of the NT…



There are several steps in which it can be altered:

1. Transmitter synthesis: altering or playing with that can either increase or decrease transmission. In the photo, steps Q,R, S produce transmitter (T)
2. Transmitter storage: putting the receptors in their little vesicles that then get released: can either increase or decrease transmission
3. Transmitter release: actual release of the vesicles with the NTs at the receptor on the other side of the synaptic cleft is triggered by the arrival of an action potential at the axon terminal

4. Receptor binding: transmitter molecules diffuse across the synaptic gap and then undergo reversible binding to receptors on the postsynaptic cell, initiating a cascade of events..
5. Termination of transmission by dissociation of transmitter from its receptors, followed by removal of free transmitter from the synaptic gap. Can be removed from the synaptic gap via different routes:
    a. 5a: Reuptake: axon terminal contains pumps that transport transmitter molecules back into the neuron from which they were released
    b. 5b: enzyme breakdown (happens following reuptake)
        i. NTs get broken down by enzymes or they get recycled… if you prevent 5a or 5b that means there are more NTs around increasing the effect.
    c. 5c: diffusion away from the synaptic gap
        i. Very slow and generally of little significance



This picture illustrates the fact that some of the receptors in the nervous system are more selective to certain types of NT. The picture is showing to contrast the scenario in which we only have one type of NT doing everything.

- Mort scenario: all the receptors are labelled as A, meaning all the receptors in our body are responding to a single NT. This means that whatever drug influenced your HR, would also affect your GI, bladder, skin, etc. This drug would have numerous amounts of adverse effects.
- Merv scenario: all the different targets have different receptors. If you give drug A, it should only affect the heart, etc.

In real life, we do not have either mort nor merv. We have certain NT that have more than one receptor. The more types of receptors we have to work with, the greater our chances of producing selective drugs.

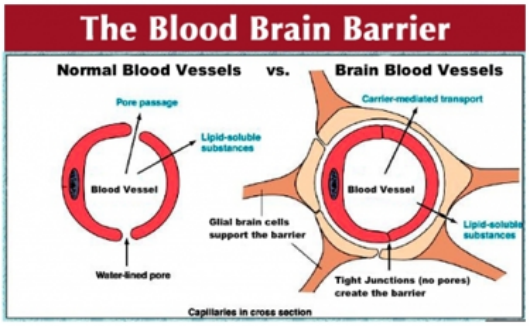
CNS Characteristics (Ch.20)

Drugs that we use that target the CNS usually target pain relief, seizure relief, anaesthesia, etc. But it is also the target for recreational drug use (stimulant/depressant; euphoria; hallucinations; etc).

Important to note, the effects on individual neurons: let's say I'm giving you a drug where its effects are to excite certain neurons, it shouldn't be translated as the overt functional effect (phenotype – what you're going to see), what we can see with our own eyes. It is possible that a drug has an excitatory effect on the neurons, but causes overt depression.

- Effects on individual neurons (ex: excitation/depression) DOES NOT EQUAL overt functional effects.

Ex: if you have neurons that act as a brake pedal, if the drug activates the brake pedal causing an excitatory effect on the neurons, but overt effect is that it will depress you.



- BBB separates the plasma from the brain with an extra protective layer to prevent harmful chemicals in reaching the CNS.
    - Protects against toxic substances: example a drug acting on the GI, you don't want it to also reach the brain and have some adverse effects. In this case, the BBB is good. Keep it in the blood, goes in other places.
    - Impairs therapeutic treatments: if you want it to reach the brain, the BBB would prevent that, your treatment would have a lower efficacy.
- Free lipid-soluble > ionized/protein-bound drugs
    - Most CNS drugs are lipid-soluble. They have an easy time crossing the BBB. They have a stronger effect on CNS.
    - Water soluble drugs don't go to the CNS, harder to treat or to cause adverse effects with them.
- Underdeveloped in infants.
    - BBB not matured yet, so vulnerable to CNS drugs.

Therapeutic Effects Disclaimer

- Limited CNS pathophysiology understanding → uncertainty of CNS agents action!
    - Mechanisms presented = plausible hypotheses/best educated guess
    - Almost always alters chemical synaptic transmission

    - This uncertainty is because of the high number of CNS transmitters (among other reasons). Their precise functional roles are unclear. The complexity of the brain clouds CNS drugs specific mechanism of action.
- High # of CNS transmitters
    - Unclear precise functional roles
    - Complexity clouds precise mechanism of action
- Affects psychotherapeutic R&D
    - Serendipitous findings - find something when we weren't looking for it
    - Poor animal models of psycho-pathologies
    - Small advances (ex: analog tweaking) vs. Major breakthrough (new molecules)
        - We try tweaking the drugs we already have rather than making new drugs from scratch.
    - Strong placebo component - either will enhance it or decrease the placebo effect
        - There is always a placebo effect in every drug, but with CNS drugs, the placebo effect is much higher.

<u>Chronic Exposure: CNS Adaptations</u>

Neuronal Plasticity!!

Because the brain is one of the organs that is very plastic (adjust/adapt), the effects of CNS drugs is much more likely to produce receptor up/downregulation, rebound effects, etc. The brain is particularly good at adjusting and creating a new state of homeostasis.

When a drug is taken chronically, their effects may differ from those produced during initial use. The brain's ability to adapt to drugs can produce alterations in therapeutic effects and side effects.

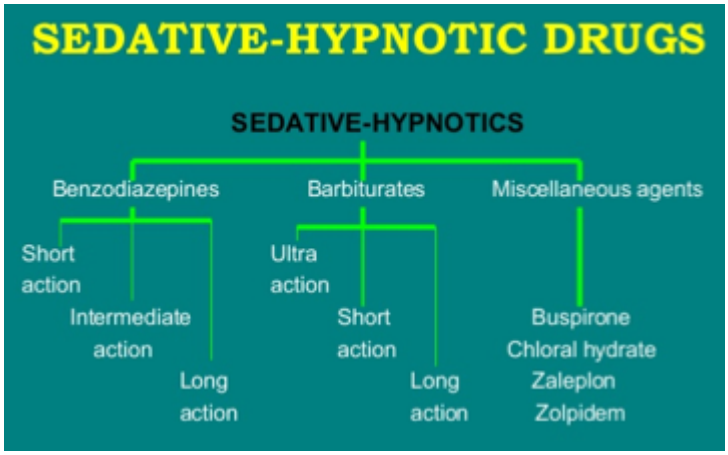
- Increased therapeutic effects (delayed onset)
    - Beneficial response from CNS adaptation rather than direct synaptic transmission alterations
        - Ex: antipsychotics & antidepressants
    - Some drugs have a delayed onset of the beneficial effects to appear, that's because it takes time for the brain to adjust to the presence of the drug. It is said that these beneficial effects are not coming directly from the drug itself, but from the brain readapting to the drug. The drug is there to create an incentive for the brain to do the work.
- Decreased adverse effects (habituation)
    - Phenobarbital sedation effect decreases over time while anti-seizure effects remain
    - Sometimes there are adverse effects when you start a medication, but once the brain has adjusted to its presence, the adverse effect will decrease over time.

- Tolerance & Dependence (review lecture 2)
    - Tolerance is a decreased response occurring of CNS adaptations
    - Physical dependence is a state in which abrupt discontinuation of drug use will precipitate a withdrawal syndrome. Withdrawal reactions continues until the adaptive changes have had time to revert, restoring the CNS to its pretreatment state.
    - Most drugs of abuse = CNS agents

SEDATIVE/HYPNOTIC DRUGS (Ch. 34)

Intro

- Family of CNS depressants - their main overt effect is to depress the brain
    - Hypnotics = promote sleep
    - Anxiolytics = decreases anxiety
- Most act on GABA receptors
    - Low dose → anti-anxiety
    - High dose → insomnia therapy
- Efficacy: benzodiazepine
- Safety: benzodiazepines >>> barbiturates
    - Both = "drugs of choice" for suicide → respiratory arrest
    - BZ: less tolerance and physical dependence, and less drug interactions >> barbiturates
    - Review table 34-1 for more details



Benzodiazepines (BZ)

Top 5 most prescribed benzos:

1. Alprazolam
2. Lorazepam

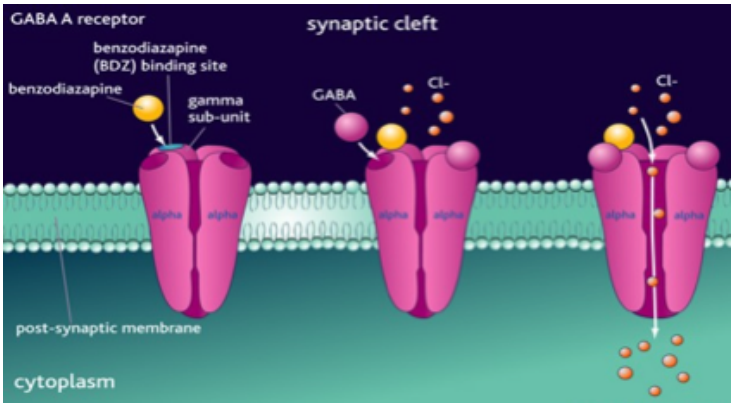
3. Clonazepam
4. Diazepam
5. Temazepam

Functions:

- Anxiolytic
- Antispasmodic
- Anticonvulsant
- Sedative-hypnotic
- Alcohol withdrawal management

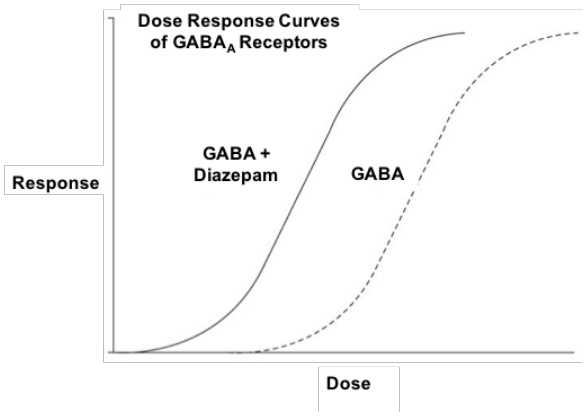
Mechanism of Action

Benzos bind to the GABA allosteric receptor. GABA is the brake pedal of the brain. Mainly inhibitory, depressing NT in the brain. On the picture below, GABA is the purple molecule and when it binds to its receptor (GABA receptor) it opens the receptor. GABA is a chloride ion receptor (ie. Chloride is negative ion). When the receptor opens, chloride goes into the neurons, hyperpolarizing it, making it more negative, making it more difficult to have an action potential in the neurons, thus decreasing the amount of activity in the neurons.
Benzos (yellow molecule in the picture), when it binds to GABA it binds to a different site, not competing with GABA. So when it binds to the receptor, the benzo increases the affinity of GABA for its own receptor.
*** benzos do not cause any action at GABA receptors by themselves. GABA binding is always required for channel opening. Benzos simply intensify the effects of GABA ***



The dotted curve is the normal dose-response of GABA alone.
When GABA combined with a Benzo, the curve shifts to the left, meaning that for the same amount of GABA in the body, you get a bigger response.

- This is a form of potentiation.



Kinetics & Usage

- Absorption: orally available
- Distribution: lipid-soluble → easy BBB crossing
- Metabolism:
    - CYP3A family hepatic enzymes → active metabolites
    - Parent drug half-life does not equal pharmacological effect half-life
    - Hepatic impairment → increased accumulation risk ++
        - Most metabolites are still active after liver metabolism.. It simply changes it into a different molecule. Therefore, you need to add up all the half lives of each molecule. Basically understand that it has a very long half life.

Nursing advice:

- Efficacy: there is not one better benzo than another. The choice of drug is based on the time course. If you want one for sleep, you'll choose one with a rapid onset, etc.
- Choice based on time course
    - Initiate sleep → rapid onset
    - Prolong sleep → slow-onset
    - Anxiety → intermediate
    - Repeated dosing → short half-life

Adverse effects/toxicity

- Common ADRs
    - Daytime drowsiness/decreased alertness
    - Anterograde amnesia → avoid triazolam
    - Sleep behaviors (ex. Sleep driving)
    - Paradoxical insomnia or anxiety
    - Respiratory depression → IV alone
    - Teratogenic → discontinue if pregnant or breast-feeding
- Tolerance

- Anxiety & hypnotic = low tolerance
- Antiseizure = high tolerance
- X-tolerance with other CNS depressants

- Dependence
  - Risk = very low
    - Have a high therapeutic index
  - Withdrawal Sx will resemble an anxiety disorder. You need to be weaned off
  - Alprazolam (xanax) > other BZ
- Serious Toxicity
  - BZ alone have a very low risk of toxicity
  - CNS depressant interaction (ex. Alcohol, opioids) → coma, respiratory arrest & death
  - 2% of IV admin (therapeutic doses!!) → severe hypotension; cardiac & respiratory arrest
  - Abrupt discontinuation of chronic use (especially short half life)

Barbiturates

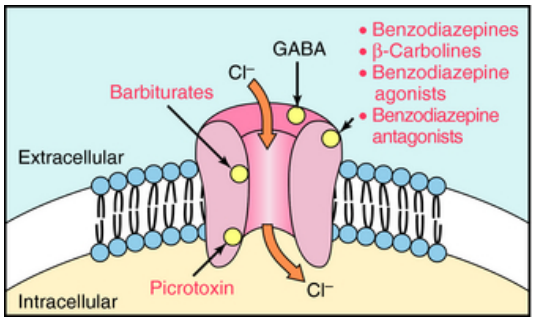
Used to be popular way back when. They are one of the oldest medications out there.

- 1864: founded by German chemist Adouf Von Baeyer
  - Used for anaesthesia at that time
- 1903: commercialized as veronal for its sedative and hypnotic effects
- 1911: phenobarbital synthesized and discovered to alleviate night seizures.

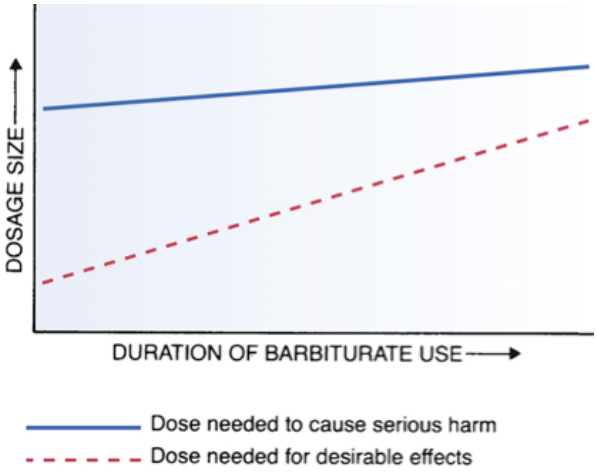
Mechanism & Effects

Barbiturates bind to the GABA receptor-chloride channel complex. By doing so, these drugs can enhance the inhibitory actions of GABA and directly mimic the actions of GABA. This is why it's much more dangerous than benzos. Because they directly mimic GABA, they have no ceiling

- Mostly used for:
  - ultra -short acting (ex: anesthesia)
  - Short to intermediate acting (ex: insomnia but rarely used anymore)
  - Long acting (ex: seizures)



- The blue line is the dose needed to get to the toxic effects
- Red dots are is the dose needed to get to the desirable effects of barbiturates.
- The graph shows that over time, the lines converge relatively quickly, becoming dangerous fast.



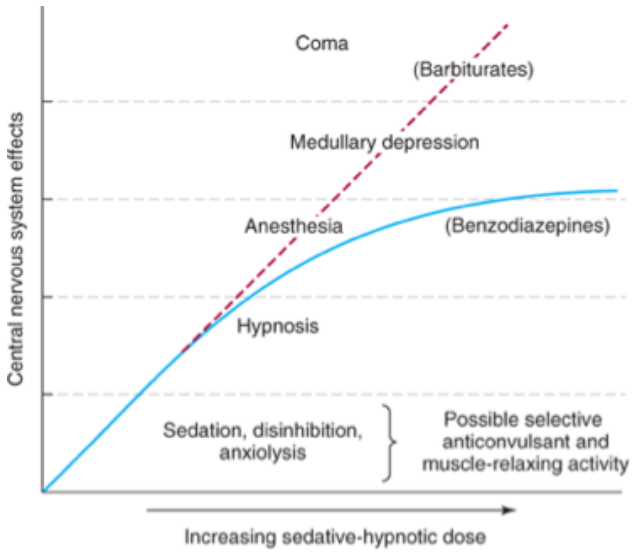
Effects:

- High risk of dependence & abuse
  - Cross-tolerance among barbiturates: this means that someone dependent on barbiturates can prevent withdrawal symptoms by taking any other CNS depressant.
- Powerful respiratory depressants → no tolerance develops against it
- Therapeutic tolerance > toxic tolerance
  - Tolerance develops to many - but not all - of their CNS effects. Specifically, tolerance develops to sedative and hypnotic effects and to other effects that underlie barbiturate abuse. However, even with chronic use, very little tolerance develops to toxic effects.
  - As tolerance builds, the doses need to be increased, causing the therapeutic dose to grow steadily closer to the lethal dose.

<u>Barbiturates vs. Benzodiazepines</u>

Nursing advices:

- Insomnia & anxiety: benzos >>> barbiturates
- Barbiturates usage: very rarely anymore



- Red line: the toxicity of the barbiturates increase almost proportionally
- Blue line: toxicity of the benzos tapers off (has a ceiling)

Benzodiazepine Receptor Agonists

	Zolpidem (Ambien)	Eszopiclone (Lunesta)
Usage Time	Short-Term	Unlimited (6-month safety study)
Therapeutic Usage	Sleep Induction & Maintenance	Sleep Induction & Maintenance
Other Infos	Peak [Plasma] ≈ 2 hours Half-Life ≈ 2.4 hours	Peak [Plasma] ≈ 1.5 hour Half-Life ≈ 6 hour Metabolism by CYP3A4

- These are drugs that are not benzo, and not barbiturates. They have a different chemistry. They bind only to alpha1-subunits of GABA receptors
    - Different GABA receptors have different subunits, and those subunits have different variations depending on genetics. Those with alpha-1 have hypnotic effects only. Because they are more selective for a specific unit, they have more selective effects.
- BRAs only have a hypnotic effect, without anxiolytic and anti-convulsive effects.
- ADRs/Toxicity Profile resembles BZ
    - Despite being more selective, the adverse effects are similar to those of benzos, same toxicity profile.

Nursing Capsule: Insomnia Management

- Insomnia = poor sleep quality → difficulty initiating/maintaining sleep
    - Common causes: disease; pain; anxiety
    - Common symptoms: daytime drowsiness; mood swings; concentration deficits
- Management

- Treat underlying cause if known medical condition
- 1st line treatment: non-drug therapies
  - lifestyle/sleep hygiene changes (ex. Decreased caffeine & nicotine; exercise; relaxation)
  - Cognitive behavioural therapy > drug therapy
- Hypnotic therapy → only if above methods failed
  - Discontinuation > dose escalation
  - Contraindication: pregnancy, respiratory diseases (COPD, sleep apnea)
  - Minimize dependency → lowest effective dose for shortest time period
  - Best choices = benzodiazepines (ex. flurazepam) & its agonists (ex. Zolpidem)

Nursing Capsule: Sedative-Hypnotic Administration

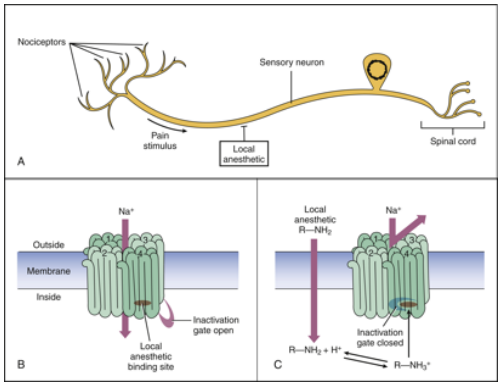
For insomnia treatment, all hypnotics should be taken shortly before bedtime.

- Benzodiazepines
  - Oral = preferred
  - IV = critical care & emergencies (ex. Alcohol withdrawal)
  - Avoid IM (except psychiatry)
  - Flumazenil = benzodiazepine antidote for sedation / Not for respiratory depression!
- Benzodiazepine agonists: all PO available

LOCAL ANESTHETICS (Ch. 26)

Mechanism of Action

The mechanism of action of local anesthetics are to block voltage-gated sodium channels which are found on the neuron's axon. By blocking the sodium channels, this prevents sodium from entering the cell, stopping the action potentials, and thereby blocking the conduction.



- Time course
  - Onset: membrane crossing properties (ex. polarity)
    - You want ideally a fast onset
  - Duration: crossing properties + regional blood flow
    - Duration is as needed depending on the procedure being done.
    - The more blood flow that goes to that region, the more quickly that drug can be "washed away" and metabolized by the liver more quickly =

shorter duration. Whereas, if the drug is in a region with low blood flow, the drug remains in the region longer, therefore being metabolized more slowly = longer duration.

- Combination with Epinephrine
    - Epi causes vasoconstriction of blood vessels. This causes the drug to remain in the region longer, decreasing its absorption, and therefore increasing its duration.
- Selectivity
    - Local anesthetics are nonselective modifiers of neuronal function. The only way to achieve selectivity is by delivering it to a limited area.
    - Blockade develops more rapidly in small unmyelinated neurons because those are usually the pain neurons. The larger myelinated neurons are typically the motor neurons, which can also be affected, it just takes longer for the effects to show.
    - Decreased pain > temperature > touch/pressure > motor

<u>Kinetics & Toxicity</u>

Pharmacokinetics

- Absorption: depends on blood flow at the site of administration
- Distribution: throughout systemic bloodstream
    - Concentration too low to have effects anywhere else than local site
- Metabolism: ester-types = in plasma vs. amide-types = hepatic enzymes
    - Metabolism of ester-types are metabolized in the plasma by plasma esterase, while amide-types are metabolized in the liver by hepatic enzymes
    - If absorption >> metabolism → toxicity increase
    - If metabolism >> absorption → decreased therapeutic success

Toxicity

- Distant effects > local effects
- CNS inhibition → coma; respiratory depression
- Heart inhibition → HR & SV decrease; cardiac arrest
- Vascular smooth muscle relaxation → hypotension
- Allergic reactions → esters > amides
- During delivery: increased labor + cross placenta
- Topical benzocaine in children → risk methemoglobinemia increase (a disorder in which Hb cannot release oxygen to its tissues)

History Capsule - Cocaine: the 1st local Anesthetic

- Excellent local anesthetic
  - Would block the sodium channels, just like the local anesthetic now (no pain)
  - Nowadays: we use lidocaine/procaine: cocaine that's modified to not give you a high and other adverse effects
- Substantial abuse potential
- CNS stimulant → risk of seizures
- CVS effects → increased HR & vasoconstriction

Esters vs. Amides

most are derivatives of cocaine with decreased CNS penetration

Procaine

- Injection only - ineffective topically
- Very low systemic toxicity
- Used to be 1st choice, replaced by amides due to **allergy risks**
- **Method of metabolism: plasma esterase**

Lidocaine

- Topical + injection
- Onset/duration/efficacy > procaine
  - Because it is metabolized by the liver, the duration is longer.
- **Allergy risk = 0**
- Systemic toxicity possible (ex. Liver failing)
- Useful for cardiac dysrhythmias - suppresses cardiac excitability
- **Method of metabolism: hepatic enzymes**

Clinical use of local Anesthetics

- Topical administration (lidocaine = preferred drug)
  - Relieve surface (ex. Burn, insect bites) or internal membrane (ex. Anal fissures) pain/irritations
  - Avoid large surface application + minimal effective dose = decreased systemic toxicity
  - EMLA patches → pediatric patients 1h prior to injections (ex. vaccines)
- Injection administration (choice of drug depends on duration and method)
  - Performed by a specialized HCP (ex. Anesthesiologist, dentist, NP)
  - Serious toxicity when IV injection → resuscitation equipment readily available
  - NEVER epinephrine combination at extremities (ex. Toes, nose, penis) → increases gangrene risk +++

- Contraindications
    - Use of any ester agents in patient with ester allergic reaction history
    - Topical benzocaine in children < 2 years old

GENERAL ANESTHETICS (Ch. 27)

Inhalation anesthetics

Goal: loss of all senses and consciousness

General anesthesia Discovery

1846 by William Morton

- Using Ether was applied on a piece of cloth and placed it on people's mouths

Before that….

- Strong men and straps holding you down
- Best butcher: fastest one = decreased bleeding = increased survival chance
- Allowed for: development of modern surgical procedure + increased patient safety & surgical success
- Surgeons can now take their time to operate

Basic Principles

Ideal properties

- Analgesia
- Unconsciousness
- Muscle relaxant
- Amnesia
- Large margin of safety
- Pleasant induction & emergence
- Efficient depth of anesthesia manipulations

Balanced anesthesia

- Combination of agents decreases effective dose → increased safety
- Most common agents and their best property
    - Induction → Propofol or short-acting barbiturates
    - Analgesia → opioids or nitrous oxide (NO)
    - Muscle relaxation → neuromuscular blockers

Hypothesized mechanism of action

- Old theory:
    - neuronal membrane dissolution → decreased transmission

    - Dismissed: same dissolution potential meant no anesthesia
    - Lipid-soluble would dissolve in cell membrane and disrupt action potential
- New theory
    - Increased inhibitory transmission + decreased excitatory
    - All potentiate GABA / except NO (NMDA inhibition) → blocking excitation and promoting inhibition
    - All depress, potentiate GABA, block excitation and promote inhibition.

<u>Pharmacokinetics & MAC</u>

Kinetic Properties

- Lung uptake proportional to
    - Inspired air concentration
    - Blood solubility & supply to lungs
- Distribution proportional to
    - Organ cardiac output (regional blood flow)
    - Ex: brain, liver, heart, kidney
- Export in expired breath
    - Same factors as uptake & distribution
    - Ex: decreased brain levels > skin & muscles
    - Hepatic metabolism = 0
    - No impact on time course of action

MAC = Minimum Alveolar Concentration

- Is the minimum concentration of drug in the alveolar air that will produce immobility in 50% of patients exposed to a painful stimulus.
- Potency index: small MAC = high anesthetic power
- Determines inspire air concentration for each agent
- Dose administered = 1.2-1.5x the MAC
- MAC influenced by external factors
    - Factors that decrease MAC (increase potency) - all some form of CNS depressant
        - Acute alcohol use
        - Advanced age
        - Anemia
        - Benzo
        - IV anesthetics
        - Hypotension
        - Hypothermia
        - Opiates

- Factors that increase MAC - CNS stimulants
  - Cocaine
  - Amphetamines

Major Inhalation Anesthetics

Nitrous Oxide

- Very low potency but very high analgesia
- Adjunct to primary anesthetic → decreases required dose
  - MAC is 105% and cannot work alone because it is impossible to give more than 100% (percentage is relative to atmospheric pressure). This means that there isn't enough pressure on the planet to induce anesthesia with this gas.
  - It is combined with other inhalational agents to enhance analgesia.
- Very safe for CNS, heart & respiration
- ADRs = postoperative nausea + vomiting

Isoflurane

- Very high potency (low MAC)
- Excellent depth of anesthesia management
- Elimination via expired breath = 100%
- ADRs = hypotension & respiratory depression
- Poor analgesic… needs to be combined

Serious ADRs of volatile anesthetics

- Respiratory & cardiac depression (almost all)
- Ventilation support almost mandatory
- Malignant hyperthermia (all except NO)
  - Muscle rigidity & severe increase in temperature
  - Risk factors: family history & when combined with succinylcholine

Nursing Capsule: Administration & Adjuncts

- Dosage & administration
  - Anesthesiologist (physician) & anesthetists (trained nurse) ONLY
  - LOTS of drugs combined + low therapeutic index = medical specialty
- Adjuncts → complement therapeutic effects or decrease adverse effects
  - Preanesthetics
    - Benzo (ex. IV midazolam) → decrease surgery anxiety & increased amnesia
    - Opioids (ex. fentanyl) → preoperative pain & cough suppression

- Alpha2-adrenergic agonists (ex. clonidine) → decreased anesthetic dose required + decreased anxiety
- Anticholinergic agents (ex. atropine) → decrease risk of anesthesia-induced bradycardia
- Neuromuscular blockers (ex. succinylcholine) → prevent muscle twitches & resistance
  - Flaccid paralysis state → risk of waking up with no way of letting the surgeon know!

- Post -anesthetics
  - Analgesics decrease post-op pain (ex. opioids)
  - Antiemetics decrease nausea & vomiting (ex. ondansetron)
  - Muscarinic agonists (decrease abdominal distension & urinary retention (ex. bethanechol)

IV anesthetics

Adjunct therapy or effects that cannot be achieved by volatile anesthetics

Propofol

- Actions & usage
  - Most popular (90% of anesthetic patients)
  - Increase GABA release → CNS depression
  - Uses: anesthesia induction & maintenance
  - Fast induction but short duration → low dose infusion
- Adverse Effects
  - VERY narrow therapeutic range!!!
  - Profound respiratory depression + hypotension
  - Lipid-soluble formulation → increased bacterial infection
  - Propofol infusion syndrome (rare): occurs if prolonged high dose infusion
    - Metabolic acidosis + Renal failure + cardiac failure + rhabdomyolysis
    - Monitor creatine PhosphoKinase (>5000/L = STOP)
- Nursing reality: propofol abuse
  - Not regulated substance → accessible
  - HCPs use it for quick naps
  - Activates brain reward center
  - Wake-up refreshed + elated
  - Overdose risk = very high

Benzodiazepines & Ketamine

- Diazepam
  - Large doses = unconsciousness + amnesia
  - Induction use; fairly safe
- Midazolam
  - Midazolam + opioid = conscious sedation
  - High risk of cardiorespiratory arrest
- Ketamine
  - NMDA blocker → dissociative anesthesia (when you see yourself from an out of body point of view)
  - Adverse psychological effects
    - Hallucination & delirium (=12% pts)
  - Controlled substance → drug abuse
  - Therapeutic usage
    - Minor surgeries/diagnostic procedures
    - In burn victims it is used to increase their cardiac output
  - Ketamine usage has increased due to the opioid crisis

OPIOIDS: CNS ANALGESICS (Ch. 28)

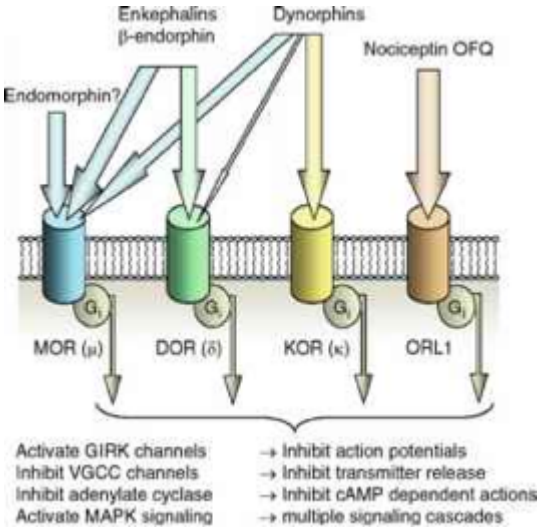
Opioids & Receptors

- Opioids are made from the opioid juices of the poppy plant
- They are classed based on their analgesic power, some are stronger than others.
  - Loperamide has no analgesic power, so they are not classified here
  - Strong analgesia: morphine and fentanyl
  - Moderate analgesia: codeine and hydrocodone
- The site of action are the different opioid receptors found in the brain, spinal cord and the GI. that is why the opioids cause constipation as a side effect.
- The receptor we are most interested in is the Mu receptor
  - Receptor that does everything (see picture below)
  - Especially responsible for the analgesia effect

Important Responses to Activation of Mu and Kappa Receptors

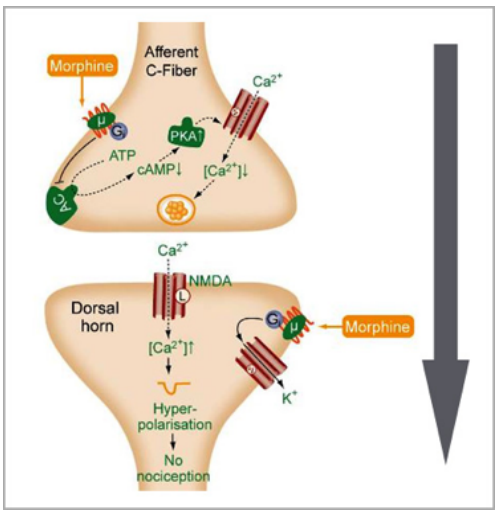
Response	Receptor Type	
	Mu	Kappa
Analgesia	✓	✓
Respiratory depression	✓	
Sedation	✓	✓
Euphoria	✓	
Physical dependence	✓	
Decreased GI motility	✓	✓

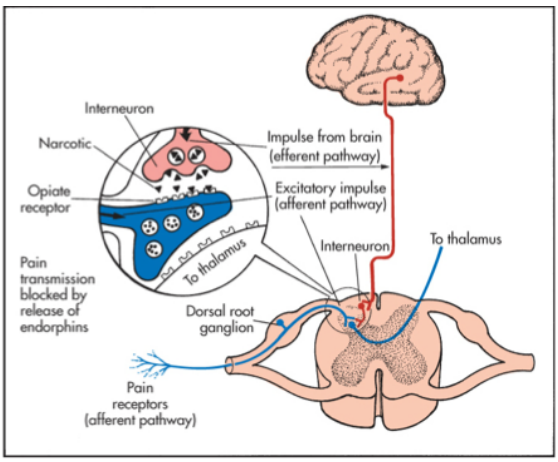
- Endogenous opioid peptides
    - We have a lot of endogenous opioid peptides which means they are peptides (proteins) similar to opioids. These are molecules released when you have pleasurable experiences or when you exercise.
    - They are called endorphins and enkephalons that are released by the brain. They also bind to the Mu receptors.



<u>Opioid Analgesic Action</u>

- Pain Modulation pathway → moderate to strong analgesia
    - They decrease the intensity of the pain signal, they don't block the pain signal at the site of the injury but rather in the spinal cord before it reaches the brain.
- No loss of consciousness & no other sense impairment
- One of the effects that opioids have that other analgesics don't have is that on top of modulating the pain response, they also change our interpretation of pain.
- Pain is a subjective measure for every individual.





Pathway:

- On the neuron, the morphine will bind to the Mu receptor on the presynaptic neuron and on the post synaptic neuron.
- On the presynaptic neuron, the binding of morphine will block the release of calcium into the presynaptic neuron (which in turn prevents the release of the vesicles on the post-synaptic). The end result is that you have barely any NT that are released towards the post-synaptic.
- At the same time, morphine binding to the post-synaptic neuron causes the opening of potassium channels, hyperpolarizing the cell, making it harder to stimulate (can't get an action potential).

<u>Other Opioid Effects</u>

- Respiratory depression
  - Most serious adverse effect
  - Tolerance develops long-term
  - Interaction with CNS depressants
  - Assess breathing frequency prior to giving the medication
  - Threshold = < 12breaths/min
  - Indirect ADR → increased intracranial pressure
- Constipation
  - Decreased gut mobility & fluid secretions
  - Management: exercises + fiber diet
  - Severe: laxatives + stool softener
  - Therapeutic effects:
    - Severe diarrhea therapy (1st usage)

        - Opioids that don't cross the BBB
        - Ex: loperamide
- Euphoria
    - Increased pain relief + risks of abuse
- Neurotoxicity
    - Decreased risk via opioid rotation
- Teratogen
    - Before conception + early pregnancy
- Sedation
    - Problematic for 'outpatients'
- Cough suppression
    - Risk of airway secretion accumulation
    - Therapeutic effect
        - Moderate agonists
        - Ex: codeine or hydrocodone

<u>Tolerance & dependence</u>

- Tolerance
    - Analgesia, euphoria, sedation and resp depression
    - cross -tolerance (and dependence!) between opioids
- No tolerance
    - Miosis (pupil constriction) & constipation
    - No cross-tolerance with CNS depressants (additive effect)
    - Cross-tolerance between opioid agonists
- **Environmental/Behavioral tolerance**
    - Environmental/behavioral tolerance: not only do you develop tolerance to a drug, but it seems that people who take drugs always consume them in the same location. For example, if someone usually takes a high dose of a drug in their home, but now they take the same dose but somewhere different, this can cause a shift in tolerance, leading to resp depression. It is believed that being in a different location causes a subconscious stress, making you more reactive to that same dose.
- Dependence/Withdrawal Syndrome
    - Intensity depends on half-life
    - Short (ex. morphine) = intense but brief
    - Long (methadone) = mild but prolonged
        - this is why it is used when someone is in withdrawal, it helps to cushion

- Withdrawal syndrome
    - Onset: ~ 10 hours after the last dose
    - About 7-10 days long
    - Symptoms: muscle spasms, GI distress, irritability
    - Almost only long-term users (>1month)
    - Extremely unpleasant but not lethal like CNS depressants
    - Gradual discontinuation decreases syndrome intensity (decrease the dose every 3 days)

Nursing Reality: Opioid Abuse

- People are hooked by the euphoria/sedation effect of it
- The use of opioids is maintained by the fear of withdrawal

Clinical Concerns

- Opioid under treatment by HCP = 75%
- Irrational fear of dependence/addiction
- Very rare in clinical setting
- Drug associated to painful experience
- Mostly acute treatment (< 3 weeks)
- Few cases = abuse-prone individuals
- Give benefit of the doubt to the patient!

<u>Strong Agonists: Morphine</u>

- Reference strong opioid agonist
- Extensive 1st pass effect → PO dosage compared to IV/IM/SubQ
    - It has a lot of 1st pass effect, that is why it is often given IV, IM or SC.
    - Still given orally, but in higher dosage
- Poor BBB crossing → increased toxicity in infants (immature BBB)
    - Even though it has poor BBB crossing, there is enough that gets across in infants, increasing the risk of toxicity.
- Therapeutic Usage: chronic severe pain
    - Subcut: most common on floors
    - Oral = administer every 4h
    - IM = only CR slow injection over 4-5 minutes
    - Epidural = long duration (about 24h) for spinal analgesia

Heroin:

- Heroin is morphine but more lipid-soluble (can cross the BBB).
- Has no therapeutic usage today, because it is too potent and highly addictive

Question: what is the origin of the names Morphine & Heroin?

- Morphine comes from the greek god's name Morphus which is the god of dreams
- Heroin comes from the soldiers that were given heroin to not feel fear and be less sensitive to pain in war, they were referred to as heroes.

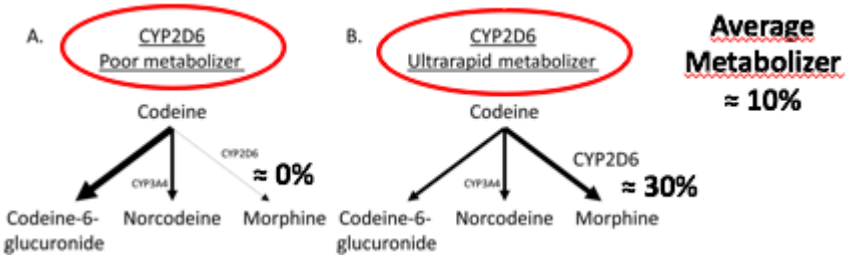
<u>Fentanyl</u>

- It's 100x more potent than morphine.
- Carfentanyl is 100x more potent than fentanyl.
- Metabolized by CYP3A4
- High risk of toxicity (ex: resp depression)
- Therapeutic usage:
    - IM or IV: surgical anesthesia induction/maintenance
    - Skin patch: persistent/severe pain in opioid tolerant patients
    - Transmucosal (ex: lollipop lozenge): Cancer breakthrough pain in very tolerant patients already on opioids around-the-clock

<u>Other Strong Opioid Agonists</u>

- HYDRO/OXYmorphone
    - Replaced morphine for most pain management
    - Among the most prescribed in clinical settings
- Meperidine
    - Not used very much anymore (safety issues)
    - Specific uses: post-anesthesia shivering
- Methadone
    - CYP3A4 metabolism
    - Longer duration than morphine
    - Used for opioid addiction therapy
        - Because of its longer half-life, it is safer and easier to control. Withdrawal symptoms are milder
    - Decreased withdrawal symptoms + suppressive therapy

Moderate Opioid Agonists



- Codeine is the most famous.
- Less pain relief but less chance for resp depression (as compared to morphine)
- Codeine: is sort of a pro-drug. In order to be active, it needs to be transformed into morphine. It's a weaker analgesic because not all the codeine is being transformed into morphine (only a percentage of the same response).
- Codeine is metabolized by CYP2D6, and there are people who are ultra-rapid metabolizers, meaning they metabolize more of the codeine into morphine. So they would need a smaller dose of codeine.
- While others have poor metabolizing CYP2D6 which means that the codeine they ingest, is metabolized into anything else but morphine because the CYP2D6 doesn't work.
    - The only way to find out is via trial and error.

Therapeutic usage of

- Codeine:
    - Alone or combined with NSAIDs for moderate analgesia
    - Excellent cough suppression
- Hydro & Oxycodone
    - Similar to codeine for analgesia
    - All available for PO
    - Oxy:
        - alone or combined
        - long acting controlled-release formulation available
        - CYP3A4 metabolism
    - Hydro:
        - Most prescribed drug in the US
        - Always combined to NSAIDs or antihistamines

Nursing capsule: Clinical Considerations of Opioids

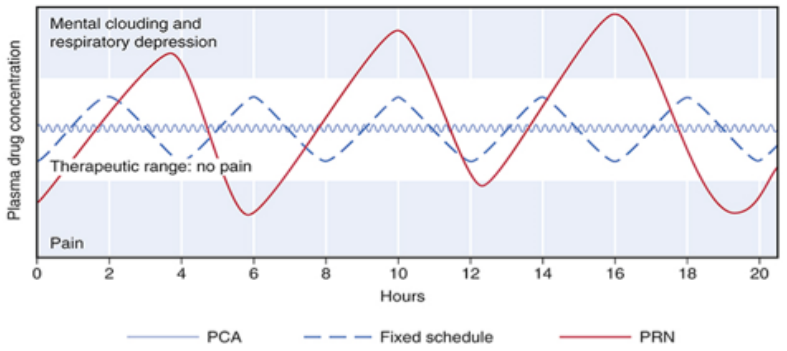
- High risk patients
    - Respiratory impairments: asthma, COPD
    - Head injuries → increases ICP

- Pregnant women → teratogen + baby dependence
- Infants & elderly → increases resp depression (dosage must be < adult dose)

- Pre-administration baseline
  - Respiratory rate, pulse & BP → withhold Rx if any decrease below baseline
  - Pain assessment → very subjective experience → risks of over-reporting & under-reporting
- Minimize abuse (real but small risk)
  - Smallest effective dose + switch to non-opioid analgesics ASAP
  - If abuse suspected: opioid/naltrexone tablets → antagonist works only if crushed or injected
    - When the naltrexone tabled is combine, it doesn't work PO. but when crushed or injected, it prevents the effects of the opioids from occurring.
- Minimize withdrawal reactions
  - Increased risk if high doses > 20 days → taper dosage over 3-10 days → decrease intensity of withdrawal symptoms.

<u>Administration Guidelines</u>

- Dosage determination
  - Open chest surgery > appendectomy
  - Adults > infants or elderly
  - Opioid tolerant > opioid naive
- Dosing schedule
  - Fixed 4 hour schedule = preferred
  - Decreases pain fluctuations & anticipatory anxiety
  - Subcutaneous on floors vs. IV in ICU
- Patient-controlled Analgesia (PCA)
  - Patient self-administration → device "lock-out timer" prevents overdose
  - Small doses at frequent intervals → decreases fluctuations → increased pain relief + decreased adverse effects
  - PCA associated with decreased hospital stay + increased physical therapy cooperation vs. fixed-schedule
  - Patient & family education = crucial for proper usage & success of PCA



Opioid Usage for Specific Pains

- Post-op
  - Decreased pain + increased movement autonomy & intentional cough
- Obstetric analgesia
  - drawback : fetal respiratory depression & decreased uterine contractions
  - Favor fentanyl and newer derivatives → short action + decreased feral impairments
- Myocardial infarcts
  - Decreased pain & BP = decreased cardiovascular demand = better cardiac recovery
- Head injuries
  - Very cautious due to increased ICP risks + hiding useful diagnosis signs (ex. Miosis, vomiting)
- Cancer-related pain (usually chronic)
  - Objective = maximize pain relief
  - Increased risks of dependence & tolerance = secondary concerns
- Chronic non-cancer pains
  - Balance 'patient rights vs. HCP concerns'
  - Try alternative pain relief first / monitor Rx & adherence more closely

Naloxone & Opioid Overdose

- Opioid Overdose Classic triad
  - Coma → profound/no arousal
  - Pinpoint pupils (miosis) → may dilate later with hypoxia
  - Respiratory depression → 2-4 breaths/min
- Opioid overdose treatment
  - Ventilatory support + Naloxone injection
- Opioid Antagonists: Naloxone
  - Given IV, IM or SubQ (not PO because of rapid 1st pass inactivation)
  - Reverses most effects of opioid agonists
  - A pt can be put in a state of acute withdrawal when naloxone is administered
  - Has a short-half-life → ~ 2 hours
    - might need to give repeated doses until pt gets to ER safely to be monitored
  - Other therapeutic uses: neonatal & post-op respiratory depression

N.B. Naloxone is an antagonist that has one of the highest affinities to the opioid receptors.

PNS physiology (Ch. 13)

PNS review

- Spinal and cranial nerves = PNS
    - Plexus = bundle of nerves innervating dermatome/common region
- Anterior root = motor fibers
- Posterior spinal ganglion = sensory cell bodies
- Mixed nerves = motor and sensory

Learning About PNS Pharmacology

What to learn for each PNS drug:

1. Receptors onto which it binds
2. Normal physiologic function of those receptors
3. Drug effect on receptor activity (increase or decrease)

Unlike the CNS, where most of the drugs for CNS we lack knowledge. For the PNS, the functioning is much more clear. A lot of the drugs we will talk about focus on the Autonomic NS.

*** Get familiar with the receptors, what drugs bind to them and their activity ***

3 main ANS regulatory functions

1. Cardiac muscle: rate and strength of contractions
2. Secretory glands: sweat, saliva, GI fluids
3. Smooth muscle regulation: Bronchi, blood vessels, GIT

Parasympathetic

- Nickname: rest and digest
- Main goal: energy optimization (homeostasis)
- 7 pharmacologically relevant functions
    - Decreases HR
    - Near vision eye focus
    - Increase gastric secretions
    - Pupil constriction
    - Bowel emptying
    - Bladder emptying
    - Bronchial airway diameter regulation

Sympathetic

- Nickname: fight or flight
- Main goal: respond to stress/threats
- 3 pharmacologically relevant functions
    - Cardiovascular regulation:

        - Brain blood supply maintenance
        - Blood flow redistribution during exercise
        - Blood loss compensation
    - Temperature regulation
        - Skin blood flow regulation
        - Skin hair erection
        - Sweat gland secretion
    - Acute stress response
        - Increased HR and BP
        - Blood flow redistribution to muscles
        - Bronchi dilation
        - Pupil dilation
        - Increased energy catabolism

ANS Regulation

Parasympathetic vs. sympathetic regulation

1. Opposite effects (majority)
2. Complementary effects (ex. Male reproduction)
3. Only one system involved (ex. Blood vessels)

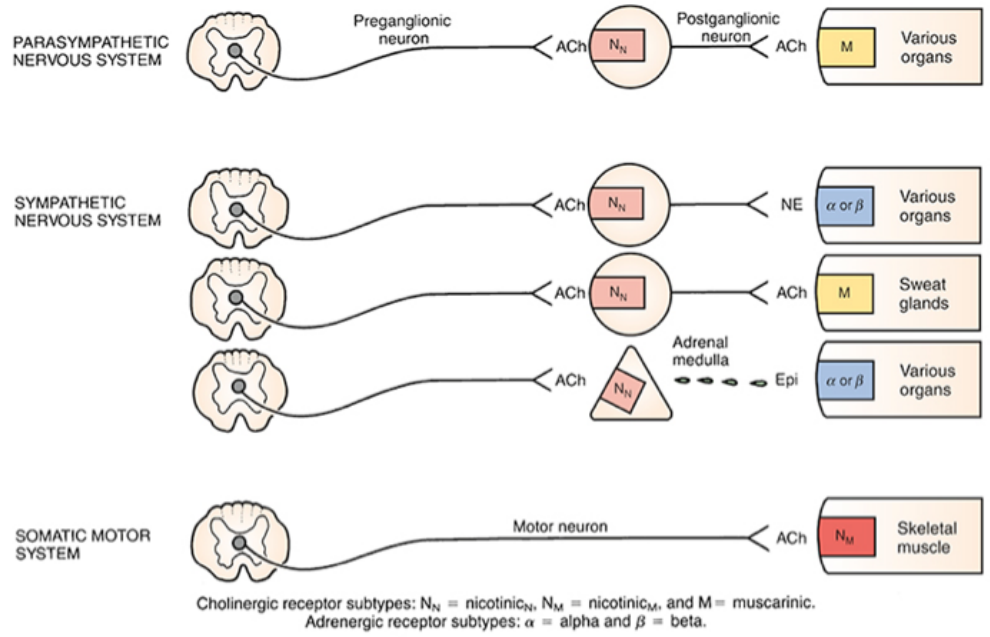
Important to keep in mind, its neither just the parasympathetic or just the sympathetic. They are in form of opposition with their function. It's not that when one is on, the other is off. It's more which one is more on/present.

You're often at rest, that's why we say the **parasympathetic system is the predominant autonomic tone**, the default state. Sympathetic is the emergency state, when you don't need it anymore, parasympathetic becomes dominant again.

At most organs, they act in opposite ways. There's some situations (rare) where they will be complimentary (ie. male reproductive system/reproduction – parasympathetic responsible for penile erection and sympathetic is responsible for ejaculation).

Feedback regulatory loop: the baroreceptor reflex regulates BP. Neurons are connected to the aorta and carotid artery. Receptors are triggered by the distention of your arteries, the signals are sent to the brain. For example, if your BP is too high (distension of the vessels), the brain will get these signals, and send them back to an effector to attempt to decrease the BP. The effectors are often smooth muscles at the blood vessels – dilate or constrict.

ANS Transmission Pathways



Cholinergic receptors are receptors onto which acetylcholine binds to.

- 3 subtypes of cholinergic receptors: nicotinic(n), nicotinic(m), and muscarinic

Adrenergic receptors (alpha/beta receptors) where epinephrine and norepinephrie bind to.

- 4 major subtypes of adrenergic receptors: alpha 1&2, beta 1&2.
- Dopamine receptor - responds only to DA NT, not NE.

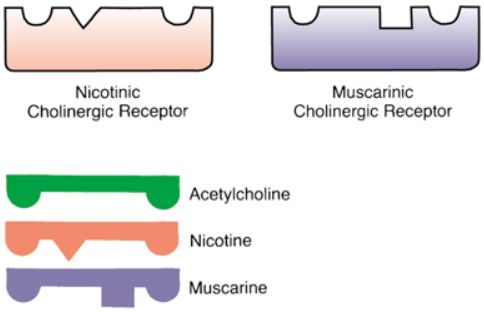
Yellow: muscarinic receptors – from the cholinergic system – received information from the parasympathetic system

- the transmission of information leave the medulla and spinal cord to a preganglionic neuron onto a second neuron, the postganglionic neuron which releases ach onto muscarinic receptors.

Blue: adrenergic receptors – sympathetic system

- the information leaves the spinal cord via the first preganglionic neuron onto a post-ganglionic neuron which releases E or NE onto adrenergic receptors.
- there's one exception for the sympathetic system, where ach is released onto muscarinic receptor. This happens at the sweat glands for temperature regulation.

Receptor Subtypes

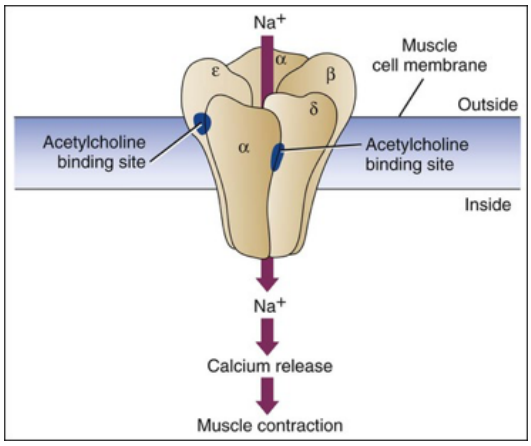


- Ach binds to both nicotinic and muscarinic receptors
- Nicotine binds only to the nicotinic receptor (each receptor has different shapes) and vice versa for muscarine
- Physiologically irrelevant: ach can bind to both receptors. The body cannot tell the difference. But from the perspective of different drugs, they are different (pharmacologically important)

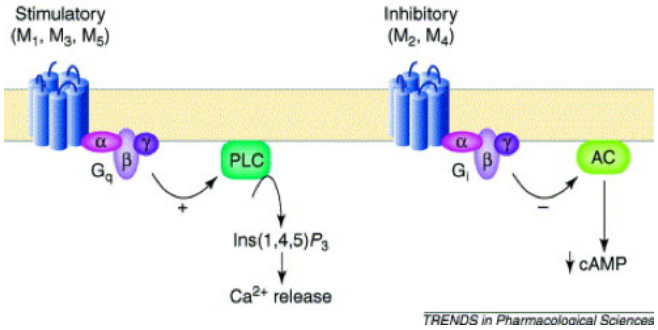
Receptor Specificity of Adrenergic Transmitters[a]

Transmitter	$Alpha_1$	$Alpha_2$	$Beta_1$	$Beta_2$	Dopamine
Epinephrine	←			→	
Norepinephrine	←		→		
Dopamine	↔		↔		↔

Nicotinic vs. Muscarinic Receptors



- Above is a ligand-gated sodium channel that 5 subunits to form a pore where sodium ions can float through.
- Subunit variations → receptor subtypes action potential transmission



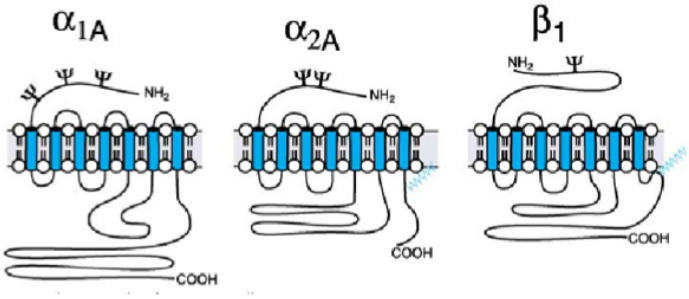
- Muscarinic receptor is from the G-protein coupled receptor type. It has 7 transmembrane domain that activates the G-protein.
- G-protein variations → receptor subtypes
- Smooth muscle contraction and relaxation regulation

Cholinergic Receptor Functions

Functions of Peripheral Cholinergic Receptor Subtypes

Receptor Subtype	Location	Response to Receptor Activation
Nicotinic$_N$	All autonomic nervous system ganglia and the adrenal medulla	Stimulation of parasympathetic and sympathetic postganglionic nerves and release of epinephrine from the adrenal medulla
Nicotinic$_M$	Neuromuscular junction	Contraction of skeletal muscle
Muscarinic	All parasympathetic target organs:	
	Eye	Contraction of the ciliary muscle focuses the lens for near vision Contraction of the iris sphincter muscle causes miosis (decreased pupil diameter)
	Heart	Decreased rate
	Lung	Constriction of bronchi Promotion of secretions
	Bladder	Contraction of detrusor increases bladder pressure Relaxation of trigone and sphincter allows urine to leave the bladder Coordinated contraction of detrusor and relaxation of trigone and sphincter causes voiding of the bladder
	GI tract	Salivation Increased gastric secretions Increased intestinal tone and motility Defecation
	Sweat glands[a]	Generalized sweating
	Sex organs	Erection
	Blood vessels[b]	Vasodilation

Adrenergic Receptors



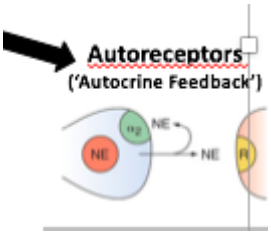
Alpha 1A	Alpha 2A	Beta1
Alpha 1B	Alpha 2B	Beta2
Alpha 1D	Alpha 2C	Beta3

*Know Alpha 1 & 2 / Beta 1 & 2

Adrenergic Receptor Functions

Functions of Peripheral Adrenergic Receptor Subtypes

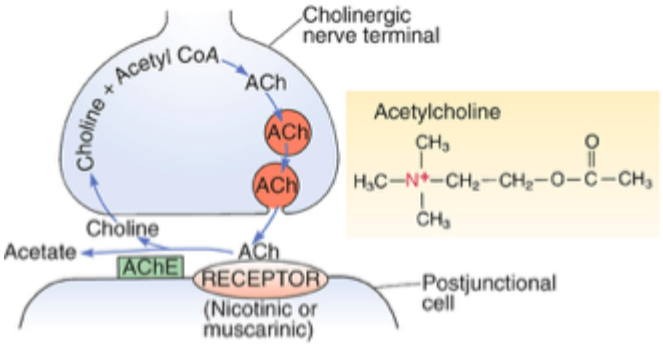
Receptor Subtype	Location	Response to Receptor Activation
Alpha$_1$	Eye	Contraction of the radial muscle of the iris causes mydriasis (increased pupil size)
	Arterioles Skin Viscera Mucous membranes	Constriction
	Veins	Constriction
	Sex organs, male	Ejaculation
	Prostatic capsule	Contraction
	Bladder	Contraction of trigone and sphincter
Alpha$_2$	Presynaptic nerve terminals	Inhibition of transmitter release
Beta$_1$	Heart	Increased rate
		Increased force of contraction
		Increased AV conduction velocity
	Kidney	Release of renin
Beta$_2$	Arterioles Heart Lung Skeletal muscle	Dilation
	Bronchi	Dilation
	Uterus	Relaxation
	Liver	Glycogenolysis
	Skeletal muscle	Enhanced contraction, glycogenolysis
Dopamine	Kidney	Dilation of kidney vasculature



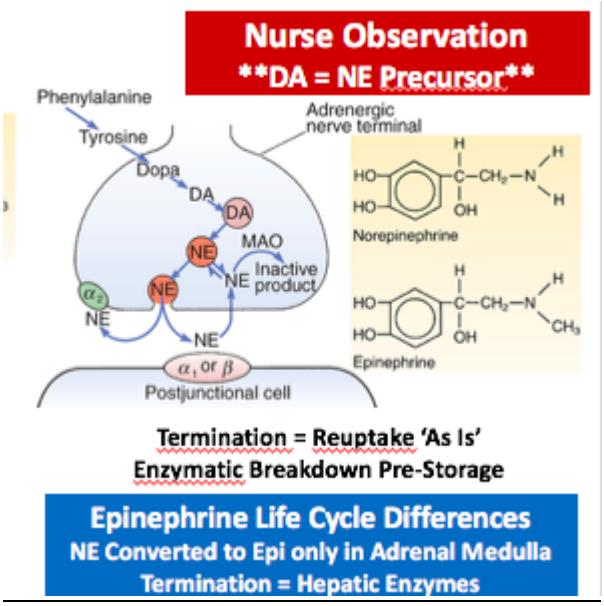
- All related to sympathetic system: bladder relaxation (retention), pupil dilation, increased HR, heart/lung/vessel dilation

- Autoreceptors: alpha 2 receptor's main role is to act as a feedback receptor, neuron releases NE onto another neuron. The neuron that released the NE has its own alpha 2 receptors, so that the NE can bind to and activate the same neuron that released it. It serves as a confirmation that the NE was in fact released. Acting to suppress further NE release when enough has already accumulated in the junction.
- Dopamine: dilation of kidney vasculature → enhance renal perfusion

Transmitter life cycles



Cholinergic life cycle – where neurons that release ach combine choline with acetylCoA forming ach. It then gets packaged into small vesicles and can then be released in the synaptic cleft, in response to action potential. Ach can then bind to the nicotinic or muscarinic receptor on the postsynaptic neuron. Ach can is then broken down by enzyme Ach-esterase into its two divided components: acetate and choline. Choline is then reabsorbed into the cholinergic nerve to be reused in the presynaptic nerve.
The termination of the cycle – enzymatic breakdown + partial reuptake & diffusion.



Adrenergic life cyle – where the NE is synthesized after a series of metabolic steps that begins with phenylalanine, which gets transformed to Dopamine. DA is a precursor of NE. DA is the NT that gets packaged into the vessel and within the vessel it gets transformed into NE. Then NE is released onto the postsynaptic cell (alpha1 or beta1 receptors) and on the autoreceptor (alpha 2 receptor). NE gets reabsorbed as is, and get either repackaged or it will be broken down in house by MAO enzyme. The breakdown happens pre-storage.

At the adrenal glands, epinephrine is released (it is more water soluble so it can be sent more as a hormone than a NT). For NE to be converted into E happens only in the adrenal glands.

Cholinergic Drugs (Ch. 14-15-16)

Intro to Cholinergic Agents

Cholinergic Drugs and Their Receptors

	Receptor Subtype		
	Muscarinic	**Nicotinic$_N$**	**Nicotinic$_M$**
Receptor Location	Sweat glands Blood vessels All organs regulated by the parasympathetic nervous system	All ganglia of the autonomic nervous system	Neuromuscular junctions (NMJs)
Effects of Receptor Activation	Many, including: ↓ Heart rate ↑ Gland secretion Smooth muscle contraction	Promotes ganglionic transmission	Skeletal muscle contraction
Receptor Agonists	Bethanechol	Nicotine	Nicotine*
Receptor Antagonists	Atropine	Mecamylamine	*d*-Tubocurarine, succinylcholine
Indirect-Acting Cholinomimetics	Cholinesterase inhibitors: Physostigmine, neostigmine, and other cholinesterase inhibitors can activate *all* cholinergic receptors (by causing accumulation of acetylcholine at cholinergic junctions)		

*The doses of nicotine needed to activate nicotinic$_M$ receptors of the NMJs are much higher than the doses needed to activate nicotinic$_N$ receptors in autonomic ganglia.

Categories of Cholinergic Drugs

Category	Representative Drugs
Muscarinic agonists	Bethanechol
Muscarinic antagonists	Atropine
Ganglionic stimulating agents	Nicotine
Ganglionic blocking agents	Mecamylamine
Neuromuscular blocking agents	*d*-Tubocurarine, succinylcholine
Cholinesterase inhibitors	Neostigmine, physostigmine

Muscarinic Antagonists: Atropine

- Atropine blocks the activation of Ach. Competitive antagonism of Muscarinic receptors
- Atropine Dose-response relationship: depending on the dosage, the affinity for muscarinic receptors will change. It doesn't bind to all muscarinic receptors equally. When you give atropine in lower dosage, it will have effects on the salivary glands and sweat glands first. As you keep increasing the dosage, it will act on the bronchial glands, heart and eyes, etc.
- The dosage to treat gastric ulcers and asthma is too high, can easily lead to toxicity, so we don't use them for these purposes.
- Therapeutic Uses:
    - Administration = topical or parenteral
    - Pre-anesthesia prophylaxis
    - Prevent decreased HR and increased airway mucus secretions
    - Decreased eye movements for ocular exams and surgery
    - Bradycardia & GI hypermotility therapy
    - Muscarinic agonist poisoning antidote
- Adverse effects/contraindications (similar to sympathetic stimulation):
    - Similar to excessive sympathetic stimulation
    - Ex: urinary retention, tachycardia, dry mouth
    - Photophobia and blurred vision (paralysis of the ciliary muscle and the sphincter of the iris)
    - Interactions with antihistamines & TCAs
    - **inappropriate for geriatric patients (because cardiac risk too high)**

Overactive Bladder (OAB) Treatment

- 1st line treatment = behavioral therapy - Scheduled voiding, Kegel exercises
    - Monitor fluids & avoiding caffeine
    - Initiate medication only if BT fails
- Drug therapy

- Table 14-5 → best strategy = target M3 subtype
- These drugs are the preferred drugs for OAB because they avoid CNS & heart adverse effects

- M3-selective muscarinic antagonists for OAB
  - Oxybutynin / darifenach /tolterodine→ block muscarinic receptors on the bladder detrusor and thereby inhibit bladder contractions and the urge to void
  - Not one is clearly superior
  - Only slightly better than placebo
  - If one fails, another could succeed → PK differences

<u>Reversible Cholinesterase Inhibitors</u>

- Anticholinesterase prototype: Neostigmine
  - Slows down break-down activity of cholinesterase (indirect way of increasing the amount of Ach in the synaptic cleft = boost in effect of Ach)
    - Neostigmine and cholinesterase become bound, remains this way for a really long time. Cholinesterase only becomes free when it has completely degraded neostigmine, meaning there is less enzyme available to breakdown Ach, therefore increasing amount of Ach available for cholinergic receptor activation.
  - No receptor selectivity
  - Similar profile to muscarinic agonists
  - It is a Quaternary Ammonium: when you have a nitrogen atom that is bound to 4 different things. It has a positive charge, not lipid-soluble. So it has poor BBB permeability and therefore only acts in the periphery.
  - **Muscarinic effects** = muscarinic agonists (ex: bradycardia, miosis, increased secretions, urinary urgency, bronchial constriction, increased tone and motility of GI)
  - **Neuromuscular effects**: therapeutic doses increase contraction force vs. toxic dose decrease force (nb. Ach is released at the neuromuscular junction. So at higher doses of neostigmine, it may start to have an effect here, where signals for muscle contractions may increase, keeping it in a state of constant depolarization).
  - **CNS effects**: depressive action → only at very high/toxic doses since difficulty crossing BBB.
  - Adverse effects/toxicity
    - Excessive muscarinic actions & respiratory muscle paralysis → reverse with atropine antidote
    - Drug interactions: increased effects of succinylcholine
  - Atropine may be used as an antidote because their actions are contradictory

<u>Irreversible Cholinesterase Inhibitors</u>

- Organophosphates Pharmacologic Effects & toxicity
  - Same as reversible but increased duration
  - Highly lipid-soluble → very toxic!!
  - Only medical application is glaucoma because of its high risk for toxicity

- Organophosphate poisoning risk: agriculture workers/warfare/suicides
- Cholinergic crisis: excessive muscarinic actions & neuromuscular blockade
- Sx mnemonics; DUMBBELS
  - Diarrhea
  - Urination
  - Miosis
  - Bradycardia
  - Bronchospasms
  - Emesis
  - Lacrimation
  - Salivation
- Treatment (antidote): atropine & pralidoxime (direct antagonist)

Myasthenia Gravis Treatment

- Autoimmune disorder where the immune system attacks nicotinic(m) receptors on skeletal muscle.
- Symptoms of disease: ptosis (drooping of eyelids), difficulty swallowing, and weakness of skeletal muscles. Difficulty breathing is caused by weakness of the respiratory muscles.
- Main therapeutic usage of anticholinesterase drugs
- Drugs of choice: neostigmine & pyridostigmine → symptomatic relief only (increasing muscle strength)
- Dosage management:
  - Administration → PO preferred if capable of swallowing
  - Individualized dosage via symptoms monitoring
- Side effects management
  - Atropine admin against unwanted muscarinic activation
  - But not routinely!!! → risks of masking early signs of cholinergic crisis (ex. Excessive salivation)
- Myasthenia crisis vs. Cholinergic crisis
  - Similar Sx → muscle weakness & respiratory muscle paralysis
  - Different Tx → neostigmine vs. atropine
  - Differential diagnosis → medication monitoring & muscarinic involvement (cholinergic crisis only)

Competitive Neuromuscular Blocker

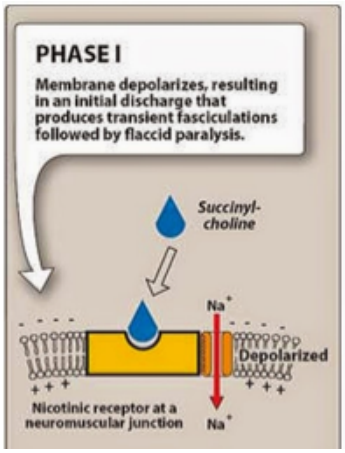
- Rocuronium
- Roc is a quaternary ammonium, so poor BBB crossing (water-soluble) and poor GI absorption. Has a similar shape as Ach so it can bind to the nicotinic receptor, preventing the binding of Ach which prevents voluntary muscle contraction.
- It is a derivative of Curare.
- Pharmacologic effects and toxicity

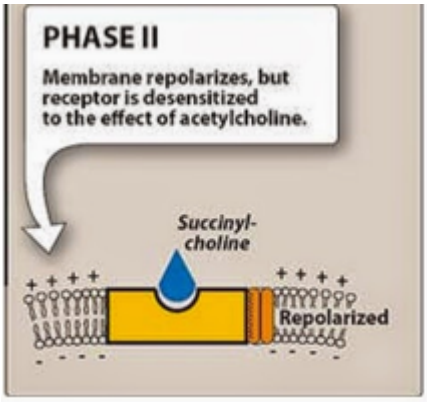
- Gradual muscle relaxation
- First effects are smaller muscles such as eyelid, mouth, then moves onto the limbs, and thankfully respiration is last.
- Can cause hypotension due to mast cell degranulation releasing histamine, promoting massive vasodilation
- No loss of pain or consciousness (cannot cross BBB)

- Contraindications
  - Myasthenia gravis & electrolyte imbalances
- Interactions
  - Increase response: antibiotics or inhalational anesthetics
  - Decrease response: anticholinesterase

<u>Depolarizing Neuromuscular Blocker</u>

- Succinylcholine
- Pharmacologic effects & toxicity
  - Same as competitive blockers EXCEPT: transient contractions, ultra short duration (4-10min)
  - Instead of just blocking the receptor, it binds to the receptor, but then remains there and maintaining it in a constant state of depolarization. So what you get is a transient contraction (small contractions), then paralysis.
  - No CNS action





- Eliminated by plasma cholinesterase: this enzyme lives in the plasma, so whenever Succ circulates in the bloodstream, it gets broken down as it travels through = short duration
- Specific toxicity
  - Post-op muscle pain
  - Malignant hyperthermia

- Contraindications
  - Low plasma cholinesterase activity → increased risk of prolonged apnea
  - Major burns/multiple trauma → increased risk of hyperkalemia
- Interactions
  - Increases response: antibiotics or anticholinesterases (competitive)

Neuromuscular Blockers: Therapeutic Uses

- General anesthesia adjunct
  - Benefits = facilitates surgeon's work & decreases anesthesia dosage
  - Remember → NO CNS action → imagine paralysis with PAIN & CONSCIOUSNESS
  - **Rocuronium** = long duration → **preferred agent**
- Mechanical ventilation adjunct
  - Benefits = decreased resistance to ventilation
  - Treat patient as if he/she is awake → pain & hearing functions are working!!!
  - Usage contraindicated in long-term mechanical ventilation (ex. ICU)
- Endotracheal intubation
  - Benefits = decreased gag reflex to ease intubation of trachea
  - **Succinylcholine** = short duration → **preferred agent**
- Electroconvulsive therapy → treatment of depression
  - Benefits = inhibit harmful muscular convulsions
  - **Succinylcholine** = short duration → **preferred agent**

Adrenergic Drugs (Ch. 17-18-19)

Adrenergic Agonists Overview

- Oral availability & duration
  - Depends on metabolism by MAO & COMT (these enzymes quickly destroy catecholamines, which is why they cannot be PO)
  - Catecholamine >> Non-catecholamine
- BBB crossing
  - Depends on metabolism by MAO & COMT
  - Catecholamine = very polar
  - Noncatecholamine = less polar

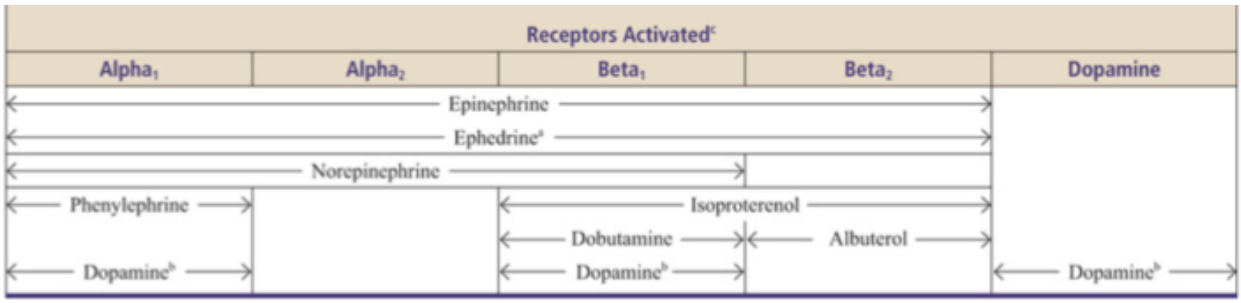
	Catecholamine	Noncatecholamine
Oral Availability	No	Yes
Duration of Action	Short	Long
BBB X-ing	Very Low	> Cathecholamine

Adrenergic Receptor Activation

Mechanisms of Adrenergic Receptor Activation

Mechanism of Stimulation	Examples
DIRECT MECHANISM	
Receptor activation through direct binding	Dopamine Epinephrine Isoproterenol Ephedrine[a]
INDIRECT MECHANISMS	
Promotion of NE release	Amphetamine Ephedrine[a]
Inhibition of NE reuptake	Cocaine Tricyclic antidepressants
Inhibition of MAO	MAO inhibitors

- Sympathomimetic drugs
  - Effects = sympathetic system stimulation
  - Ex: bronchodilation; increase CO, increased blood glucose

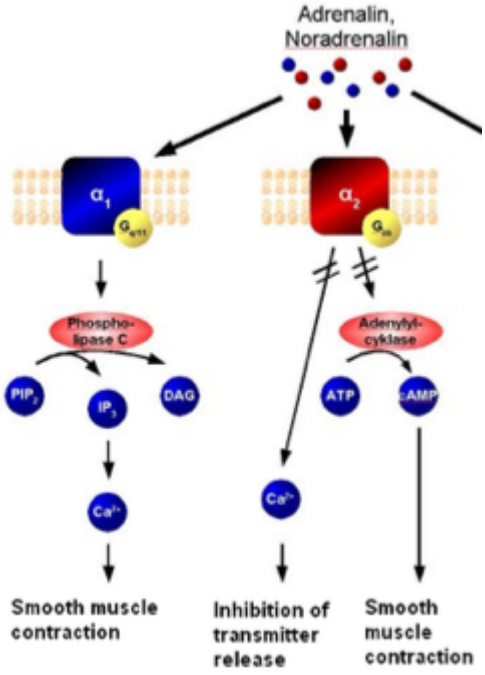


Alpha-Adrenergic Actions

Alpha-1

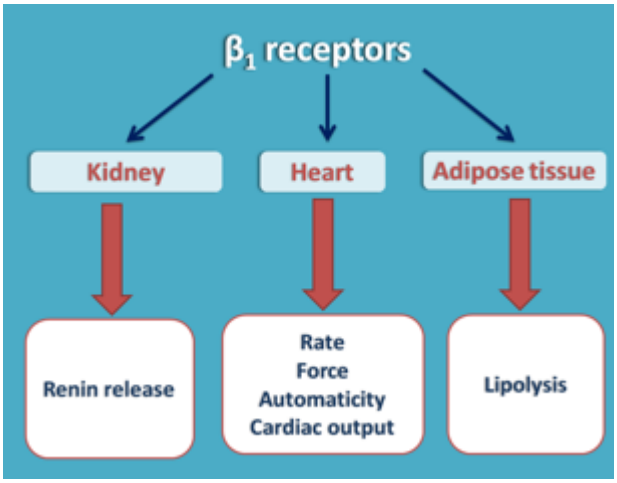
- Effects
  - Vasoconstriction
  - Mydriasis (pupil dilation)
- Therapeutic usage: uncommon
  - Hemostasis
  - Nasal decongestion
  - Adjunct to local anesthesia
  - Hypotension
  - Mydriasis for eye exam & surgery
- Adverse effects
  - Hypertension (IV administration increases risk)
  - Extravasation tissue necrosis (hypoxia)
  - Bradycardia (baroreceptor reflex trigger)

Alpha-2

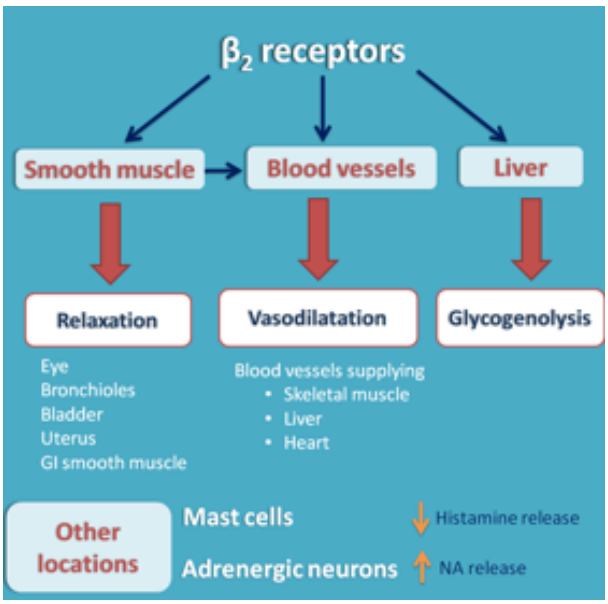


- Effects
  - Presynaptic autoreceptors (if there is activation of the autoreceptor, it inhibits further release of the NT)
  - Inhibit transmitter release
- Therapeutic usage
  - PNS alpha-2 = no therapeutic application
  - CNS alpha-2 → see indirect alpha blockers
    - Severe hypertension
    - Pain relief
- Adverse effects:
  - PNS = no significant ADR
  - CNS = rebound hypertension & CNS depression

<u>Beta-Adrenergic Actions</u>



- Therapeutic usage = mostly heart
  - Heart failure
  - Shock
  - Short-term AV block therapy
  - Cardiac arrest (last resort)
- Adverse effects:
  - Tachycardia → dysrhythmias
  - Angina pectoris (atherosclerotic patients)



- Therapeutic usage = lungs & uterus
  - Asthma (selective beta-2 agonists)
  - Delay preterm labor
- Adverse effects
  - Hyperglycemia (diabetic patients)
  - Transient muscle tremor

Dopamine receptors are only found on the kidney. Promotes renal vasodilation. Only used for shock treatment

Adrenergic Agonists Summary

Drug	Epinephrine	Dopamine
Chemistry Kinetics	Catecholamine → Topical/IM/IV Administration & Short $T_{1/2}$	
Receptor Affinity	α1 / α2 / β1 / β2	DA Moderate Dose → β1 Very High Dose → α1
Therapeutic Usage	Prolong Local Anaesthesia (α1) Topical Hemostasis (α1) ↑ BP (α1) AV Block Therapy & Cardiac Arrest/Shocks (β1) Anaphylactic Shock (α1 + β1+ β2)	Shock (DA & β1)
Adverse Effects	Hypertensive Crisis & Extravasation Necrosis (α1) Dysrhythmias & Angina Pectoris (β1) Diabetic Patients Hyperglycemia (β2)	β1-Related High Doses: α1-Related
Drug Interactions	MAO Inhibitors → ↑ $T_{1/2}$ Tricyclic Antidepressants → ↑ Effects Inhalational Anaesthetics → ↑ Dysrhythmias Adrenergic Blockers → ↓ Effects	Idem Epi Diuretics → ↑ Benefits

Drug	Isoproterenol	Albuterol
Chemistry Kinetics	Catecholamine Topical/IM/IV Administration & Short $T_{1/2}$	Noncatecholamine Inhalation & Longer $T_{1/2}$
Receptor Affinity	β1 / β2	β2-selective High Dose → β1
Therapeutic Usage	AV Block Therapy (β1) Cardiac Arrest/Shocks (β1)	Asthma (β2)
Adverse Effects	Idem Epinephrine Except no α1-Related	Minimal at Therapeutic Doses Tremor & Tachycardia at High Doses
Drug Interactions	Idem Epi	Adrenergic Blockers

<u>Anaphylactic Shock Treatment</u>

Life threatening emergency allergic reaction

- Common causes = food allergy, bee stings, penicillins

Pathophysiologic manifestations → severe decreased tissue perfusion

- Widespread vasodilation → hypotension
- Bronchoconstriction → airway obstruction
- Edema of glottis → airway obstruction

Treatment

- Epinephrine (Epipen) IM or IV
- Activation of beta1 → Increased CO → increased BP
- Activation of beta2 → bronchodilation → decreased airway obstruction
- Activation of alpha1 → vasoconstriction → increased BP + decreased glottis edema
- ***antihistamines = insufficient** many more mediators involved

Prevention

- At risk individuals should always carry Epipen with them
- Hospitalization recommended after Epipen administration

<u>Therapeutic Beta-Blockers (Ch.18)</u>

- Propranolol - 1st generation
- Metoprolol - 2nd generation
- Cardioselective > Nonselective
- 3rd Gen vasodilating → unclear benefits over 2nd Gen

Prototypes Beta-Blockers

Propranolol: nonselective beta 1 & 2 blocker

- Highly lipid-soluble → widespread distribution
- Hepatic metabolism + renal excretion
- Therapeutic usage & Adverse effects (see previously)
- Specific toxicity/contraindications:
    - Very rare CNS toxicity (ex. Insomnia; depression)
    - Placental barrier crossing → neonate toxicity
    - Inhibits Epipen → avoid in allergic patients
    - Calcium channels blockers interaction → increase effects
- Dosage considerations:
    - Therapeutic dose depends on sympathetic activity
    - MUST be individualized by patient via monitoring

Metoprolol: selective beta 1 blocker

- Highly lipid-soluble → widespread distribution
- Hepatic metabolism + renal excretion
- Therapeutic usage & adverse effects (see previously)
    - Safer for asthmatic & diabetic patients

Indirect Adrenergic Blockers

- Indirect decrease of peripheral adrenergic activation
    - Its indirect because its action is in the CNS but the effects are in the PNS
    - 1. Alpha-2 autoreceptor agonists → clonidine
    - 2. Decrease adrenergic transmitter release → reserpine
- Pharmacologic effects & toxicity
    - = adrenergic antagonists
    - Decreased CO + increased vasodilation = decreased BP
- Contraindications
    - Geriatric patients / pregnancy
- Specific toxicity
    - clonidine: CNS depression and rebound hypertension
- Therapeutic usage
    - Clonidine: severe hypertension / pain / ADHD
    - Methyldopa: severe HT during pregnancy

Diabetes Pharmacology (Ch. 57)

Pathophysiology Review Slides

Diabetes Mellitus

Diabetes Mellitus (DM): Defective Insulin Secretion → Hyperglycemia

Type 1 DM:

- Cell-mediated autoimmune destruction of beta-cells
- Insulin-dependent
- Juvenile form (75% < 30 years old)
- Prone to ketoacidosis

Type 2 DM:

- Insulin resistance → decreased insulin OR increased secretions → increased resistance
- Associated with obesity; HTN & dyslipidemia
- Adult-onset form (but % childhood cases are increasing)
- Ketoacidosis only under stress
- Genetic predisposition

Gestational (GDM):

- Onset or 1st recognition during pregnancy
- Obesity; family history of GDM; ethnicity & > 25 y.o. = increased risk

Other specific types:

- Genetic defects in beta-cells or insulin action
- Pancreas impairments (cystic fibrosis; pancreatitis; infections)
- Endocrine disorders (ex. Hyperthyroidism; acromegaly; cushing's disease)

DM Diagnostic

Marker	Dx Threshold
Glycosylated Hemoglobin (HbA1c) - Measure avg. plasma glucose exposure to RBC	>6.5% (5.7% to 6.4% = increased risk)
Fasting plasma glucose (FPG) - Fasting = 8 hours minimum	> 126mg/dl or 7.0 mmol/L (100-125 mg/dl = increased risk)
Oral glucose tolerance testing (OGTT) - 2-hour plasma glucose with 75g glucose dose	> 200 mg/dl or 11.1 mmol/L (75-199 mg/dl = increased risk)
Random Glucose Levels (RGL) - Only in patients with classic hyperglycemia Sx	> 200 mg/dl or 11.1 mmol/L

Type 1 DM vs. Type 2 DM

Characteristics	Type-I (β-cell defect)	Type-II (Insulin resistance)
Incidence	Common childhood disease (0.17%)	45-64 yo: 10.5% 65-74 yo: 18.4%
Age of Onset	Peak = 11-13 years Rare < 1 or 30+	Highest Risk between 40-70
Gender	Similar	Similar
Racial Distribution	Whites ≈ 2x ↑ Risk	↑ Risk black & native Americans
Obesity	Usually Normal BMI	Important Contributing Factor ∝ Degree & Distribution of Obesity
Heredity	≈ 5-10%	≈ 10-15%
Antibodies	Islet Cell & Insulin Autoantibodies	Abs not Prevalent
Insulin	Resistance unusual Severe Deficiency to No Secretion	Resistance at Dx Secretion declines over time

Gestational Diabetes Mellitus (GDM)

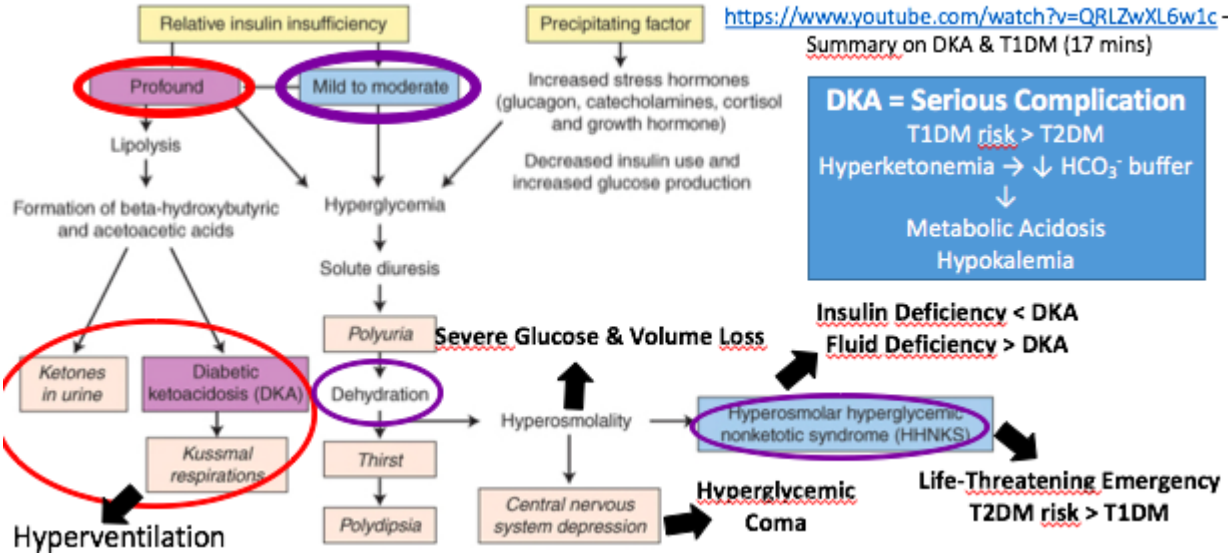
- Unknown pathophysiology
- Insulin resistance + hypoinsulinemia
- Prevention
  - Early screening
  - Glucose monitoring pre/post/during
  - Healthy diet + physical activity
- Pregnancy complications
  - Baby puts on extra weight → C-section
  - Increased T2DM risk for baby
  - Increased early delivery → respiratory distress
- Complications for mother
  - Increased T2DM risk & future GDM
  - Increased risk preeclampsia & HTN

Hypoglycemia

- Insulin shock
  - Plasma glucose < 45 mg/dl (<30 newborns)
  - T1DM risk > T2DM
  - Preventable with monitoring
- Neurogenic Sx = increases SNS activation
  - Tachycardia
  - Tremor
  - Anxiety
- Neuroglycopenic Sx = brain hypoglycemia
  - Dizziness
  - Confusion
  - Seizures
  - Coma

- Treatments
    - Exogenous glucose
    - Glucagon injections

Diabetic Ketoacidosis (DKA) & Hyperosmolar Hyperglycemic Nonketotic Syndrome (HHNKS)



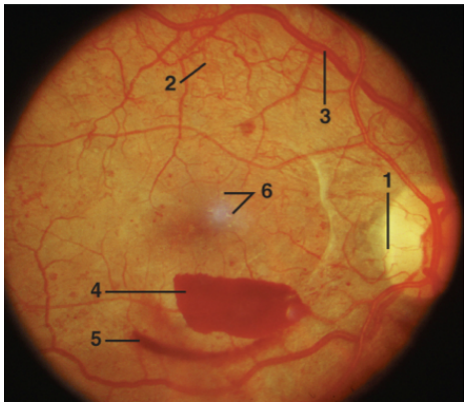
Microvascular Diseases

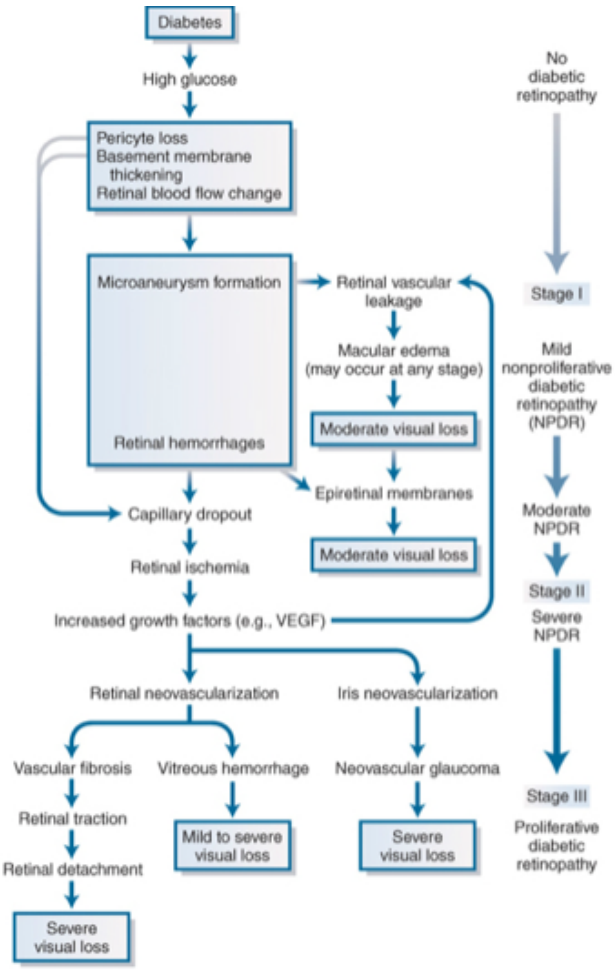
- Hyperinsulinemia + Hyperglycemia → oxidative stress → increased glycosylated hemoglobin → microvascular angiopathy
- Chronic hyperglycemia → T2DM patients have increased risk
- Organs most affected:
    - Retina → diabetic retinopathy
    - Kidneys → diabetic nephropathy
    - Nerves → diabetic neuropathy

Diabetic Retinopathy (DR)

- 1 & 2 = neovascularisation
- 3 = engorged veins
- 4 & 5 = hemorrhage
- 6 = solid exudate

- Increased risk of cataract; glaucoma; blindness





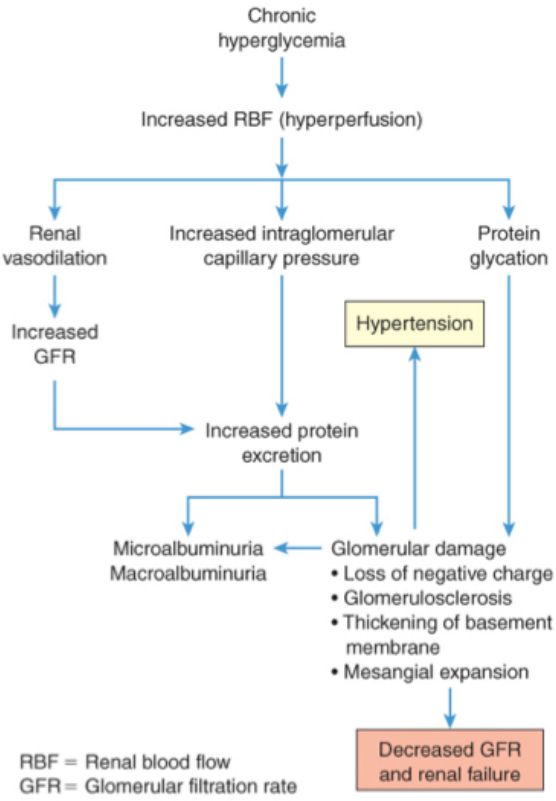
<u>Diabetic Nephropathy (DN)</u>

- Most common cause of end-stage kidney disease (ESKD)
- Microalbuminuria = loss 30-300mg/day → 1st sign

  ↓
- Macroalbuminuria = loss > 300mg/day

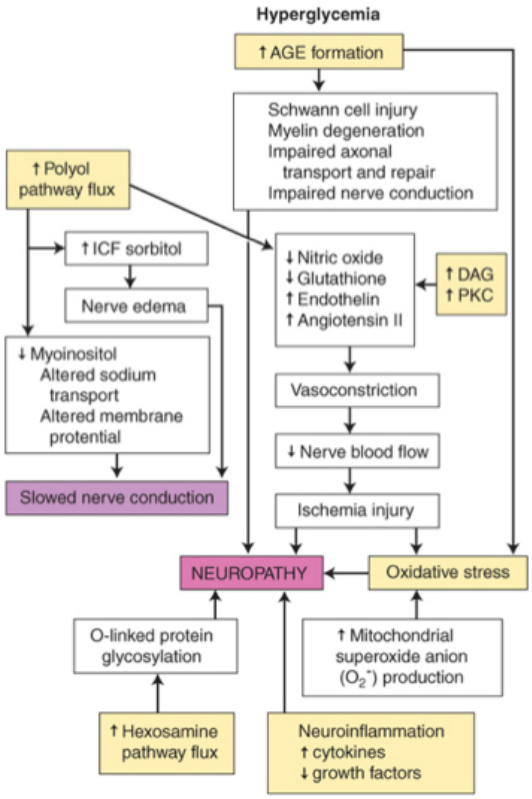
  ↓
- Clinical proteinuria → diabetic nephropathy

  ↓
- Acceleration of diabetic nephropathy & cardiovascular complications



Diabetic Neuropathy (DPN)

- Most common DM complication
- Nerves = vulnerable to hyperglycemia
- Sensory deficits → motor deficits
- Peripheral damage 1st; ANS 2nd
- Ex: neuropathic pain; decreased proprioception; decreased coordination; muscle weakness; autonomic GI & cardiac complications

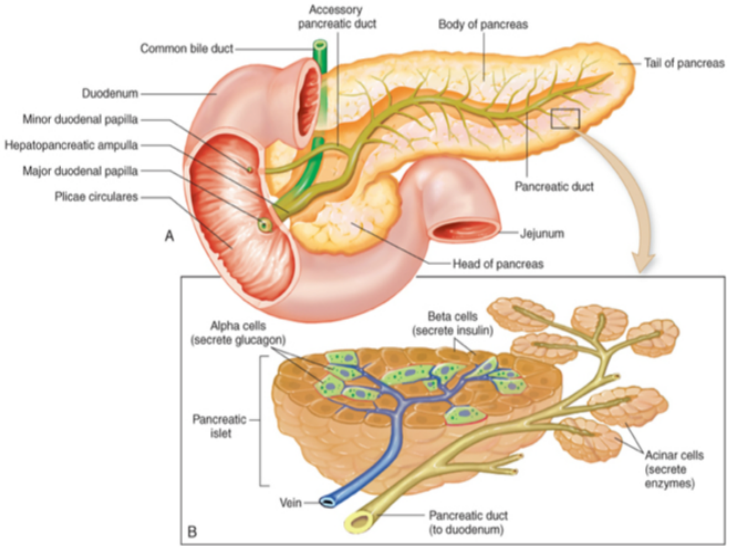


Macrovascular Diseases

- Coronary artery disease (CAD)
  - Accelerated damage → plaque instability
- Stroke
  - Risk is increased 2x vs. non-diabetic
- Peripheral arterial disease (PAD)
  - Very common with T2DM
  - Occlusion → ulcers → gangrene → amputation

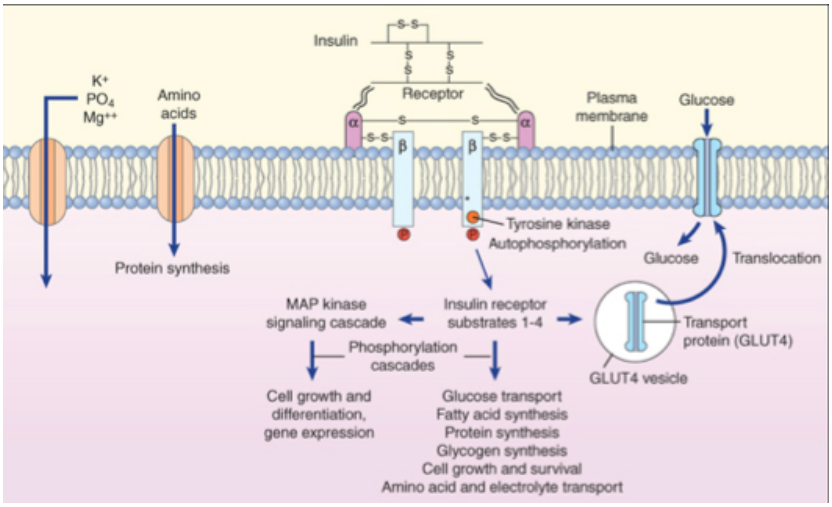
Endocrine Pancreas

- 99% exocrine (discussed in GI lectures)
- 1% endocrine → islet of Langerhans
  - Highly vascularized
- 4 hormone-secreting cells:
  - Alpha cells → glucagon
  - Beta cells → insulin & amylin
  - Delta cells → somatostatin & gastrin
  - F cells → pancreatic peptides



Insulin

- Anabolic peptide hormone
- Receptors on most cells
    - NOT THE BRAIN → hypoglycemic shock
- Primary action = decreased glucose
    - Increased GLUT4 channels → increased uptake
    - Increased usage as fuel
    - Decreased glycogenolysis



- Other actions:
    - @ liver: increased fatty-acid synthesis
    - @ adipose tissues: decreased lipolysis / increased fat storage
    - @ muscle tissues: increased amino acid uptake & protein synthesis

Factors increasing secretion	Factors decreasing secretion
• Increased glucose or amino acids • Increased GI hormones • Parasympathetic stimulation of beta-cells	• Decreased glucose • Increased insulin (Negative feedback) • Sympathetic stimulation of alpha-cells (glucagon)

BACK TO PHARM!!

Overview of Treatment

- **Primary goal**: keep glucose levels in “healthy range” (which will vary between individuals, which is why we need to get a baseline value for our patients)
- Prevent long-term complications (ex. Micro & macrovasculature diseases)
- Diet & physical activity = central components
- Physical activity increases glucose uptake & insulin-sensitivity

Type-1 DM

- Extensive patient education
- Must couple insulin replacement with carb intake (because these individuals do not produce insulin
- Weight maintenance with physical activity
- Combine with appropriate antihypertensive drugs
    - ACE-inhibitors; Statins

Type-2 DM

- Management of comorbidities = crucial
- Will not necessarily get insulin
- See Canadian guidelines at the end of the section

Tight glycemic control

- Around-the-clock blood glucose level maintenance

General Glycemic Treatment Targets for Nonpregnant Adults With Diabetes

A1C	<7.0%[a]
Premeal plasma glucose	80–130 mg/dL[a]
Peak postmeal plasma glucose	<180 mg/dL[a]

Type-1 DM

- Benefits outweigh the risks
- Drawbacks:
    - Increased hypoglycemia risk & weight gain
    - Increased cost/complexity of therapy

Type-2 DM

- Benefits limited to microvasculature complications (meaning we can reduce these, but not so much for the rest)
- Benefits increases in younger & recent-onset patients as compared to an older patient

Individualized goals based on:

- Duration of diabetes
- age/life expectancy
- Comorbid conditions
- microvascular/cardiac complications
- Hypoglycemia awareness
- Other individual considerations

Contraindications

- Advanced vascular complications
- Limited life expectancy
- Limited resources/support system
- Long-standing T2DM
- Severe hypoglycemia
- Extensive comorbidity

Insulin Deficiency Consequences

Catabolic state: increased breakdown of fat, glycogen & proteins

↓

Gluconeogenesis: fat & amino acid conversion to glucose

+

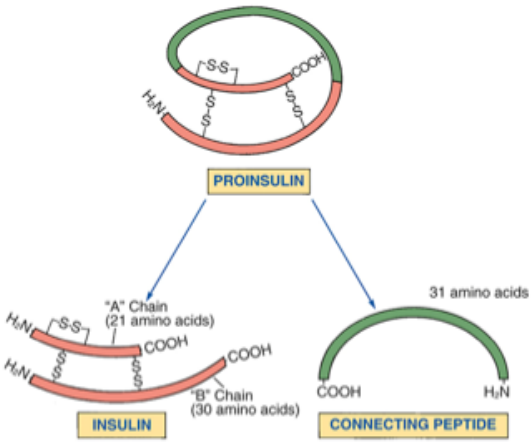
↓ glucose usage/cellular uptake

↓

Hyperglycemia

↓

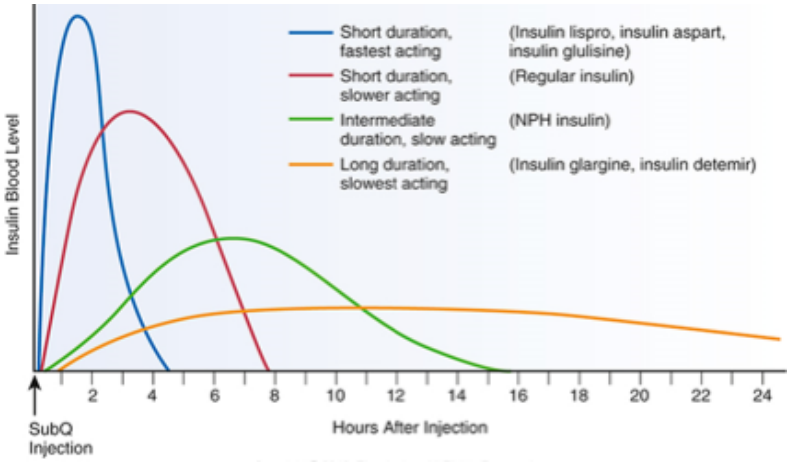
Diabetic signs & symptoms



The diagram to the right points out that one of the synthesis markers for the presence of insulin or lack thereof, is this connecting peptide when insulin is produced by the pancreas. It comes first in this long section (top image) and then it needs to be cut in two to form insulin. The connecting peptide is discarded and ends up in the bloodstream and excreted in the urine. Measuring the amount of this peptide will give us an indication of how much insulin (or lack of) is produced by the individual.

Insulin Types

- Types of insulin DOES NOT EQUAL time course
- High-alert agent = increased medication error risks



- Only available parenteral (SubQ) - it is completely digested if administered PO because it is a protein
- All synthesized via DNA recombination
    - Short duration - rapid acting : control postprandial blood glucose rise
    - Short duration - slower acting : control postprandial blood glucose rise, basal glycemic control
    - Intermediate : basal glycemic control between meals
    - Long duration & slowest acting : daily basal glycemic control of T1DM & T2DM
- Nursing Advice: insulin appearance
    - Clear, colorless solutions (except NPH insulin)
    - Always inspect insulin quality
    - Discard if colored or cloudy
    - NPH insulin must be gently mixed
    - Note date of bottle opening

<u>Insulin: Administration</u>

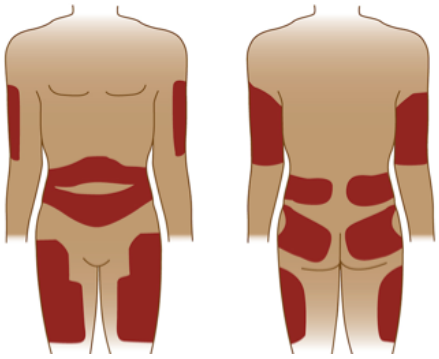
Administration

- Subcutaneous = preferred for all
- Via syringe/Pen/Jet injectors
- Pre-filled syringe stored in fridge upright
- Gently agitate to re-suspend prior to injection
- IV: emergency ketoacidosis

Concentrations	Indication
U-100 (units/mL) U-200	Routine replacement therapy
U-300	Daily basal insulin coverage
U-500	Specifically for insulin resistant patients

Nursing advice: Insulin Mixing

- Only NPH insulin can be mixed with short-acting insulins
- Premixed preparations = preferred to decrease errors

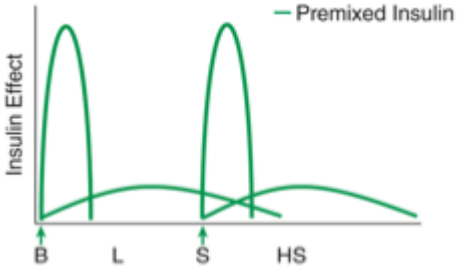


Fast absorption in the abdomen
Slow absorption in the thighs

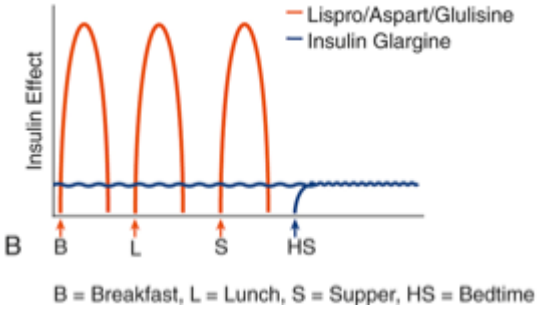
<u>Insulin: Diabetes Therapy</u>

- Major indication: required for all T1DM patients and many T2DM
- Dosing schedules: dosage should be adjusted proportionally to carbohydrate intake
- Twice-daily premixed (fig. A): Only 2 injections but less “need-based” adjustment

- Premixed (intermediate with short acting insulin)
- Should be administered around breakfast and then supper time
- Drawback: less need-based adjustments
- Benefit: fewer injections throughout the day



- Intensive basal-bolus (Fig. B): good meal & basal coverage → perfect for T1DM
  - Involves the use of a long-acting in addition to a short-acting
  - Goal is to have coverage for all three meals of the day.
  - At bedtime you get a long acting to cover you until bedtime the following day.
  - Drawback: more administrations per day.



B = Breakfast, L = Lunch, S = Supper, HS = Bedtime

- Continuous Subcut infusions (CSI): steady infusion + automated adjustments
- IV infusions: critical care

*** Patient education, healthcare team program & active patient participation ***

Insulin therapy complications:

- Major: hypoglycemia (see pathophys review slide)
- Risk factors: intense exercise, childbirth, meal skipping, excessive alcohol consumption
- Treat rapidly via fast acting oral glucose dose (ex. Orange juice, non-diet soda, etc.)
- Minor: hypokalemia, lipohypertrophy, allergic reactions (rare)

Drug interactions:

- Hypoglycemic agents (ex. alcohol) & hyperglycemic agents (ex. glucocorticoids)
- Beta-blockers → can hide/delay early detection signs

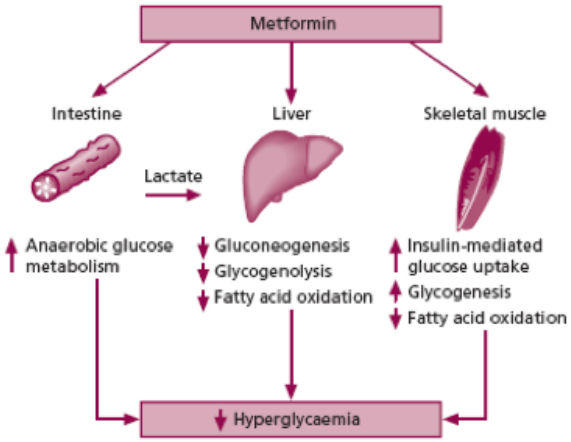
Non-Insulin Medications for Diabetes

Biguanides: Metformin

- Drug of choice for T2DM
- Weight neutral: it won't make you gain or lose weight (unlike other agents)

Pharmacokinetics	Orally Available No Metabolism → 100% Kidney Excretion
Adverse Effects (All GI Related)	↓ Vit. B12 & Folic Acid Absorption ↓ Appetite; Nausea & Diarrhea **'Weight-Neutral'**
Toxicity (Very Rare)	**Lactic Acidosis; ↑ risk if Renal Impairment**
Drug Interactions	Alcohol & Cimetidine (H2-Blocker)
Therapeutic Uses	
Glycemic Control	**↓ Blood Glucose without ↑ Insulin** **Hypoglycemia risks = Low** Synergy with other Antidiabetic Agents Safe for individuals skipping meals
T2DM Prevention	Delay T2DM development in High Risk Individuals **Not as much as Diet + Exercises!!**
Gestational Diabetes	Benefits = Insulin
PCOS	↓ Androgens levels + ↑ Insulin Sensitivity Off-Label Usage

- Mechanism of Action: acts directly on the organs.
  - At the intestine: it increases anaerobic glucose metabolism - increase the breakdown of glucose before it is absorbed.
  - At the liver: decreases the gluconeogenesis
  - At skeletal muscles: increase insulin sensitivity and glycogenesis (synthesis of glycogen)
- Metformin is decreasing the amount of glucose that is getting into the bloodstream.



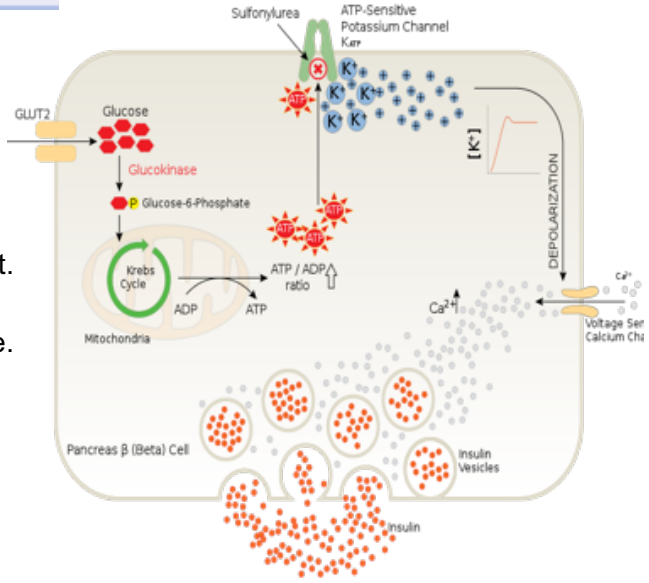
Sulfonylureas (2nd Gen) & Glinides

- Oldest oral antidiabetic agent
- 2nd Gen safety >>> 1st Gen
    - 2nd gen is much more potent and less drug-drug interactions

Pharmacokinetics	Orally Available Mix of hepatic metabolism & kidney excretion
Adverse Effects (All GI Related)	↑ Risk if Liver or Renal Impairment Hypoglycemia in normo & hypoglycemic patients Weight Gain → **'Weight-Positive'**
Drug Interactions	Alcohol & Other Hypoglycemic Agents Beta-Blockers (↓ Insulin release)
Therapeutic Uses	
Glycemic Control	↑ Insulin Secretion (so ineffective for T1DM) Most often used in combination

Glinides (Repaglinide & Nateglinide)	
Mechanism of Action & Adverse Effects	**Same as Sulfonyureas**
Pharmacokinetics	Vs. Sulfonylureas = Short Time Course Administered with meal intake

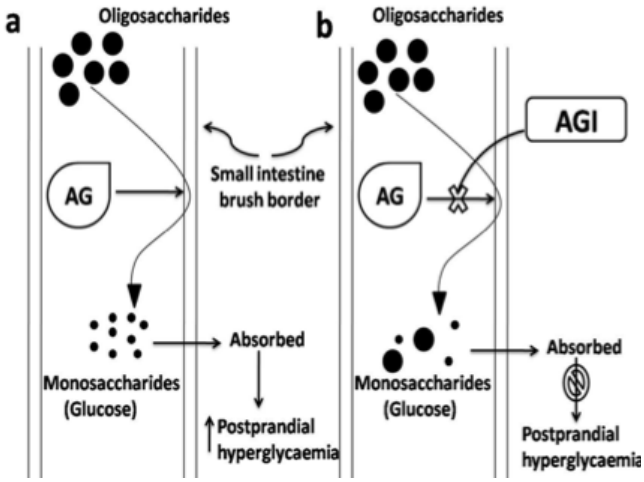
- Mechanism of action: it acts on the pancreatic beta cells. The little vesicles filled with insulin are released when the cell is activated. The drug activates the cells a bit more than they normally are by blocking a potassium channel. By blocking the K+ channel, it prevents the K+ from leaking out. As a result, the cell becomes depolarized, thereby permitting influx of calcium, causing insulin release.



Alpha-Glucosidase Inhibitors (AGI)

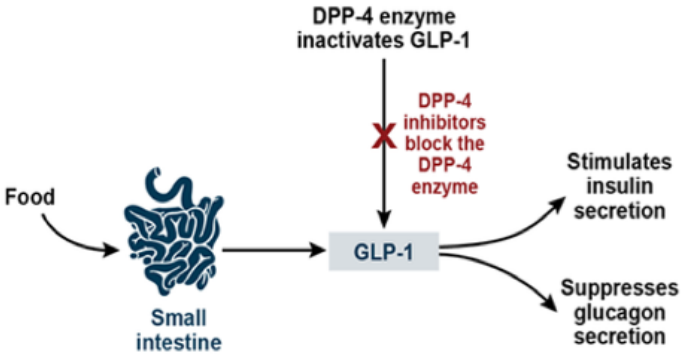
- AGIs: Acarbose & Migitol
- Therapeutic use:
    - T2DM glycemic control
    - Decrease A1C levels & postprandial glucose peaks
- Kinetics:
    - Only 2% absorbed → very few systemic effects
    - Stays where it acts (in the gut!!)
    - Inactivated by GI enzymes & bacteria
- Adverse effects:
    - GI distress (ex. Cramps, flatulence, diarrhea)

  - Decreased iron absorption → increased anemia risks
  - Hypoglycemia only in combination
  - Very rare risks of liver dysfunctions
- Mechanism of action: prevents the enzyme AG from breaking down larger structures from which glucose comes from. So if you prevent the breakdown of oligosaccharides into monosaccharides, the oligosaccharides are too large to be absorbed.
- Variable prescription pattern in North America due to GI adverse effects (not preferred drug)



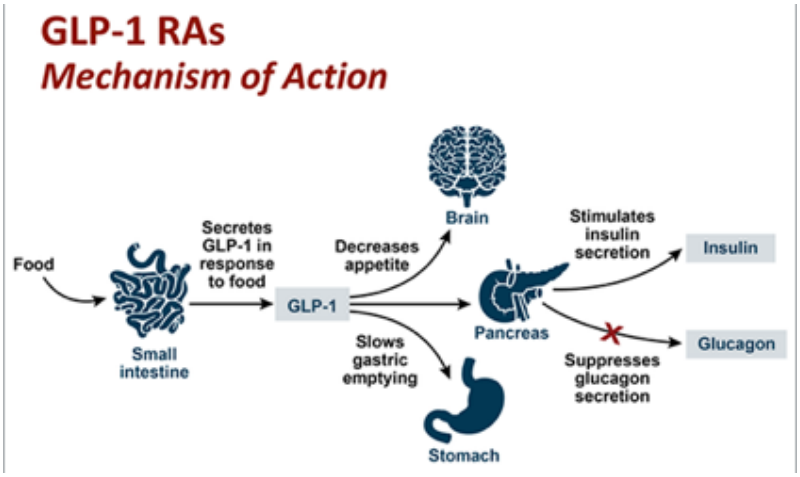
DPP-4 Inhibitors

- DPP-4 Inhibitors: Gliptins (ex. Sitagliptin)
- Therapeutic use:
  - second-line drug to T2DM therapy
  - Small decrease in A1C → yet clinically significant
- Kinetics: ~100% absorbed / ~100% kidney excretion
- Adverse effects: Very few → well tolerated
  - Hypoglycemia & respiratory infections = placebo
  - Severe pancreatitis (rare) → monitor
  - Unconfirmed allergic reactions → monitor
- Drug interactions:
  - Nothing significant → good benefit
- Mechanism of action: it acts on the incretin hormone GLP-1 pathway. GLP-1 is released by the small intestine when food arrives. Its goal is to increase the release of insulin and suppress glucagon. DPP-4 inhibitors blocks the DPP-4 enzyme, whose job is to inactivate the GLP-1 hormone.
  - NB. because it works on increasing insulin secretion, this drug will not work in T1DM.



Injectable GLP-1 Agonists: Liraglutide

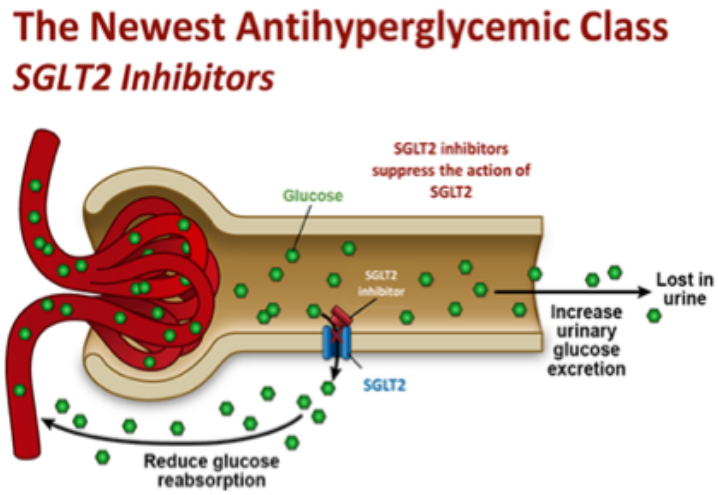
- Therapeutic use:
  - Improve glycemic control of T2DM
  - Weight - neutral
  - Injections: 2x/day or once a week extended release
- Kinetics:
  - Subcutaneous injections = best absorption
  - ~ 100% kidney excretion
- Adverse effects:
  - Frequent hypoglycemia with sulfonylureas
  - Some GI distress & risk of severe pancreatitis
  - Possible renal impairment
  - Possible teratogen → avoid during pregnancy
- Drug interactions:
  - Decreased absorption of PO drugs (contraceptives & antibiotics)
- Incretin Mimetics resistant to DPP-4 metabolism (it will not get inactivated by DPP-4)
  - Said to be a superior drug because of this
- Mechanism of Action: incretin mimetic (simulates the same action) as the one produced by your body.



SGLT2 Inhibitors

- SGLT2 = sodium glucose ligand transporter #2
- Drugs: Empagli**flozin** & Canagli**flozin**
- Action:
  - Decreased glucose kidney reabsorption
  - Weight loss via urinary caloric loss
- Specific Usage:
  - Best options for patients with CVD comorbidities already on Metformin
  - Improves cardiovascular & renal outcomes
- Adverse effects
  - Orthostasis & increased urinary tract infections
  - Rare: euglycemic DKA

- Mechanism of Action: it inhibits the SGLT2 transporter (which carries sodium and glucose) which are found in the kidney tubules. By blocking these transporters, it prevents the reabsorption of glucose, so it can be excreted, decreasing blood glucose.

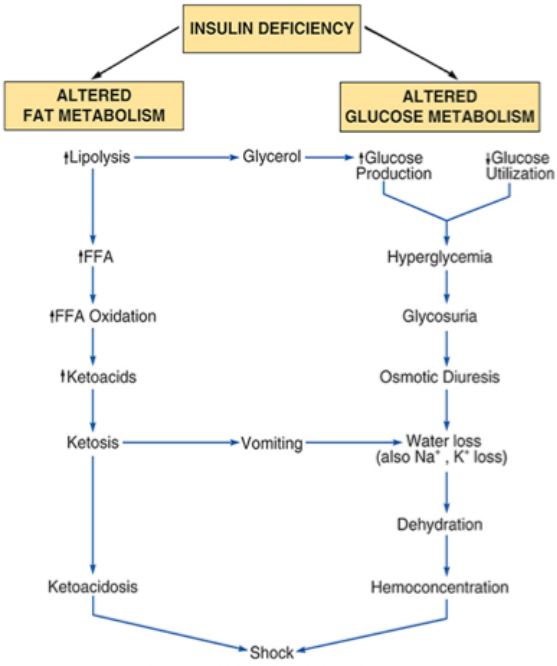


<u>Poor Glycemic Control</u>

Diabetic Ketoacidosis (DKA) therapy

*****Life threatening emergency*****

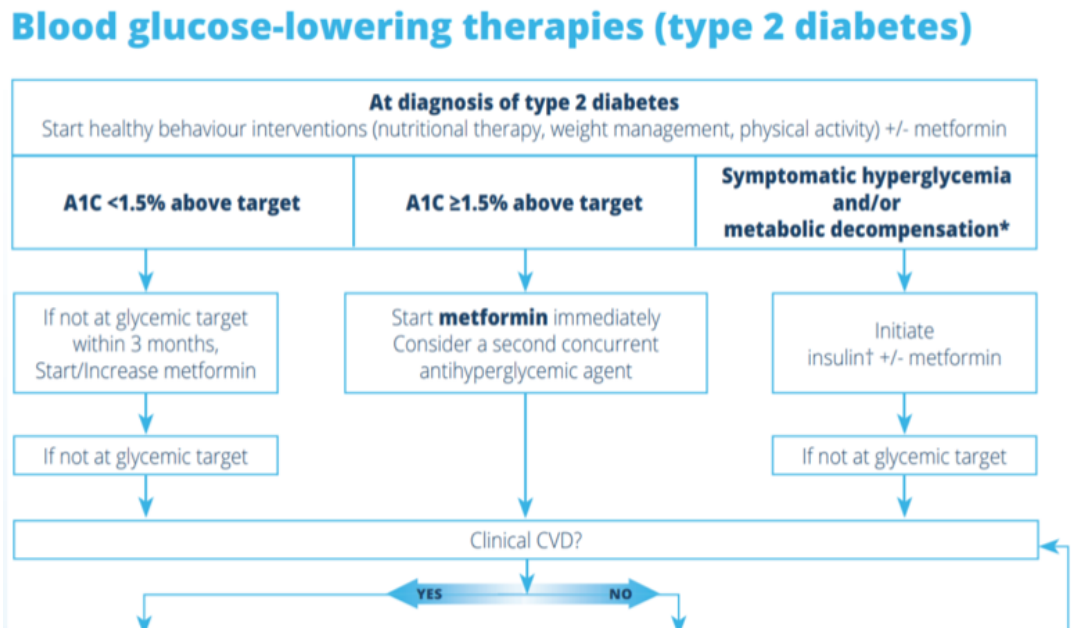
- Must correct hyperglycemia & acidosis
- IV fluids & electrolytes for rehydration
- IV insulin to gradually decrease blood glucose
- Rapid decrease in blood glucose can exacerbate condition

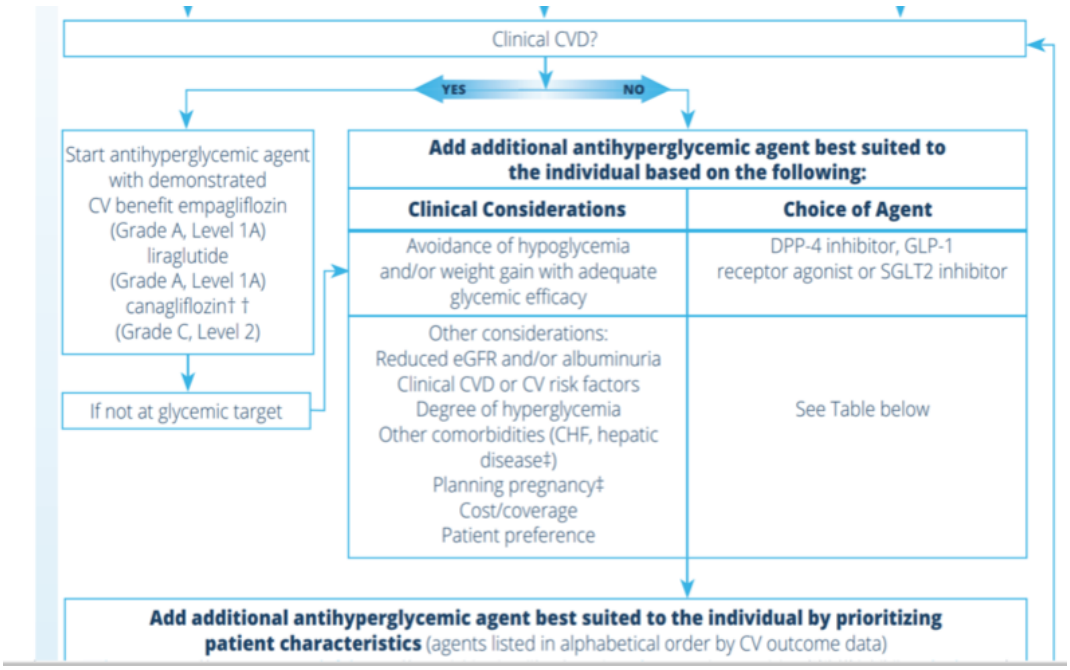


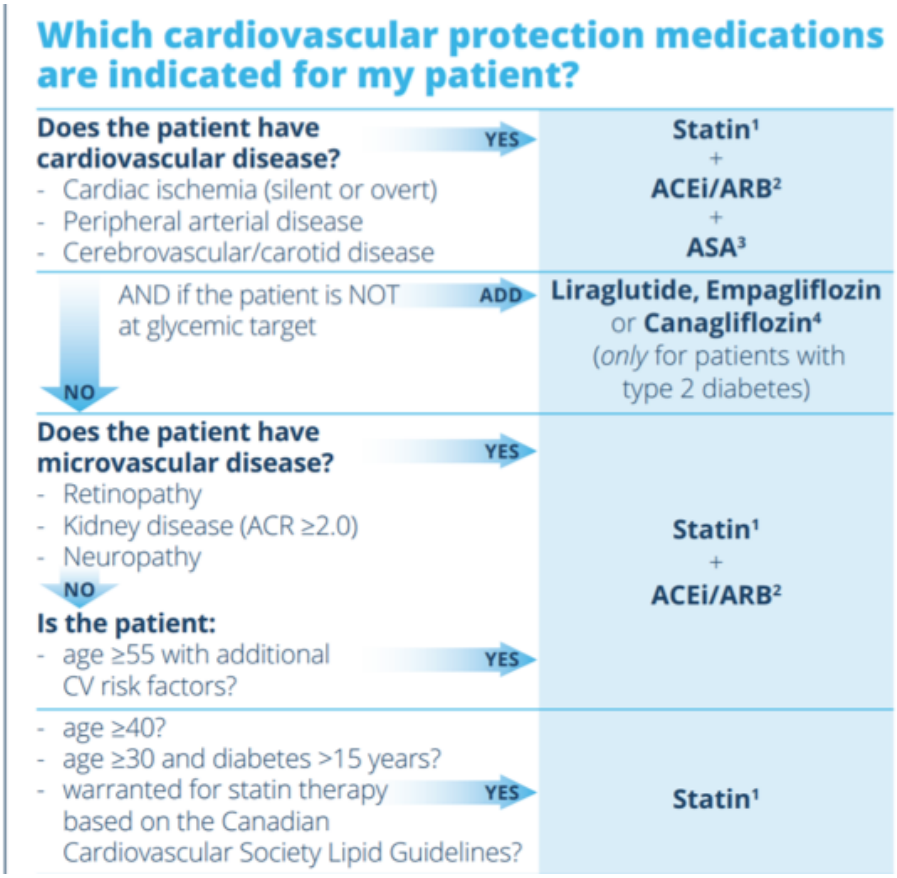
Severe hypoglycemia therapy:

- When self-treatment with oral carbohydrates fails:
  - IV glucose = preferred option (immediate effect)
  - If not an option (ex. Unconscious at home) → glucagon subcut

Canadian Diabetes Guideline
See following site: http://guidelines.diabetes.ca/docs/CPG-quick-reference-guide-web-EN.pdf







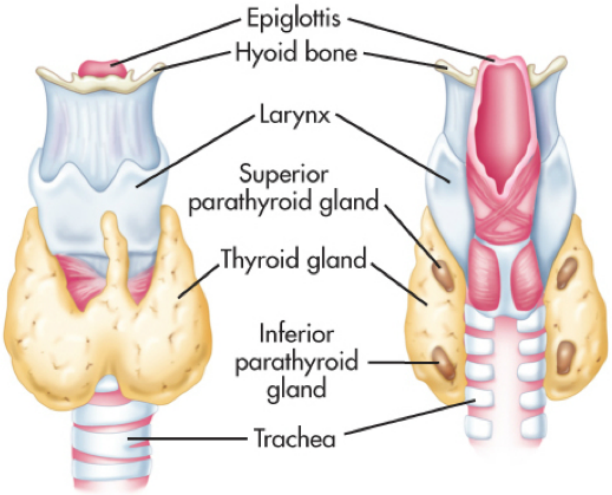
Key Nurse Takeaway

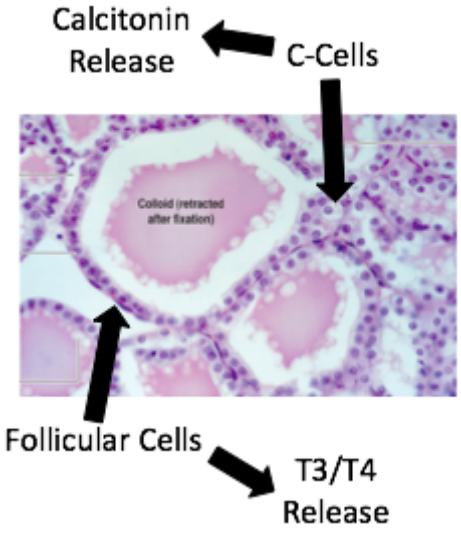
- Risk of hypoglycemia with insulin vs. oral antidiabetic Rx
- Insulin increases uptake by almost all cells (except brain!!!)
- Oral antidiabetic Rx do not influence insulin levels as much
    - Works via decreasing glucose entry into the circulation so levels don't drop drastically, they simply stop increasing too much.
- Patients are often confused with this and confuse the causal relationship between meal intake and insulin or metformin administration
    - They must eat because they took insulin
    - NOT take insulin because they ate

THYROID DISORDER DRUGS (Ch. 58)

Pathophysiology Review

Thyroid Hormones (TH)





Thyroid Hormone Regulation

TRH secretion → release of glycoprotein TSH

↓

TSH binds to TSH-receptors on follicular cells

↓

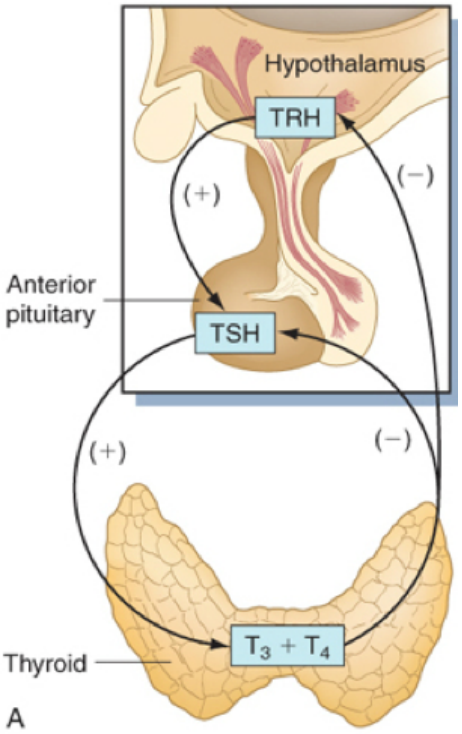
Increases release of T3 & T4

+

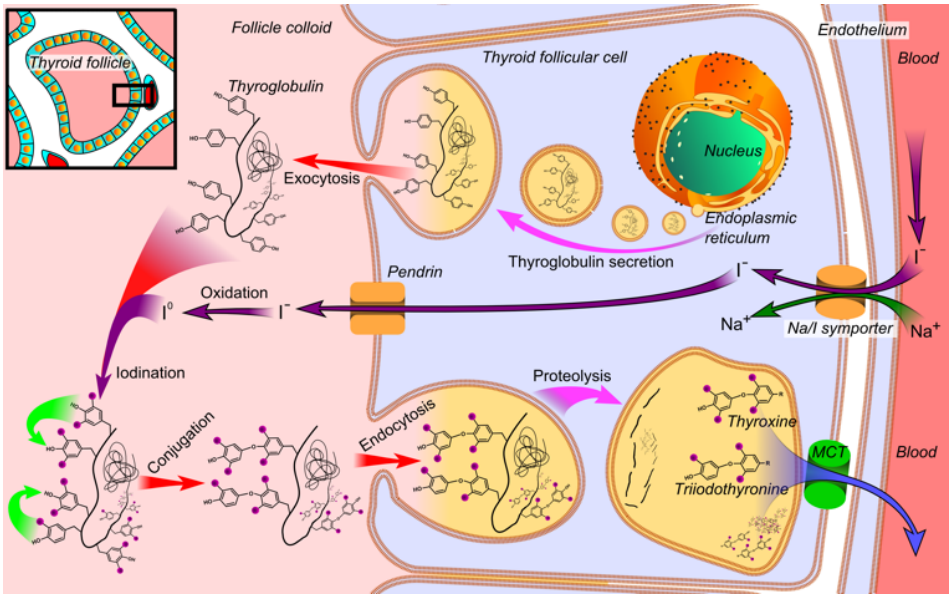
Increased iodine uptake & T3/T4 synthesis

+

TSH increases thyroid gland hypertrophy & hyperplasia



Thyroid Hormone Synthesis



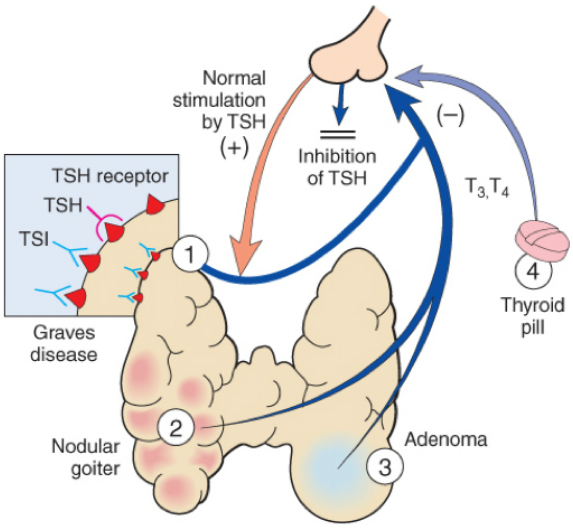
Thyroid Hormone Functions

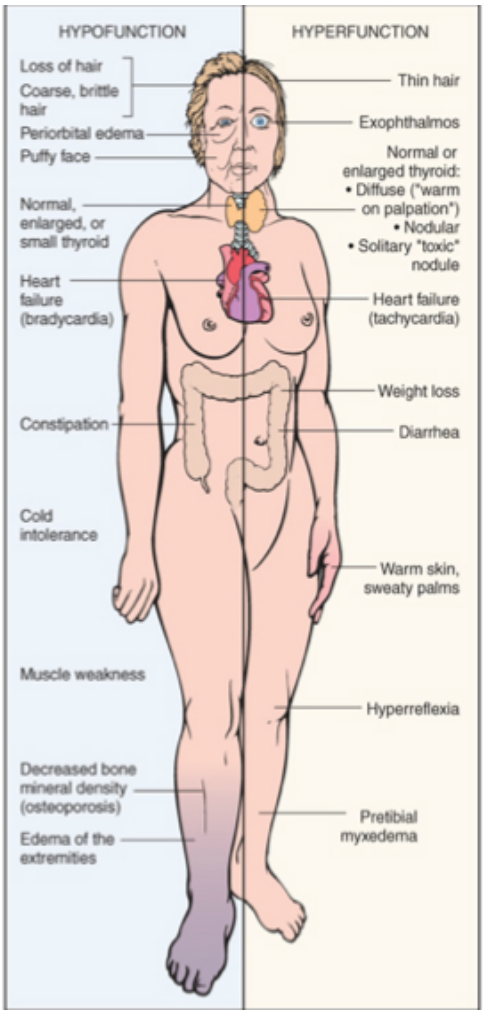
- TH are amines but act like steroids!! → alter protein synthesis
- T3-T4 transported bound within the bloodstream → T4 metabolised into T3 → T3 binds intracellular receptors

Main effects of T3 & T4:

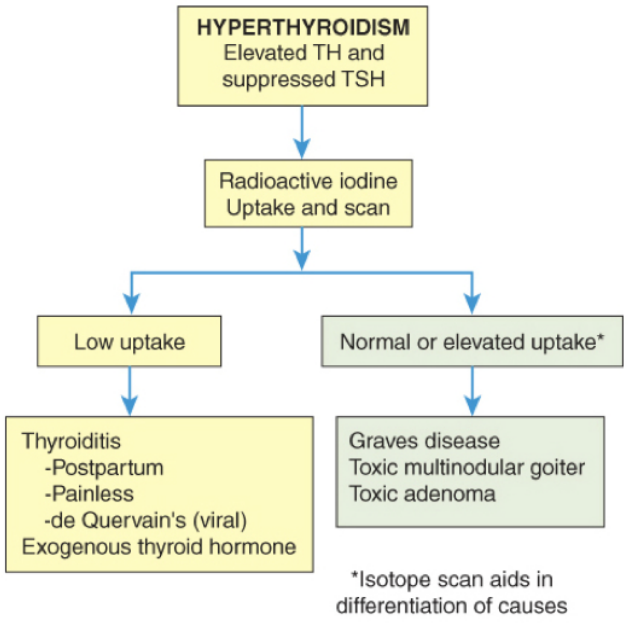
- Fetal + infant CNS development (neurogenesis)
- Increased basal metabolic rate (BMR) → especially lipid turnover & cholesterol synthesis
- Increased BMR → increased body heat & oxygen consumption
- Increased GH secretion + skeletal/muscular maturation
- Pathophysiological levels → increased cardiac contractility, HR & CO

Hyperthyroidism





Hyperthyroidism Evaluation



Graves Disease

- 50-80% of thyrotoxicosis
- Type-II hypersensitivity reaction
- Thyroid-stimulating immunoglobulins (TSI) → thyroid hyperplasia + T3/T4 synthesis = toxic goiter.
- Symptoms:
    - Exophthalmos (50% cases) - TSI interact with ocular fibroblast receptors
    - Visual impairments & pain
    - Fat accumulation
    - Edema
    - Inflammation
    - Subcutaneous swelling & erythematous skin
    - Pretibial myxedema/Graves dermopathy (smaller fraction of cases) - fibroblasts & T-cells stimulate hyaluronic acid production

Nodular Thyrotoxicosis & Thyroid Storm

Nodular Goiter:

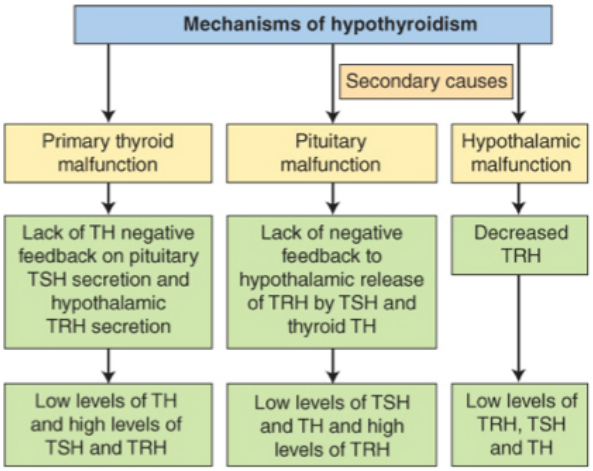
- Thyroid hyperplasia in response to increase TSH (ex. Puberty; pregnancy; iodine-deficiency)
- Follicular cells continuing to secrete excessive T3/T4 after response = toxic nodules
- Increased risk of thyroid cancer
- No exophthalmos or pretibial myxedema
- Other manifestations develop slowly

Thyroid storm or crisis:

- Drastic increase in T3/T4
- Rare but potentially lethal
- Patients with undiagnosed or mistreated
- Hyperthyroidism = increase risk
- Cause: acute stress (ex. Surgery, infection, emotional distress)
- Manifestations: hyperthermia, tachycardia, delirium

Hypothyroidism

- Normal TH + increased TSH = **subclinical hypothyroidism**
- Hashimoto Disease (autoimmune)
- surgery/radiotherapy
- Congenital
- Iodine deficiency → rare in developed countries thanks to enriched salt!



Hypothyroidism Manifestations

- Edema
- Tongue thickening (myxedema) → slurred speech
- Cretinism → hypothyroidism at birth or childhood
    - Mental and physical retardation

BACK TO PHARM

General Strategy

Adult hypothyroidism

- Lifelong hormone replacement
- T4 alone > T3/T4 combination
- Adequate replacement eliminates all symptoms

Infantile Hypothyroidism

- Initiate replacement ASAP (because it has an effect on the brain)
- Within days of birth: normal development
- 3-4 weeks delay: some permanent disabilities
- Assessment after 3 years: determine if permanent therapy necessary

Grave's disease (hyperthyroidism)

1. Surgical thyroidectomy + replacement
2. Thyroid destruction via radioactive iodine
3. Anti-thyroid drug to decrease synthesis

- Best option for adults is #2
- Best option for younger patients = #3
- For exophthalmos: surgery or glucocorticoids
- Beta-blocker = adjunct therapy (quick action!!)

Toxic Nodular Goiter (hyperthyroidism)

- #1 or 2 preferred

Levothyroxine (T4)

General Information:

- Should be taken on an empty stomach in the morning
- Rapidly converted into T3 by the body
- 99.9% protein-bound → Half-life = 7 days → therapeutic delay
- Indication: all forms of hypothyroidism
- Therapeutic doses = very few adverse effects
- Toxic doses = hyperthyroidism symptoms
- Biggest drawback: several known drug interactions
    - Ex: warfarin, catecholamine, GI drugs

Therapeutic Goal

- Compensate deficiency precisely (dosage changes from pt to pt)
- Use clinical symptoms + Lab tests to adjust dosage
- TSH levels 6-8 weeks post-inhibition = best test
    - Low TSH levels are indicative of treatment success
- Symptomatic relief DOES NOT EQUAL cure

Nursing Consideration: Brand Equivalence

- Several brands/generic formulations: no one can own a patent on a hormone our bodies produce.
- Debate over the equivalence & interchangeability
- Recommendations:
    - Maintain patients on same product when possible
    - If switch: retest TSH serum at 6 weeks & adjust

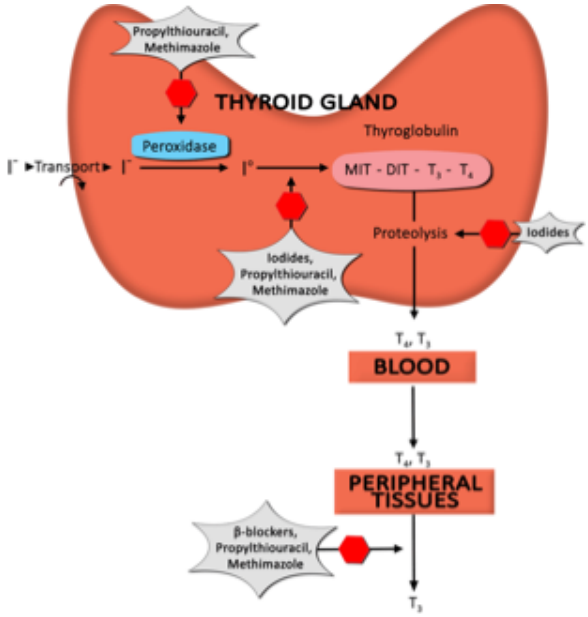
Lyothyronine (T3)

- Short action & increased cost
- Only better if require speedy onset
    - Ex: myxedema coma

Antithyroid Drugs: Thionamides

- Decrease thyroid hormone synthesis

	Methimazole	Propylthiouracil (PTU)
Kinetics	Half-Life long enough for 1-day dosing Very Lipid-Soluble → Placenta X-ing	Short Half-Life → 2-3x/day Poor Placental X-ing
Therapeutic Uses	Graves' Disease Radiation Therapy Adjunct Thyroidectomy Preparation Thyrotoxic Crisis Prophylaxis	**When PTU > Methimazole:** Thyroid Storm 1st Trimester Pregnancy Methimazole Intolerance
Adverse Effects	Avoid during 1st Trimester & Breast-Feeding Monitor for **Agranulocytosis (↓ WBC)** Hypothyroidism	Severe Hepatotoxicity ↑ Risk in Infants Agranulocytosis



- Mechanism of Action: used to decrease thyroid hormone synthesis. They block the conversion/introduction of iodine in the thyroid hormone synthesis pathway.

Radioactive Iodine (^{131}I)

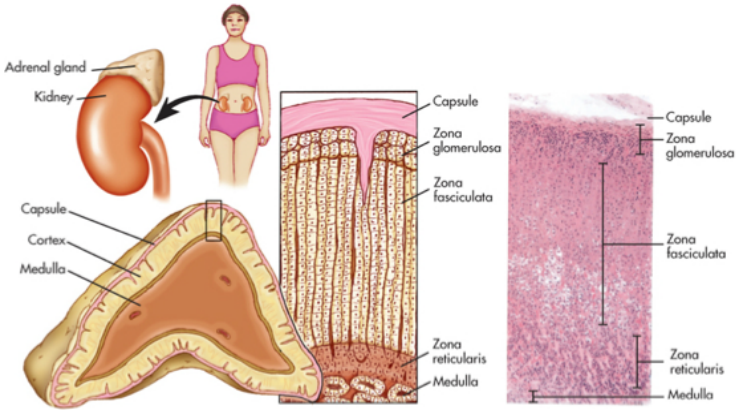
- Partial destruction of thyroid tissue
  - Damage to thyroid only
  - Delayed hypothyroidism
- Graves disease cured with single treatment in 66% patients
  - Delayed therapeutic effect → maximal = 2 months
- Indication for: adults with hyperthyroidism
- Inappropriate for: young children, pregnancy & lactation
- Advantages: low cost, no surgery, no risk of death, no effect on other tissues
- Disadvantages: delayed effect onset, delayed hypothyroidism (90%)
- Other usages:
  - Smaller doses → thyroid function diagnostic
  - Higher doses → thyroid cancer

DRUGS FOR ADRENAL CORTEX DISORDERS (Ch. 60)

Pathophysiology Review

Adrenal Glands

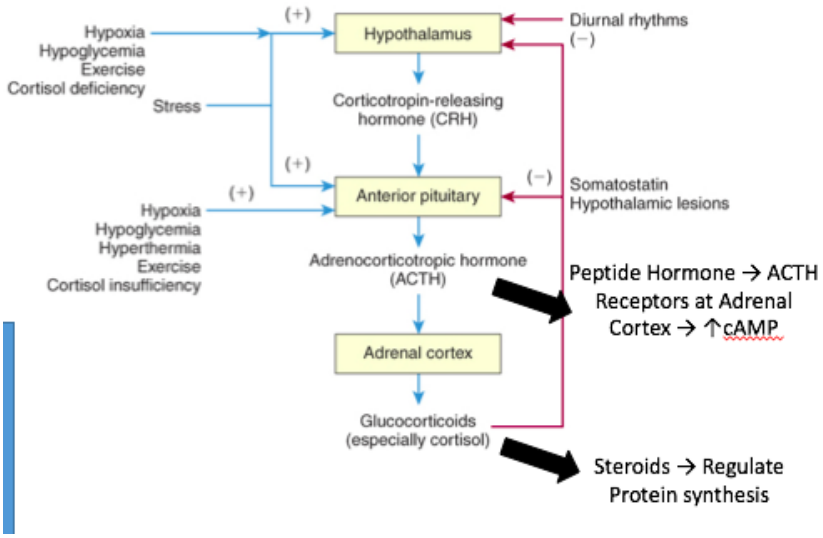
- 2 glands in 1!
- Cortex → glucocorticoids, mineralocorticoids, & a bit of estrogen & testosterone
    - Zona fasciculata → glucocorticoids (cortisol)
    - Zona glomerulosa → mineralocorticoids (aldosterone)
- Medulla → Epinephrine (adrenaline) & Norepinephrine



Glucocorticoids (GCC)

3 main regulators:

1. Cortisol levels
2. Stress
3. Diurnal rhythms

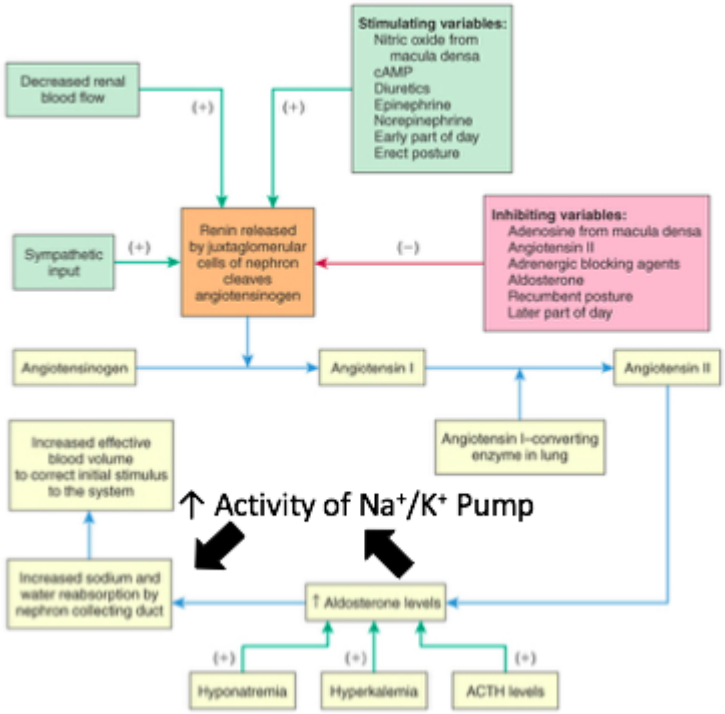


Main effects:

- Increase blood glucose
- Increase glycogen & protein catabolism
- Increase neuronal functions
- Powerful anti-inflammatory
- Anti-growth (ex. Decreased bone deposition)

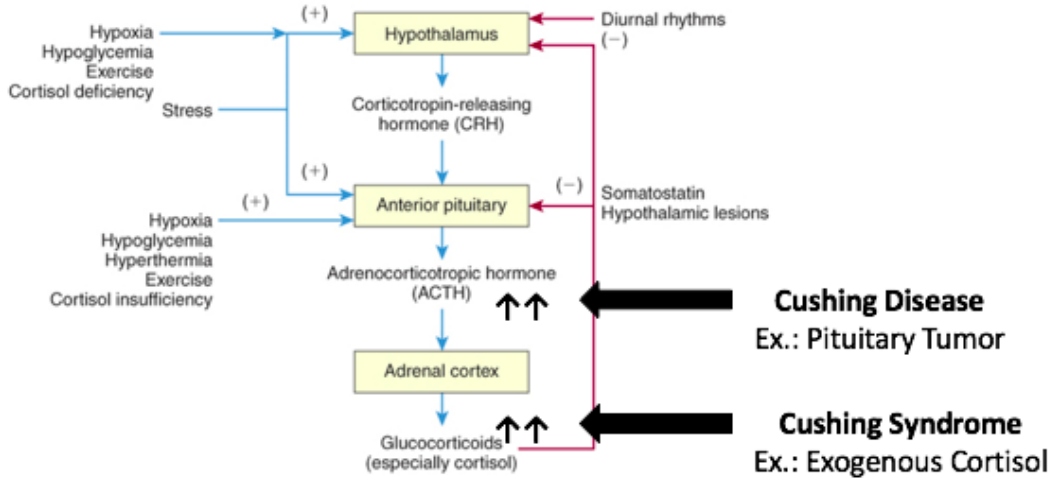
Aldosterone

- Main regulator = renin-angiotensin system activation
    - Decreases blood volume
    - Increases sympathetic input & ACTH
    - Hyperkalemia or hyponatremia
- Main effects → ionic regulation
    - Increased Na+ & water retention
    - Increased K+ & H+ excretion



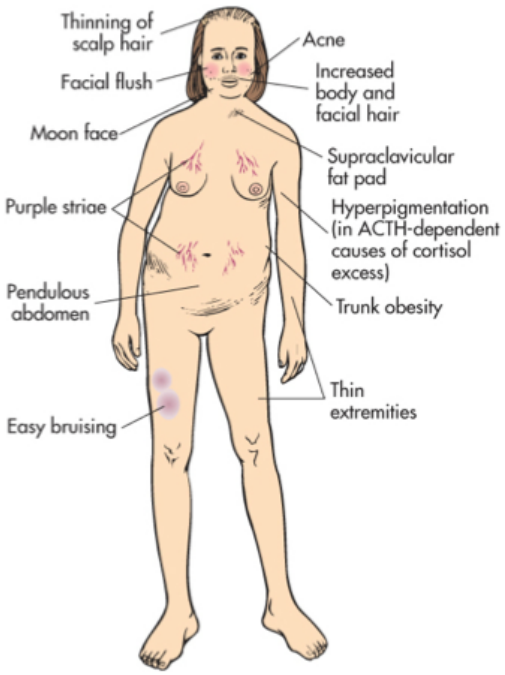
Cushing's Disease vs. Syndrome

- High levels of cortisol
- HP-adrenal gland axis shut down
- No circadian rhythms & stress response



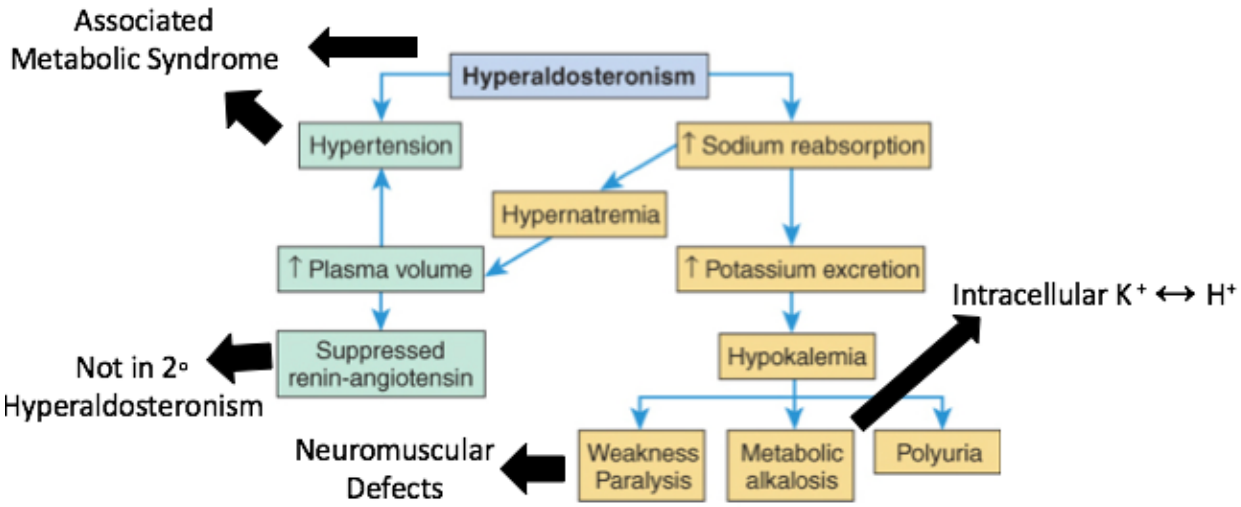
Cushing's Manifestation

- Insulin-resistance → diabetes in 20% of cases
- Increased catabolism → osteoporosis & muscular atrophy
- Hypertension → increased risk of metabolic syndrome & CVS events
- Immunosuppression → increased infections
- Physical Sx:
  - Weight gain
  - Moon face
  - Acne
  - Increased body/facial hair



Hyperaldosteronism

- 1° hyperaldosteronism = adrenal cortex tumor
- 2° = extra-adrenal stimulus (ex: increased renin/angiotensin II)



Addison's Disease

- Insufficient adrenal stimulation (ex. Exogenous cortisol → decreased ACTH) or insufficient cortisol synthesis or secretion
- Most common cause = autoimmune destruction of adrenal cortex
  - Can lead to adrenal atrophy & decreased cortisol or aldosterone or both
- Main manifestations:
  - Hypocortisolism
  - GI distress → nausea, vomiting, diarrhea
  - Hypoglycemia → fatigue, weakness, confusion

- Severe hypotension → vascular collapse & shock

BACK TO PHARM

Adrenocortical Alterations Management

Red = Adrenal Hypofunction vs. Green = Adrenal Hyperfunction

Pathology	Strategy
Cushing's Syndrome	**Adrenal Adenoma:** Surgical Removal + Hormonal Replacement **Pituitary Adenoma:** Partial Surgical Removal to ↓ ACTH Levels Ketoconazole ↓ Cortisol Synthesis but High Toxicity (not preferred)
Primary Hyperaldosteronism	**Adrenal Adenoma:** Surgical Removal + Hormonal Replacement **Bilateral Adrenal Hyperplasia:** Aldosterone Antagonists (ex.: Spironolactone)
Addison's Disease	**Hormonal Replacement (ex.: Hydrocortisone)**
Secondary & Tertiary Adrenal Insufficiency	**Glucocorticoid Replacement Only** Mineralocorticoid levels are usually ok!
Acute Adrenal Crisis	**Rapid Replacement of: Fluid + Salt + Glucocorticoids** Ex.: Hydrocortisone IV Bolus → Saline + Dextrose IV Infusion
Congenital Adrenal Hyperplasia	Genetic Enzyme Deficiency → ↓ Glucocorticoid → ↑↑ ACTH Release **Exogenous Hydrocortisone → ↓ ACTH → Stabilise Symptoms**

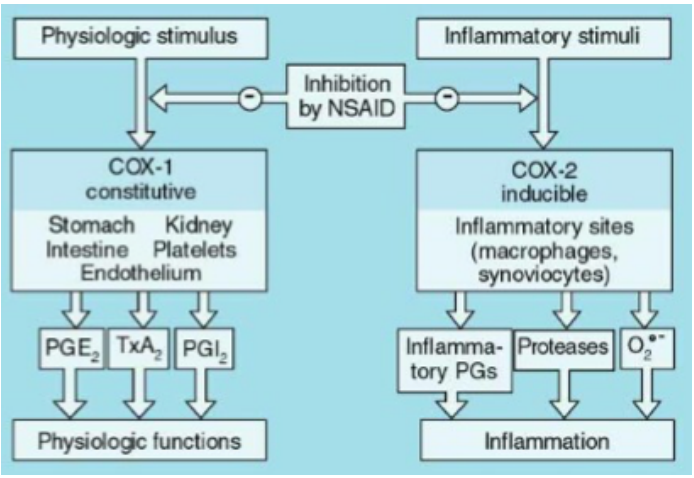
Adrenocortical Agents

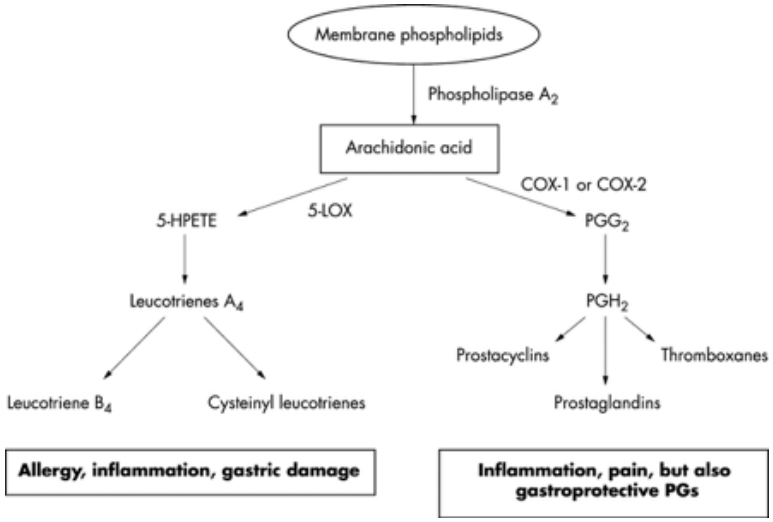
Drug	Hydrocortisone	Prednisone	Dexamethasone
Action	Glucocorticoid & Mineralocorticoid activity	Only available mineralocorticoid	Glucocorticoid activity only
Replacement therapy	Preferred agent for adrenal insufficiency	Alternative to hydrocortisone	N/A
Non-endocrine therapy	Allergic reactions/anti-inflammation cancer therapy	Asthma, COPD, rheumatoid arthritis	Cushing syndrome diagnosis, brain tumors, cancer-induced nausea/vomiting
Adverse effects	Only at high and chronic doses Cushing's syndrome / hyperglycemia / osteoporosis / increased infection risk Hyperaldosteronism if mineralocorticoid activity only		

*At high chronic doses, you can develop Cushing's syndrome: because of the negative feedback loop, the drugs overtime will shut down the adrenal glands, relying exclusively on the drugs.

NSAIDs (Ch. 71)

Mechanism of Action





- Ex: Aspirin and ibuprofen
- They work by blocking the active site of the enzymes COX-1 and/or COX-2 depending on if the NSAID is selective or not.
- Damaged cells release arachodonic acid – COX-1 and COX-2 are enzymes that convert it to prostaglandin H2. Those prostaglandins are then converted into other chemicals that cause inflammation and pain. There are active sites on COX-1 and 2 that bind to the prostaglandins that lead to their activation.
- Note: On the top left picture, COX-1 is constitutive - this means that it is always on, it's default state is to be active at any time. COX-2 is inducible - this means it is turned on and off.
- Aspirin works by entering this active site for these molecules and breaks off so it permanently blocks the enzymes (meaning the effect is temporary until these enzymes are recycled).
- Ibuprofen works by entering the active site but it doesn't change the enzyme so its not permanently blocking the enzymes binding site. Eventually ibuprofen can be released from the active site and cox-1 and 2 would be free to bind to other molecules. While the NSAID is bound, the enzyme can't bind prostaglandins–this prevents the pain signalling.

Something to note is that COX-1 and COX-2 enzymes are involved in producing gastroprotective prostaglandins. By blocking COX-1 and 2, we are removing this gastroprotective effect. This is why taking NSAIDS can lead to GI complications such as ulcers.

Hypothesis that anti-inflammatory prostaglandins (PGs) were produced through constitutive expression of COX-1, whereas the proinflammatory PGs were produced via induction of the COX-2 isoform. The traditional NSAIDs were known to inhibit both isoforms of COX and their adverse GI toxicities were attributed to the inhibition of gastroprotective PGs produced via the COX-1 pathway. Shortly thereafter, scientists from the academic community and

pharmaceutical companies focused their efforts on the design of selective COX-2 inhibitors in order to develop superior anti-inflammatory and analgesic agents with reduced adverse effects compared to traditional NSAIDs

COX Inhibitors Classification

There are two generations of NSAIDs that work differently.

- The only NSAID that is used for **prevention of MI and stroke is Aspirin** because it blocks Thromboxane A2 which is a platelet aggregator in the body.
    - No Tx A2 = no platelet aggregation = increased risk of bleeding. None of the other NSAIDS have this property.
- Some of the second generation NSAIDS can increase the risk of MI and stroke.
- **2nd generation** is just as effective as first but has a **lower risk for GI side effects**, but increased risk for MI or stroke

Another thing to note is that acetaminophen is not an NSAID. Acetaminophen does NOT reduce inflammation. It has analgesic and antipyretic properties but it does nothing for inflammation.

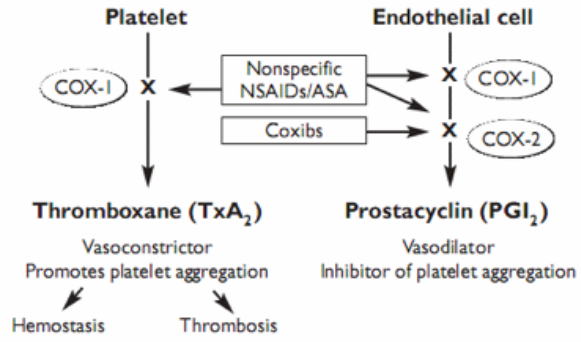
	First-Generation NSAIDs: Aspirin	First-Generation NSAIDs: All Others	Second-Generation NSAIDs (Coxibs)	Acetaminophen
INDICATIONS				
Inflammation	Yes	Yes	Yes	No
Pain	Yes	Yes	Yes	Yes
Fever	Yes	Yes	No	Yes
Prevention of MI and stroke	Yes	No	No	No
ADVERSE EFFECTS				
Gastric ulceration	Yes	Yes	Yes*	No
Renal impairment	Yes	Yes	Yes	No
Bleeding	Yes	Yes	No	No
MI and stroke	No	Yes	Yes	No
Liver damage with overdose	No	No	No	Yes

Studies conclusively demonstrated that selective COX-2 inhibitors may tip the natural balance between prothrombotic thromboxane A2 (TxA2) and antithrombotic prostacyclin (PGI2) potentially increasing the possibility of a thrombotic cardiovascular event - VIOXX

- Platelets do not have a nucleus.
- Irreversible COX-1 inhibition = forever
- Coxibs: decrease vasodilation → increases vasoconstriction

You would think that the blocking of the COX enzymes would cancel out the vasoconstriction and vasodilation and therefore remain the same. This is not true.

- Because platelets do not have a nucleus, they cannot replace the COX enzymes that are



inhibited. The blocking of the thromboxane is going to go on for as long as the platelets live (about 1 week).

- On the other hand, the endothelial cells have a nucleus and can replace the COX enzymes that are being inhibited, so that over a long period of time, the inhibition of prostacyclin will diminish over time so you will have more vasodilation and less platelet aggregation.

Aspirin - General Infos

Irreversible COX inhibitors:

- COX-1 actions: MI & stroke prophylaxis
- COX-2 actions: pain, fever & inflammation
- Adverse effects: gastric ulcers & renal impairment

Pharmacokinetics:

- Excellent oral availability
- 80-90% plasma protein-bound
- Half-life low dose = 2h (1st order) / High dose = 20h (0-order)
- Kidney excretion: alkaline urinary pH increases clearance

Aspirin, also known as **Acetylsalicylic acid,** has been used for thousands of years. It was discovered to be a molecule found in willow tree leaves and bark and gets converted to this active chemical in our bodies – people used to chew them to relieve any discomfort before they even knew how it worked.

Aspirin and ibuprofen are considered to be non-selective COX inhibitors, meaning they bind to both COX-1 and 2. By blocking COX-1, you prevent platelet aggregation and therefore risk of MI and stroke and prevent gastroprotective effects. By blocking COX-2, you reduce fever, pain and inflammation because you're blocking the proinflammatory response. There is a risk of ulcers due to the inhibited gastroprotective effects of COX.

Studies have shown that NSAID-induced sodium retention in healthy and elderly patients is mediated by the inhibition of COX-2, whereas a decreased glomerular filtration rate is associated with inhibition of COX-1. These studies confirm that both COX isoforms are involved in renal physiology.

COX-1–mediates prostaglandins that are involved with protection of the stomach lining
COX-2–mediates prostaglandins responsible for pain and inflammation

Aspirin - Therapeutic Uses

Action	Examples
Anti-Inflammation	**Drug of Choice: Arthritis (Rheumatoid, Osteo, Juvenile)** Other indications: Rheumatic Fever; Tendinitis Required dosage > Analgesia or Antipyretic
Analgesia	**Mild to Moderate Pain** **Best in Joints, Muscles & Headache** / Poor for intense Visceral pain No tolerance/dependence → Safer than Opioids
Antipyretic	Drug of Choice for Adults / **Contraindicated in children!!** Only ↓ Temperature induced by inflammatory pyrogens
Dysmenorrhea	↓ Prostaglandins in Uterus → **↓ Cramps** **Ibuprofen > Aspirin**
Antiplatelet Aggregation	#1 Use of Aspirin Today → **More on that one NEXT WEEK** Recommended if risk/previous history of Strokes or Myocardial Infarcts
Cancer Prevention	**Colorectal Cancer:** Low dose ↓ incidence & mortality via COX-2 Inhibition Mixed evidence for all other solid tumors

Question

You are a nurse working in a community setting and a mother asks if she could give her 2y.o. child aspirin. You reply:

- NO! Used to be given to children if they were sick but it was linked with **REYES SYNDROME**. It affects young children and can cause swelling in the liver and brain. Acetaminophen = better option.

Aspirin Adverse Effects

➔ Most common during long-term anti-inflammatory use
➔ Most are uncommon unless risk factors present

- Gastric ulcers, perforation & bleeding
  - This is due to the blocking of COX-1 enzymes which stimulate the secretion of gastric secretions to form a barrier.
  - Risk factors = age, smoking & alcohol, history of ulcers
  - Prophylaxis: proton pump inhibitor & H2 antagonists
- Bleeding: antiplatelet action
  - Discontinue 1 week before elective surgery
- Acute renal impairment: edema & increased blood urea nitrogen
  - Risk factors = age, hepatic cirrhosis, heart failure, kidney damage
- Salicylism: high levels of salicylic acid in the body
  - Light early signs of aspirin toxicity (ex. tinnitus)
- Reye's syndrome: rare but mortality = 30-40%
  - Link between NSAIDs + chickenpox/influenza in kids → use acetaminophen
- Others: hypersensitivity reactions, teratogen + prolonged labor

Aspirin - Interactions & Poisoning

Significant interactions:

- Anticoagulants: increased antiplatelet effect

- Glucocorticoids: increased risk of gastric ulcers
- Alcohol: increased risk of gastric bleeding
- Other NSAIDs: decreased MI/stroke prophylaxis
- Angiotensin inhibitors: increased renal impairment
- Decreased vaccine effectiveness
    - because these drugs are antiinflammatory, and by preventing the antiinflammatory response you're preventing the effectiveness of the vaccines.

Acute poisoning:

- Acute medical emergency = 20-25g for adults; 4g for children
- Salicylism alkalosis → respiratory depression → acidosis + electrolyte imbalance → coma & death
- Treatment: respiratory support + bicarbonate infusion (to neutralize some of the acid buildup, and hopefully reverse the acidotic state) and discontinue the drug.

<u>Other 1st Gen NSAIDs</u>

- Main difference vs. Aspirin → **reversible COX inhibitors**
- As such:
    - Slightly less renal & GI adverse effects
    - Increased risk of stroke and MI
- All have similar clinical safety & efficacy
- Unexplained individual variations in response & tolerance

Ibuprofen (Advil, Motrin, etc.)

- Greater relief of dysmenorrhea than aspirin
- Decreased risk of GI bleeding & antiplatelet than aspirin

Recent study: ductus arteriosus closure - Indomethacin reduces need for surgery

- Ductus arteriosus is a blood vessel that allows blood to go around the baby's lungs before birth. Soon after the infant is born and the lungs fill with air, the ductus arteriosus is no longer needed. Most often closes a couple days after birth.
- If the vessel doesn't close → Indomethacin (indocin) is an NSAID used to close the patent ductus arteriosus (PDA).
- Indomethacin → blocks the enzyme cyclooxygenase inhibiting prostaglandin synthesis thereby facilitating ductal closure.

<u>2nd Gen NSAIDs: Coxibs</u>

- Theory: COX-2 selective inhibition = decrease pain/fever/inflammation + no GI ulcers
- Reality: only small decrease in GI ulcers & huge increased risk of MI & stroke

- VIOXX scandal: VIOXX was made by Merck as a selective COX-2 inhibitor. It was marketed to treat osteoarthritis, acute pain and period cramps and scientists had really high hopes that it would work. Early on, there was evidence supporting an increased cardiovascular risk but this evidence was ignored/fudged. Data was altered and the drug

was produced. VIOXX rapidly became a blockbuster drug bringing in millions of dollars per year. In 2004, Merck removed the drug from the market because studies showed a huge increase in heart attacks and strokes from patients taking this medication. The data could no longer be ignored – too many adverse events were being reported. It cost Merck hundreds of $ in legal expenses and is one of the most widely used drugs to be pulled from the market.

- Prototype: Celecoxib
    - Proven to have better efficacy and be safer
    - Similar uses & adverse effects as other NSAIDs
    - Extra use: decrease colorectal cancer risks in FAP patients
    - GI ulcers: increased safety at 6 months, disappears at 12 months (risk becomes the same as other NSAIDs)
    - Significant interaction: increases warfarin anticoagulation action
        - monitor closely for risks of bleeding

Question

Your friend went out drinking last night and now has a bad headache. He asks you if he should take Tylenol. You reply:

- NO! Alcohol enhances acetaminophen metabolism into a toxic product, potentially causing liver damage.

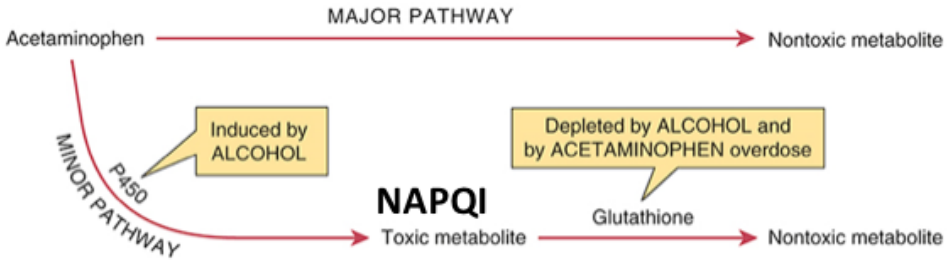
The Black Sheep: Acetaminophen

- Analgesic & antipyretic actions → best option
- No antiinflammatory & antiplatelet effects
- No gastric ulcers, renal impairment & Reye's syndrome
- Hypothesis: CNS-selective COX inhibition
- Potential risk of hypertension with daily intake
- Interactions: increases warfarin action / decreases vaccine power

Acetaminophen mechanism of action:

- It is metabolized in two pathways by the liver.
- The major pathway converts it into a nontoxic metabolite.
- The minor pathway involves the p450 enzymes that convert it into a toxic metabolite called NAPQI. This metabolite is normally neutralized by glutathione.
    - When you drink alcohol and take acetaminophen, the p450 enzymes are induced by alcohol so there's a much greater amount of toxic metabolites in your system.
    - You need a lot of glutathione to neutralize this amount of toxic metabolite. What happens is the body runs out and the toxic metabolite accumulates → causes an overdose. The liver is unable to metabolize both acetaminophen and alcohol, and cell death may result.
- Treatment (antidote) is acetylcysteine which increases the amount of glutathione available so the toxic metabolite is converted into a non-toxic form.

*nb. Glutathione is an antioxidant, an agent that prevents certain highly reactive, oxygen-containing molecules (ie. reactive oxygen species) from damaging the cells.



Acute toxicity: Liver damage
- Overdose + alcohol
- Hepatic necrosis = 48-72h
- Tx: acetylcysteine → increases glutathione
    - Nb. acetylcysteine is the precursor to glutathione

Nursing Capsule: AHA Statement - Chronic Pain & COX Inhibitors
Musculoskeletal pain management in cardiovascular event high risk patients (only move to next step if previous one fails):
- Step 1: non-drug interventions → physical therapy, heat/cold applications, weight loss
- Step 2: acetaminophen or aspirin are preferred (because they have the smallest CVS risk compared to the others)
- Step 3: other non-selective NSAIDs (ex. Naproxen, Ibuprofen)
- Step 4: COX-2 selective inhibitors (ex. Celecoxib)
    - Opioid if pain too intensive
    - This is the last resort because non-selective NSAIDs have a higher risk of CVS events compared to selective NSAIDs

➔ Try the minimum effective dose for the shortest amount of time to reduce risks of toxicity.
➔ For high risk of thrombosis patients: add low-dose aspirin + proton pump inhibitor or H2-antagonist (to reduce risk for GI ulcers)

Headache Medications (Ch. 30)

PATHO REVIEW
Migraine
- Episodic headaches
    - 4-72h at a time
    - With or without aura
    - Women > men
- Common manifestations:
    - Pulsatile pain
    - Nausea/vomiting

    - Photo/phonophobia
- Multifactorial disorder with several comorbidities
    - Includes: GI, pulmonary, CVS, neurological, sleep and psychiatric disorders

Migraine Aura

People suffering from migraines often know when they're going to get one because they see this "aura" - a visual disturbance

Episodic vs. Chronic Migraine

- Chronic migraines: 15 days of migraine/month or 3+ months of episodic migraines
- Prophylactic Tx relieves Sx before start of migraine which is what we want to do

Migraine: Pathophysiology

- Involvement of trigeminal nerves; cortical depression and vasomotor activity
- Clinical phases of a migraine:
    - 1. Premonitory → Sx hours before aura and onset of headache (ex. Neck pain, yawning)
    - 2. Migraine aura (~1h) → cortical spreading depression (CSD) from occipital lobe
        - Visual Sx caused by decreased electrical activity & blood flow to occipital area
    - 3. Headache → several proposed pain mechanisms (see next part)
    - 4. Recovery (several hours)

Proposed Headache Mechanisms

1. Activation of trigeminal cervical afferents
   ↓
   Release of vasoactive peptides + inflammatory mediators → CGRP
   ↓
   Activation of cerebral vessel nociceptors
2. Abnormal processing of trigeminal pain afferent signals at thalamus & primary sensory cortex
3. Central sensitization (allodynia) of the thalamus
4. Dilation of carotid artery terminal branches

Preclinical evidence suggests that, during a migraine, activated primary sensory neurons (meningeal nociceptors) in the trigeminal ganglion release CGRP from their peripherally projecting nerve endings located within the meninges. This CGRP then binds to and activates CGRP receptors located around meningeal vessels, causing vasodilation, mast cell degranulation, and plasma extravasation. Human observations have further implicated the role of CGRP in the pathophysiology of migraine. Activation of primary sensory neurons in the trigeminal vascular system in humans can cause the release of CGRP.

- During some migraine attacks, increased concentrations of CGRP can be found in both saliva and plasma drawn from the external jugular vein.

CGRP (calcitonin gene-related peptide) – produced in central and peripheral neurons. It is a potent vasodilator and functions in the transmission of nociception (aka pain).

Migraine & Estrogen

- Increased estrogen levels (ex. menstruation)
    - Stimulation of trigeminal ganglia
    - Vasoactive regulation at vascular smooth muscles & hypothalamus
- No direct link between estrogen & increased frequency & severity of migraines
    - Only hypothesized to explain sex differences

BACK TO PHARM

Treatment Overview

- Role of CGRP & 5-HT in migraine
    - 1. CGRP levels rise during migraine attack while 5-HT (ie. serotonin) levels drop
    - 2. 5-HT administration can decrease CGRP release
- Theory: decreased CGRP = decreased vasodilation = decreased nociception transmission = decreased pain

The activation of 'trigeminovascular system' causes release of various vasodilators, especially CGRP that induces pain response. At the same time, decreased levels of the neurotransmitter serotonin have been observed in migraineurs. Serotonin receptors have been found on the trigeminal nerve and cranial vessels and their agonists, especially triptans, prove effective in migraine treatment. It has been found that triptans act on trigeminovascular system and bring the elevated serum levels of key molecules like CGRP to normal (increase serotonin, and decrease CGRP).

- Non-pharmacological interventions
    - On a daily basis: healthy exercise, sleeping and diet patterns decrease the intensity and frequency of migraines
    - During migraine attack: relax in dark quiet room + ice pack on neck
- Available medications aim to:
    - 1. Abort ongoing migraines → decrease pain, nausea & vomiting
        - Mild to moderate pain: NSAIDs (non-specific drugs)
        - Moderate to severe pain: 5-HT agonists (migraine-specific drugs)
        - Last resort: opioids
    - 2. Prevent future migraines → anti-epileptic / beta-blockers / tricyclic antidepressants
    - 3. Adjunct drugs: antiemetics (ex. metoclopramide) → can allow PO administration of above drugs.
        - If you are experiencing a migraine and N/V and taking PO pills to stop it without addressing the N/V, you're just going to vomit the medication. Taking an anti-emetic will address the N/V so the other PO medications can be taken.

- Migraine prophylaxis should be considered when one or more of the following are present:
    - 1) recurring migraines that significantly interfere with the patient's daily activities, despite acute treatment
    - 2) frequent headaches
    - 3) failure, overuse, or contraindication of acute treatments
    - 4) adverse effects of acute treatment
    - 5) presence of rare migraine conditions which can potentially cause neurologic damage

A good example of a pre-emptive approach to treatment is the patient who suffers from migraine headaches triggered by sexual activity or by exercise. Can take NSAIDS beforehand. Preventive would be more in general. Preemptive is more time-limited

Nursing Capsule: Medication Overuse Headache (MOH)
*Patient education opportunity: chronic use of headache medication CAN trigger headaches!!

As each dose of medicine wears off, the pain comes back, leading them to take even more. This overuse causes your medicine to stop helping your pain and actually start causing headaches. Medication-overuse headache, in contrast, is a dull constant headache which is often worse in the morning. It is present on most days or part of every day. The need to alleviate these withdrawal symptoms perpetuates further use of painkilling drugs and can result in a cycle of medication overuse.

- Affects all abortive migraine medications
- Rebound headache withdrawal intensity:
    - Triptans (5 HT agonist) = mild
    - Analgesics & ergots = longer + intense
- Prevention:
    - Abortive drug use: < 2-3x/week
    - Alternate between abortive drugs
    - Initiate non-pharmacological & prophylactic measures

Ways to prevent MOH but the treatment is to discontinue the abortive medication.

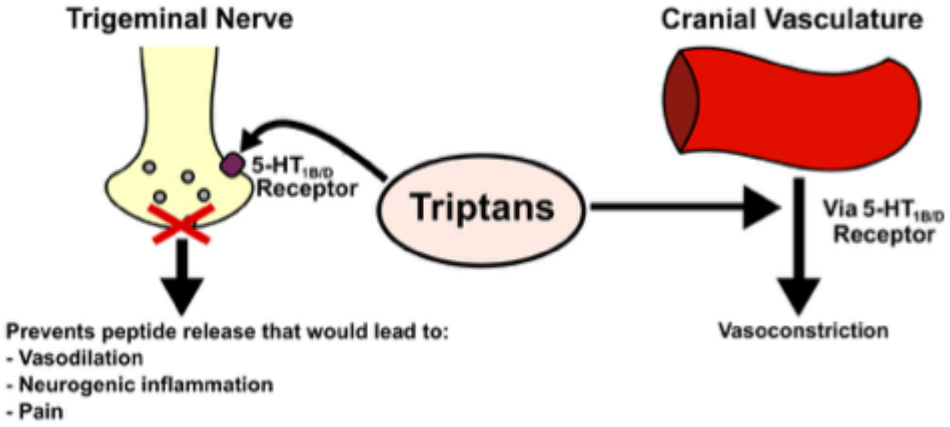
1. Medication-overuse headache (MOH) is a chronic daily headache and a secondary disorder in which acute medications used excessively causes headaches in a headache-prone patient.
2. MOH is clinical diagnosis and a history of analgesic use more than 2-3 days per week in a patient with chronic daily headache is indicative of this diagnosis.
3. MOH most commonly occurs in people with primary headache disorders like migraine, cluster, or tension-type headaches using less effective or nonspecific medications resulting in inadequate treatment response and re-dosing
4. MOH development is linked to baseline frequency of headache days per month, acute medication class ingested, frequency of acute medications ingested, and other risk factors.

5. MOH has been found to render headaches refractory to both pharmacological and non-pharmacological prophylactic medications, and also reduces the efficacy of acute abortive therapy for migraines.
6. The most effective method to treat MOH is discontinuation of the medication that is overused and a combination of pharmacological, non-pharmacological, behavioral and physical therapy interventions.
7. Use of certain classes of acute medications such as opioids, barbiturate-containing analgesics and butalbital, aspirin and caffeine is associated with increased risk of chronic migraine

<u>1. Serotonin 1B/1D Agonists: Sumatriptans</u>

Action:

- Triptans are serotonin (5-HT) agonists with high affinity for 5-HT1B and 5-HT1D receptors.
- Migraine returns ~ 40% of patients
- Uses: relief of all migraine symptoms by causing cranial vasoconstriction, most likely through action at postsynaptic 5-HT1B receptors on the smooth-muscle cells of blood vessels.
- It is also now theorized that triptans also block the release of vasoactive peptides from the perivascular trigeminal neurons through their action at presynaptic 5-HT1D receptors on the nerve terminals.
- In addition, triptans **bind to presynaptic 5-HT1D receptors in the dorsal horn**, and this binding is thought **to block the release of neurotransmitters** that activate second-order neurons ascending to the thalamus. **Triptans may also facilitate descending pain inhibitory systems**.
- Sumatriptan is most effective when taken early at the start of a migraine. It does not prevent future migraines or lessen how often you get migraine attacks - ABORTIVE!



Kinetics:

- PO, Nasal or Subcutaneous administration
- MAO metabolism → half-life = 2.5 hours

Adverse effects:

- Teratogen!!!
- 50% of patients → chest pressure
- Very rare: coronary vasospasms

Interactions:

- Other triptans/Ergot alkaloids → additive effects
- MAO & reuptake inhibitors → increases effects

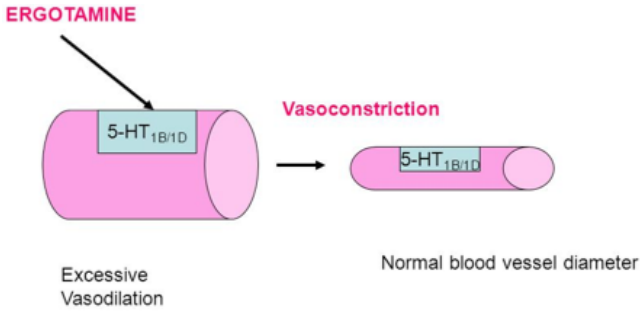
Other Triptans Advantages:

- Naratriptan → delayed onset + long duration
- Rizatriptan → most consistent efficacy
- Almotriptan → chest pressure only in 0.3% patients
- Frovatriptan → lowest rate of migraine return
- Eletriptan → fastest onset

2, Ergot Alkaloids

Ergotamine

- Alpha-adrenergic + DA + 5-HT1B/1D partial agonist
- Mechanism = triptans + other unknown effects
- 2nd line drug for migraine attacks
- It has biological activity as a vasoconstrictor
- Used to treat acute migraines (sometimes with caffeine). The common form of prescription is Cafergot which is a combination of caffeine and ergotamine.
- Derived from a fungus ergot
- Mechanism of action is complex: The molecule shares structural similarity with neurotransmitters such as serotonin, dopamine, and epinephrine and can thus bind to several receptors acting as an agonist. The anti-migraine effect is due to constriction of the intracranial extracerebral blood vessels through the 5-HT1B receptor, and by inhibiting trigeminal neurotransmission by 5-HT1D receptors. Ergotamine also has effects on the dopamine and norepinephrine receptors. Its side effects are due mainly to its action at the D2 dopamine and 5HT1A receptors



Kinetics:

- PO, sublingual or rectal administration
- CYP3A4 metabolism → half-life = 2 hours
- Effects observed more than 24h post-administration

Adverse effects:

- Increased nausea and vomiting = 10% of patients
- Known teratogen
- Increased physical dependence

Interactions:

- Triptans/other ergot alkaloids → additive effects
- CYP3A4 inhibitors → increased toxicity → ERGOTISM
    - if you are taking another drug that is a CYP3A4 inhibitor, you are not metabolizing the ergotamine and there is an increased toxicity that leads to ergotism.

Dihydroergotamine

Advantages:

- Same mechanism & efficacy
- No nausea & physical dependence
- Decreased peripheral vasoconstriction

Drawbacks:

- Prominent diarrhea
- Parenteral & nasal spray only

History Capsule: Ergotism & Witches

- Ergotism is caused by a fungus that affects rye, wheat and other cereal grasses. When first infected, the flowering head of a grain will spew out sweet, yellow-colored mucus, called “honey dew,” which contains fungal spores that can spread the disease. Within them are potent chemicals: ergot alkaloids, including lysergic acid (from which LSD is made) and ergotamine (now used to treat migraine headaches).
- The alkaloids affect the central nervous system and cause the contraction of smooth muscle — the muscles that make up the walls of veins and arteries, as well as the internal organs.
- Toxicologists now know that eating ergot-contaminated food can lead to a convulsive disorder characterized by **violent muscle spasms, vomiting, delusions, hallucinations, crawling sensations on the skin**, and a host of other symptoms.
- Ergot thrives in warm, damp, rainy springs and summers. Those exact conditions had been present in 1691. Nearly all of the accusers lived in the western section of Salem village, a region of swampy meadows that would have been prime breeding ground for the fungus.
- At that time, rye was the staple grain of Salem. The rye crop consumed in the winter of 1691-1692 — when the first unusual symptoms began to be reported — could easily have been contaminated by large quantities of ergot. The summer of 1692, however, was dry, which could explain the abrupt end of the “bewitchments.” Still a hypothesis…

3. Analgesics

NSAIDs

- Aspirin + metoclopramide (antiemetic)
- Efficacy = Sumatriptan
- Less expensive and less adverse effects < Sumatriptan
- Excedrin is also used for migraines and consists of acetaminophen, aspirin and caffeine.
- Other NSAIDs: diclofenac/naproxen

Opioids

- Only severe migraines when other Tx failed
- Butorphanol nasal spray = preferred
    - CNS effects: sedation & dizziness
    - N/V are common
    - Increased perspiration is often experienced
- Meperidine = 2nd choice (increased adverse effects)

Preventive Agents

- Goal = decrease intensity + frequency + duration
- Indications = chronic migraines / severe migraines / failure of abortive drugs

Migraine headache: drugs for preventive therapy:

- **Beta-adrenergic blocking agents** (best prophylaxis option - effective > 70% of patients)
    - Metoprolol
    - Propranolol → interacts with 5HT receptors and inhibits production of NO.
- **Antiepileptic drugs** (only decrease frequency - cost & adverse effects > beta blockers)
    - Divalproex
    - Topiramate
- **Tricyclic antidepressants** (benefits = propranolol - cardiac adverse effects)
    - Amitriptyline
- **Estrogens** (for menstrual associated migraines +/- 2 days of menses - triptans can also help)
    - Estrogen gel
    - Estrogen patch

ANTIHISTAMINES (Ch. 70)

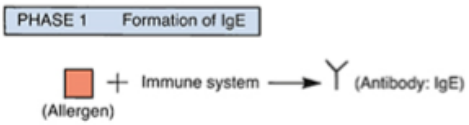
Histamine

Histamine is a compound involved in:

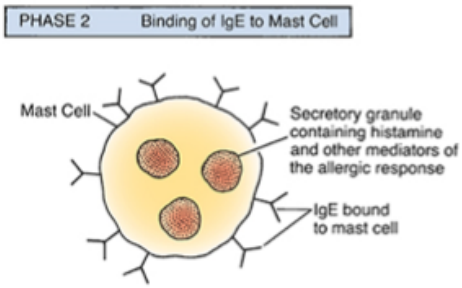
- immune responses
- regulating physiological function in the gut
- acting as a neurotransmitter for the brain, spinal cord, and uterus
- involved in the inflammatory response, and it is made by basophils and mast cells.

Clinical significance:

- Mild allergic responses
- Peptic ulcers

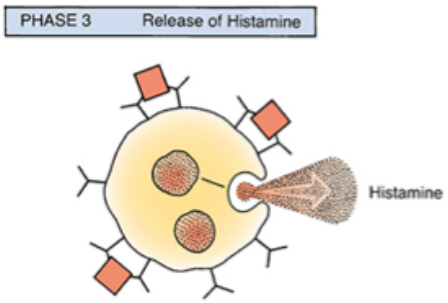


Histamine mainly increases the permeability of the capillaries to white blood cells and some proteins, to allow them to engage pathogens in the infected tissues



Most histamine in the body is made in granules in mast cells and in white blood cells (leukocytes) called basophils. Mast cells are especially numerous at sites of potential injury — the nose, mouth, and feet, internal body surfaces, and blood vessels.

We are interested in histamine release in an immunological context. Mast cells and basophil cells, if sensitized by IgE antibodies attached to their membranes, degranulate when exposed to the appropriate antigen.



So in summary, an allergen (such as pollen) makes the immune system make IgE antibodies. IgE antibodies bind to mast cells. This causes the mast cells to degranulate, or release histamine.. Histamine binds to H1 and H2 receptors. H1 receptor activation causes those potential effects listed. H2 receptors on the other hand cause gastric acid secretion.

Storage/synthesis

- Mast cells → GI, lungs, skin, CNS neurons

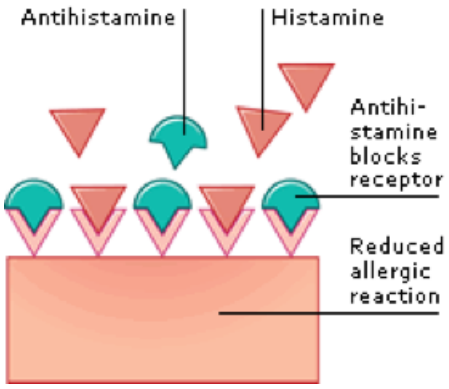
Histamine receptor effects:

- H1-receptors:
  - Vasodilation
  - Increased capillary permeability → edema
  - Bronchoconstriction (exogenous histamine only)
  - Cognition, memory, & sleep cycle
  - Pain, itching, and mucous secretions
- H2-receptors:
  - Gastric acid secretion

H1-Antagonists Pharmacology

Actions:

- Block histamine action (not release!) at the H1 receptor which is caused by IgE binding to mast cells
- Some are also muscarinic blockers
    - This lack of receptor specificity is why some first H1 receptor blockers have poor tolerance.
- Periphery: decreased pain, edema and mucous secretions
- CNS: 1st gen = sedation!! vs. 2nd gen = non-sedative
    - 1st gen has a greater range of side effects due to its lack of receptor specificity (ex. Benadryl/Diphenhydramine)
    - 2nd gen is more selective to peripheral H1 receptors, so it has reduced side effects (ex. Loratidine/Claritin)
- Sedation tolerance develops within days
- toxicity/overdose = CNS stimulation → convulsions
- Large margin safety



Therapeutic Uses:

- Mild allergic responses → hay fever, acute urticaria
- Anti-motion sickness effects: decreases nausea and vomiting
- Insomnia → via CNS sedation
- Fun fact: OTC insomnia meds = ineffective dose

Adverse effects:

- GI effects: nausea, constipation, diarrhea
- Elderly patients: dizziness and confusion
- Anticholinergic effects: dry mouth and increased bronchial mucus
- Interactions: alcohol and CNS depressants
- Caution with pregnancy and breastfeeding

H1-Antagonists Preparations

1st Gen agents:

- Promethazine: avoid if possible because it has profound anticholinergic effects in the elderly.
- Alkylamine: least sedation
- Advantage over 2ng gen: cost

Pharmacologic Effects of H_1 Antagonists Used for Systemic Therapy

Drug	H_1-Blocking Activity[a]	Sedative Effects[a]	Anticholinergic Effects[a]
FIRST-GENERATION AGENTS			
Alkylamines			
Brompheniramine	+ + +	+	+ +
Chlorpheniramine	+ +	+	+ +
Dexchlorpheniramine	+ + +	+	+ +
Ethanolamines			
Clemastine	+ to + +	+ +	+ + +
Diphenhydramine	+ to + +	+ + +	+ + +
Phenothiazines			
Promethazine[b]	+ + +	+ + +	+ + +
Piperazines			
Hydroxyzine	+ + to + + +	+ + +	+ +
Piperidines			
Cyproheptadine	+ +	+	+ +

2nd Gen agents:

- Similar efficacy & safety → choose cheapest
- Low CNS distribution - crosses the BBB at a lower rate because they are very polar
- Fexofenadine: best efficacy/safety ratio
- Interaction with some fruit juices

SECOND-GENERATION (NONSEDATING) AGENTS			
Cetirizine[c]	+ + +	+	±
Levocetirizine[c]	+ + +	+	±
Fexofenadine	+ + +	±	±
Loratadine	+ + to + + +	±	±
Desloratadine	+ + to + + +	±	±

[a] ±, Low to none; +, low; ++, moderate; + + +, high.

[b] Promethazine is contraindicated in children younger than 2 years owing to a risk of fatal respiratory depression. *Parenteral* promethazine can cause severe local tissue injury.

LAXATIVES (Ch. 79)

PATHO REVIEW

Terminus: Large intestine

Remember from pathophys, the large intestine is the last part of the GIT. Water is absorbed here and the remaining waste material is stored as feces and removed by defecation.
There are no villi in the large intestine, they are only in the small intestine. They increase surface area for better absorption of nutrients.

Colon

There are 3 states.

1. One is the irregular rhythm of contraction, which is baseline rhythm.
2. Then there's the **gastrocolic reflex** → gastric secretions increase colon motility
3. Finally there's the **defecation reflex**, which feces (the leftover of what cannot be absorbed) in the rectum goes into the internal anal sphincter

Constipation

- Infrequent/difficult defecation
    - Significant only if quality of life or health decrease
    - Frequency varies → look for individualized decrease in frequency (normal BM frequency is 3x/day to 3x/week)
- Common manifestation = rectal pain & bleeding, anal fissures, hemorrhoids
- Functional constipation = normal rate but difficult evacuation
    - Risk factors = sedentary lifestyle, dehydration, fiber-poor diet, increased emptying suppression
- Slow transit constipation = impaired colon motility or stool block
- Pelvic constipation = decreased pelvic muscle strength or anal sphincter relaxation
- Secondary constipation = complication of disorders or treatments
    - Ex. opioids, neurogenic or endocrine disorders (Parkinson's, diabetes), pregnancy, aging

BACK TO PHARM

General Considerations

Vocab:

- Laxative effect = slow production of soft stool
- Catharsis = prompt/accelerates evacuation of bowels
    - May be an effective means of ridding the lower GI tract of toxins. However, they carry a risk of electrolyte imbalances and dehydration, so they should be used cautiously.

Healthy Bowel Function:

- Fluid reabsorption for soft-but-formed stool
- Frequency of evacuation = large individual variations
- 20-60g dietary fibers daily → optimize bowel function

Constipation:

- Diagnostic: stool hardness > infrequent evacuation
- Best treatment: increase fluid and fiber intake
- Good adjuncts: mild exercises & laxatives (group III)

Other Laxatives Applications:

- Anti-helmintic (parasites) therapy adjuncts
- Pre-surgery bowel emptying (group I)
- Removing ingested poisons

Laxatives Contraindications:

- Any GI inflammation/injuries
- Long-term management of constipation
- Caution during pregnancy/breast-feeding

Bulk-Forming Laxatives

Examples	Psyllium / Methylcellulose (Group III)
Actions	≈ Dietary Fibers Non-digestable or absorbable Colon stretch → ↑ Peristalsis
Indications	Best for Constipation Irritable Bowel Syndrome (IBS) & Diverticulosis
Adverse Effects	No absorption = No Systemic Effects May exacerbate existing intestinal obstruction Esophageal Obstruction if insufficient Fluid with intake

- Psyllium is mainly used as a dietary fiber, which is not absorbed by the small intestine. It is used to relieve the symptoms of both constipation and mild diarrhea.
- The purely mechanical action of psyllium mucilage is to absorb excess water while stimulating normal bowel elimination/softening the stool.
- Psyllium can cause bowel obstructions and bloating. Choking is a hazard if psyllium is taken without adequate water as it thickens in the throat
    - ***Remind patients to take with a full glass of water/juice

Stimulant Laxatives

Examples	Bisacodyl; Senna (Group II) Castor Oil (Group I)
Actions	Stimulate Peristalsis Inhibit intestinal absorption & ↑ GI Secretions
Indications	Opioid-Induced Constipation Slow-Transit Constipation
Adverse Effects	Frequently Abused

- Works by stimulating enteric nerves to cause colonic contractions.
- It is also a contact laxative; it increases fluid and salt secretion
- Castor Oil has a fast action, acts on the small intestine and is too powerful for constipation management.
- Bisacodyl suppository can act in 15 min!

Osmotic Laxatives

Examples	Magnesium or Sodium Salts / Polyethylene Glycol (PEG)
Actions	Poorly Absorbed Salts → Osmotic Pull of Water Stretching of Intestinal Wall → ↑ Motility Low-Dose = Group II vs. High-Dose = Group I
Indications	Poison or Parasite Purge/Evacuation Pre-Surgery Emptying
Adverse Effects	Dehydration Kidney Impairment → ↑ Magnesium Imbalances Sodium Imbalances → ↑ Heart Condition

- PEG is an osmotically acting laxative, that is an inert substance that passes through the gut without being absorbed into the body.
- It relieves constipation because it causes water to be retained in the bowel instead of being absorbed into the body. This increases the water content and volume of the stools in the bowel, making them softer and easier to pass, as well as improving gut motility.

More Laxatives

Surfactant Laxatives	**Docusate Sodium or Calcium (Group III)**
Actions	↓ Feces Surface Tension → ↑ Water Penetration + Inhibit intestinal absorption & ↑ GI Secretions
Other Laxatives	**Lubiprostone (Group III)**
Actions	Chloride Channel Activator ↑ Intestinal Secretions & Motility
Indications	Chronic Idiopathic Constipation IBS with Constipation in women Opioid-Induced Constipation
Adverse Effects	GI Distress (Nausea & Vomiting) & Headaches Rare: Chest Pain + Difficulty Breathing

- Lubiprostone is a fatty acid that acts by specifically activating chloride channels on gastrointestinal epithelial cells, producing a chloride-rich fluid secretion. These secretions soften the stool, increase motility, and promote spontaneous bowel movements.

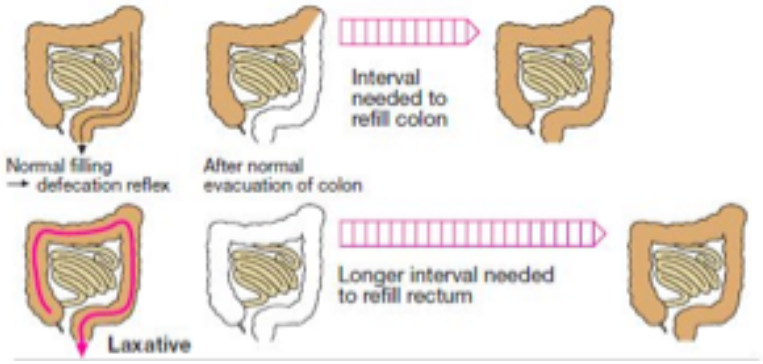
Colonoscopy Bowel Cleansing

Bowel Cleansers	**Infos**
PEG+Electrolyte Solution	**Safest option**: Isotonic → No dehydration or electrolyte imblance **Drawback**: Requires significant fluid intake
Sodium Phosphate	Discussed under osmotic laxatives **Advantage** over PEG: Easier Administration **Drawback**: Hypertonic → Dehydration/Electrolyte Imbalances
Salt Combination	Stimulant + Osmotic Laxatives **Advantage** over PEG: ↑ Cleansing Efficacy **Drawback**: Same as Sodium Phosphate

Nursing Capsule: Laxative Abuse

Causes:

- False belief of mandatory daily bowel movement + aggressive OTC laxative marketing
- Bowel emptying inhibits evacuation until ~ 2-5 days later → misdiagnosed as constipation



Consequences:

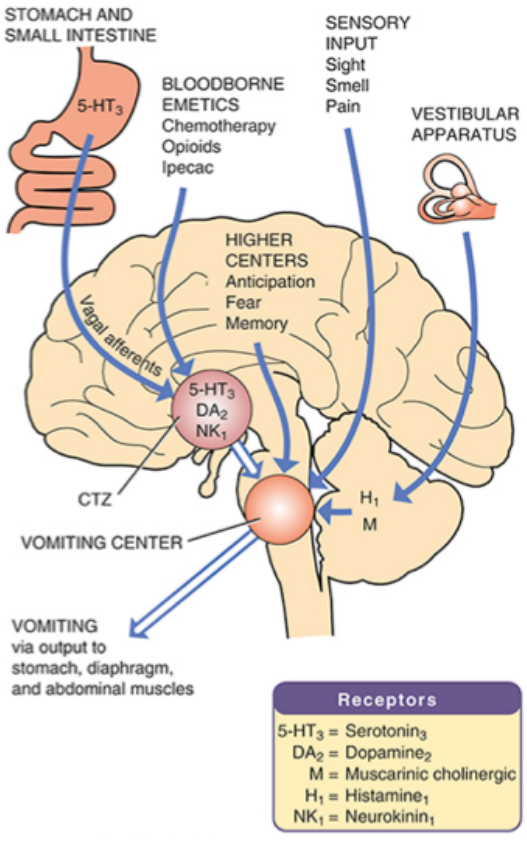
- Inhibition of normal defecation reflex → dependence on laxatives
- Dehydration, electrolyte imbalances, colitis

Treatment:

- Abrupt laxative discontinuation
- Patient education: anticipate few days without evacuation/stool quality > daily movement
- Suggest dietary fiber + daily exercises
- If laxative used again: short-term + lowest effective dose

ANTIEMETICS (beginning of Ch. 80)

- An antiemetic is a drug that is effective against vomiting and nausea.
- Typically used to treat motion sickness and the side effects of opioid analgesics, general anesthetics, and chemotherapy directed against cancer.



Emetic Response

Vomiting (pathophys review)

- Vomiting center in medulla = regulator
- Preceded by nausea & GI muscular events → parasympathetic control
- Nausea = tachycardia + hypersalivation before vomiting → subjective experience

Muscular events:

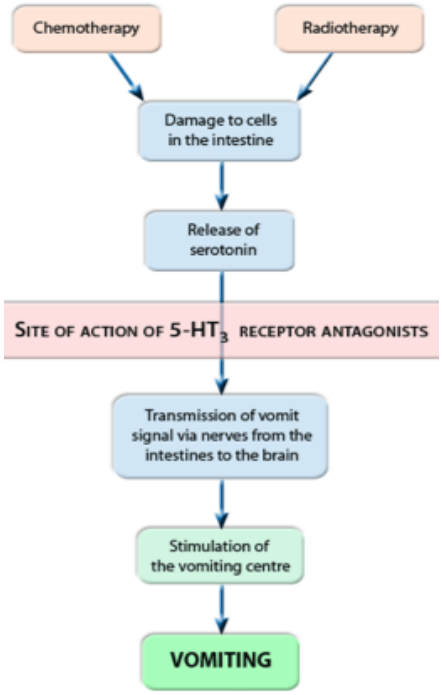
1. Duodenal + gastric retrograde peristalsis
2. LES relaxes + diaphragm & abdominal contraction
3. Increase in thoracic pressure force open UES → chyme expulsion
   Retching = muscular events without fluid expulsion

- Excessive vomiting → fluid, electrolyte & acid-base disorders
- Direct stimulation (increased ICP, tumor, lesion) → projectile vomiting

- Indirect stimulation → anxiety/pain, vestibular system, 5-HT or CTZ stimulation
- CTZ = chemoreceptor trigger zone → outside BBB → drug/toxins

Serotonin Antagonists

Examples	**Ondansetron / Dolasetron / Granisetron**
Actions	5-HT3 Antagonists at CTZ & GI Afferent Neurons
Indications	Chemotherapy-Induced Nausea & Vomiting (CINV) Nausea/Vomiting from Radiotherapy & Anesthesia
Adverse Effects	Headache / Diarrhea / Dizziness **Prolong QT interval**



- These drugs act by blocking serotonin from binding to the 5-HT3 receptor
- Most common is Ondansetron (Zofran) - used to prevent nausea and vomiting in chemotherapy and post-op pts
- Use of ondansetron has been associated with prolongation of the QT interval, which can lead to the potentially fatal heart rhythm known as torsades de pointes → abnormal heart rhythm that can cause sudden cardiac death.
    - So if the MD orders a huge IV dose of Ondansetron, you need to question it and see if the pt has any known cardiac Hx or get a baseline EKG
- Ondansetron is a highly specific and selective serotonin 5-HT_3 receptor antagonist. Serotonin is released by cells in the small intestine in response to chemotherapeutic agents and may stimulate vagal afferents (via 5-HT_3 receptors) to initiate the vomiting reflex.
- Palonosetron is a 5-HT3 antagonist, used to delay emetic response b/c it has a longer half-life (~ 40h)

Other Antiemetic Agents

Antiemetic Drugs: Uses and Mechanism of Action

Class	Prototype	Antiemetic Use	Mechanism of Antiemetic Action
Serotonin antagonists	Ondansetron [Zofran, Zuplenz]	Chemotherapy, radiation, postoperative	Block serotonin receptors on vagal afferents and in the CTZ
Glucocorticoids	Dexamethasone (generic only)	Chemotherapy	Unknown
Substance P/neurokinin$_1$ antagonists	Aprepitant [Emend]	Chemotherapy	Block receptors for substance P/neurokinin$_1$ in the brain
Dopamine antagonists	Prochlorperazine (generic only)	Chemotherapy, postoperative, general	Block dopamine receptors in the CTZ
Cannabinoids	Dronabinol [Marinol]	Chemotherapy	Unknown, but probably activate cannabinoid receptors associated with the vomiting center

- Most effective combination for chemo induced N/V: Serotonin antagonists + glucocorticoids
- CTZ: chemoreceptor trigger zone (CTZ) is an area of the medulla (in the brainstem) that receives inputs from blood-borne drugs or hormones, and communicates with other structures in the vomiting center to initiate vomiting.

- Extrapyramidal symptoms(EPS), also known as extrapyramidal side effects (EPSE), are drug-induced movement disorders that include acute and tardive symptoms.
    - Sx: dystonia (continuous spasms and muscle contractions), akathisia (motor restlessness), parkinsonism (characteristic symptoms such as rigidity), bradykinesia (slowness of movement), tremor, and tardive dyskinesia (irregular, jerky movements).
- Cannabinoids are 2nd line drugs if other antiemetics are not well tolerated
    - 2nd line drugs
    - Anticipate increased use

Drugs for Motion Sickness

Anticholinergics	Scopolamine [Transderm Scōp]	Motion sickness	Block muscarinic receptors in the pathway from the inner ear to the vomiting center
Antihistamines	Dimenhydrinate (generic only)	Motion sickness	Block H_1 receptors and muscarinic receptors in the pathway from the inner ear to the vomiting center

- Scopolamine:
    - Used for motion sickness and post-op nausea/vomiting. Sometimes also used pre-op to decrease saliva.
    - Can be given IV, SubQ, PO or skin patch
    - Usually referred to as a nonspecific anti-muscarinic
    - Most effective
    - Less toxicity with transdermal patch
    - Common ADE = drowsiness
    - Other side effects: dry mouth, blurred vision, headache, urinary retention, and dizziness can occur even at a low dose used in the transdermal patch
    - Overdose: tachycardia, dilated pupils, toxic psychosis, confusion, vivid hallucinations, seizures or coma
- Antihistamines:
    - See H1-blockers discussed earlier
    - Less effective vs. scopolamine + sedation effects = 2nd choice

Nursing Capsule: Chemotherapy & Pregnancy Nausea

Chemotherapy:

- Severe nausea & vomiting → fluid/electrolyte imbalances → patients discontinue treatment
- 3 types of chemotherapy-induced emesis
    - Anticipatory = memory from previous treatment emesis
    - Acute = minutes to 1 day post treatment
    - Delayed = >1 day post treatment
- Treatment: antiemetics most effective for prevention
    - Administer before chemotherapy

Nausea and Vomiting of Pregnancy (NVP)

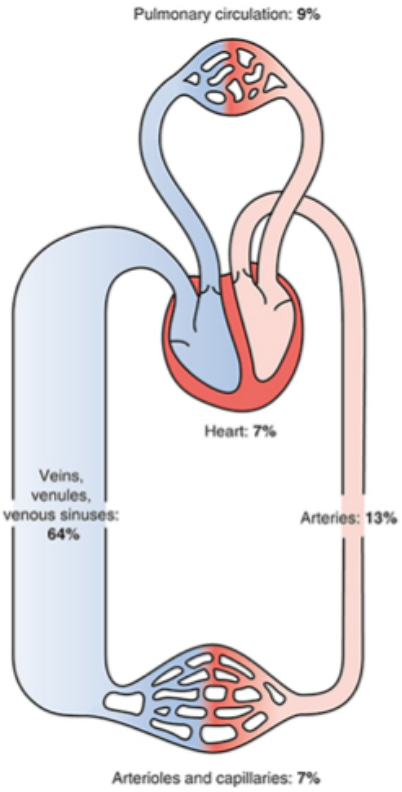
- 75% of pregnant women during 1st trimester
- 90% resolves before week 20
- Treatments:
    - Non-drug measures = small portions / avoid fatty & spicy foods

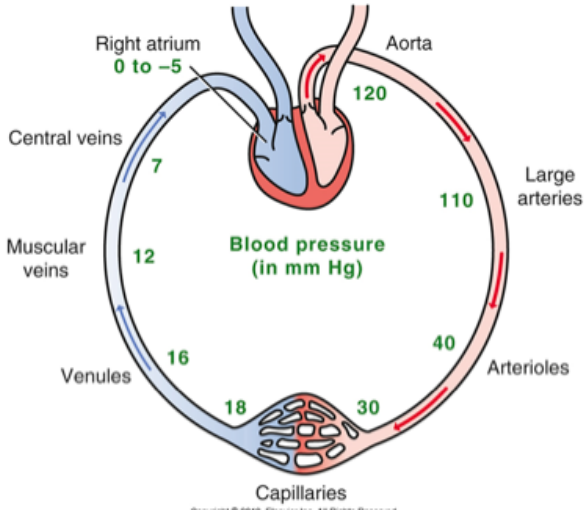
- Drug regimen: best & safest option = **doxylamine + vitamin B6 combination** (Diclectin/Diclegis)
  - Doxylamine is an antihistamine & drug combination of pyridoxine/doxylamine
  - Metoclopramide, ondansetron & methylprednisone = last resorts

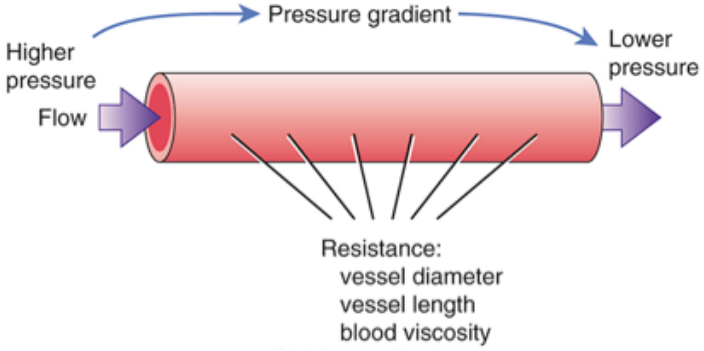
PATHO REVIEW

Hemodynamics Review (Ch. 43)

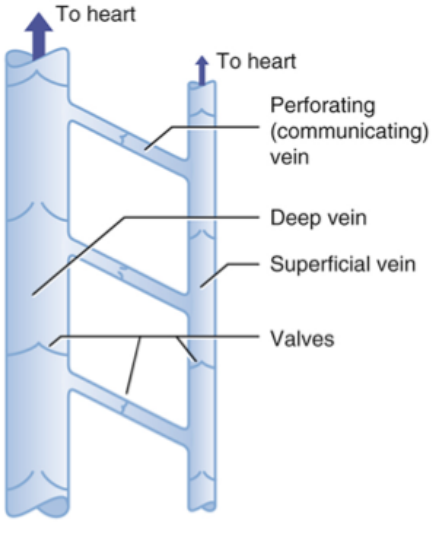
Flow, Pressure & Resistance

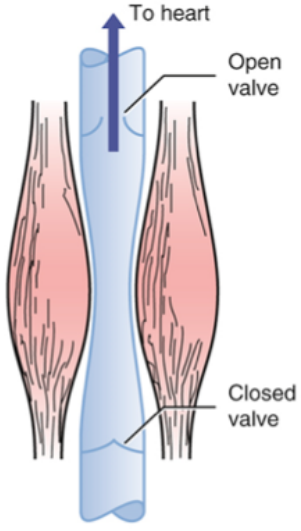






How blood gets back to the heart





Pressure & Resistance

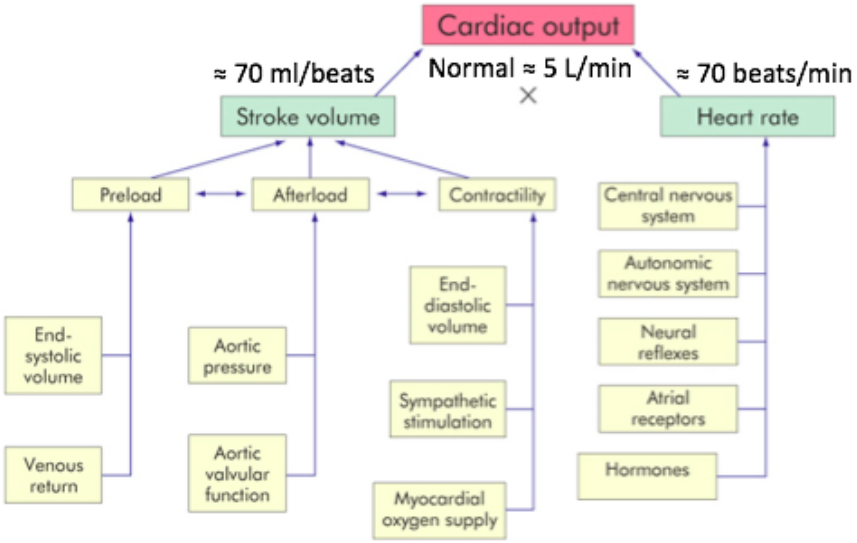
- Flow = pressure (BP) / resistance
  - Increased resistance → decreased flow
  - Increased pressure → increased flow
  - Constant flow: increased resistance → increased pressure
- Resistance = vessel diameter
- Series vs. parallel
- Flow does not equal velocity (riverbed analogy)
- Cross-sectional area ∝ 1/blood velocity

Poiseuille's Law:

$$R = \frac{8vL}{\pi r^4}$$

Cardiac Output (CO)

- Ejection Fraction = SV/EDV
  - Normal ~ 55-65%

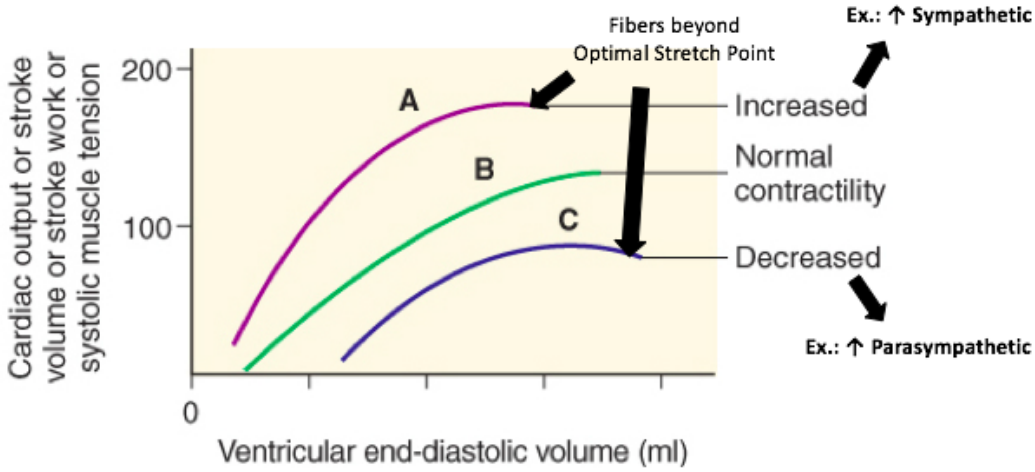


Determinants of Stroke Volume

- Preload = end-diastolic pressure
  - Increased preload (physiologic range) → increased SV
- Afterload = resistance to blood ejection
  - Increased afterload → decreased SV
- Contractility = contraction strength
  - Increased contractility → increased SV
  - Frank-starling Law

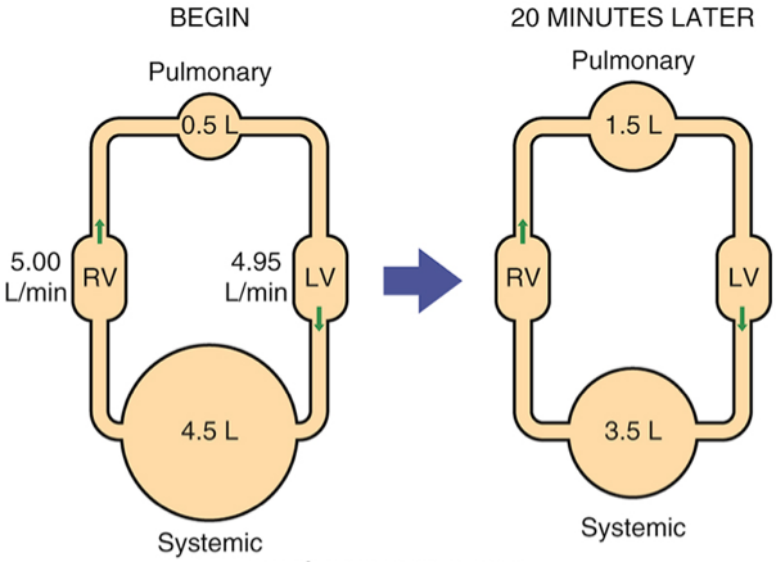
Frank-Starling Law

Increased Muscle tension (increased EDV) → increased contractility (increased SV)

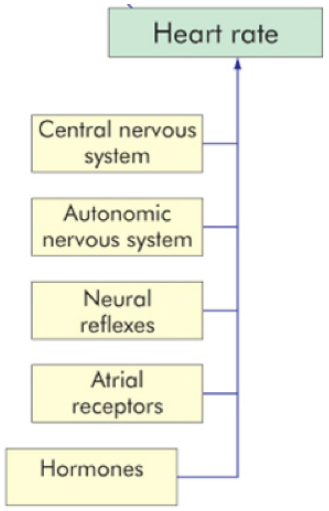


Systemic-Pulmonary Imbalance

Failing heart → systemic pulmonary imbalance → back-flow of blood

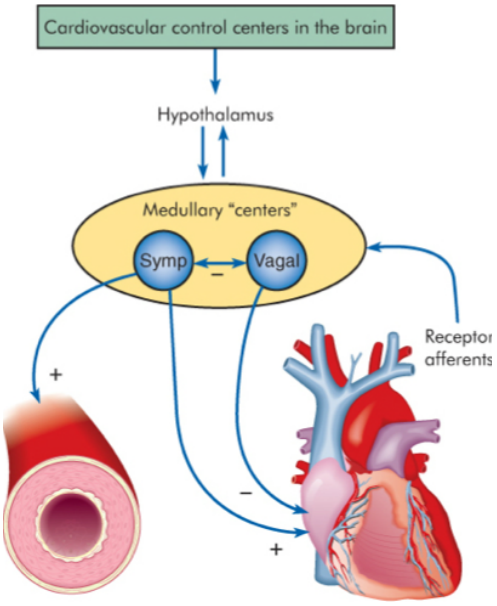


Determinants of Heart Rate



- Cardiovascular control centers = ANS + CNS
  - Medulla (HR & BP), hypothalamus (temperature), amygdala (emotions)
  - Vagal (parasympathetic) tone → resting HR
- Sinus arrhythmia:
  - Inspiration → increased HR
  - Expiration → decreased HR
- Baroreceptor Reflex:
  - Increased BP → decreased HR + vasodilation
  - Decreased BP → increased HR + vasoconstriction
- Hormones
  - Fight-or-flight → adrenal glands → increased NE/epi
  - Thyroid hormone (T3) → increased HR + contractility

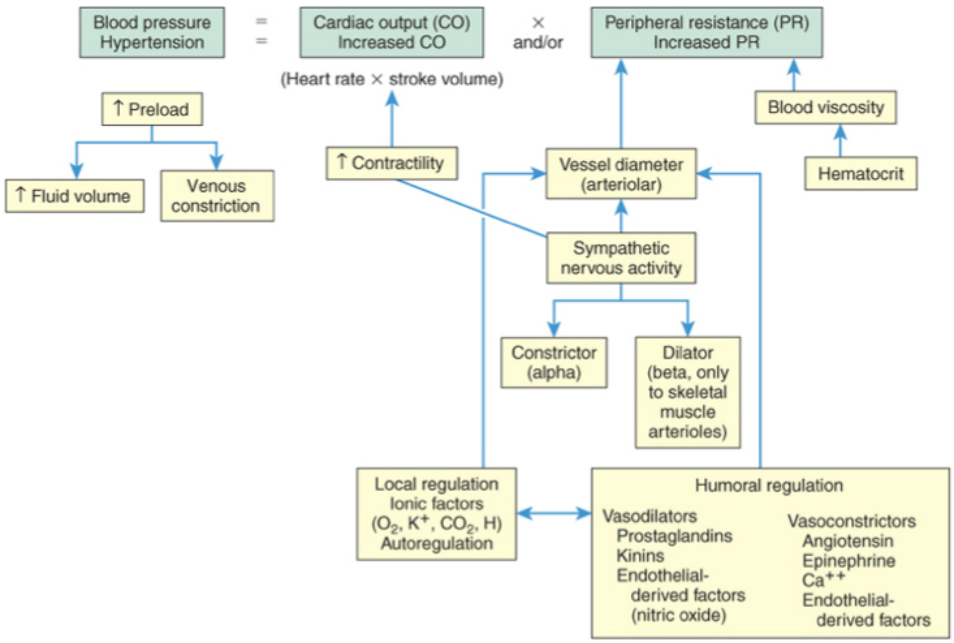
ANS Regulation of the Heart



- Unnecessary for heart beating
- Adjust heart function to the body's needs:
  - Vasodilation vs. vasoconstriction
  - HR (chronotropy)
  - Contractility (inotropy)
- Sympathetic increase in HR & contractility + vasomotor
- Parasympathetic only decreased HR

BP Regulation

- Pressure = flow (CO) x resistance (TPR) (V=IR)
- MAP = P_D + ⅓(Pulse pressure) = 92mmHg
  - Pulse pressure = P_S - P_D
- Hyperemia = increased blood flow
  - Active → exercise
  - Reactive → ischemia reperfusion injury



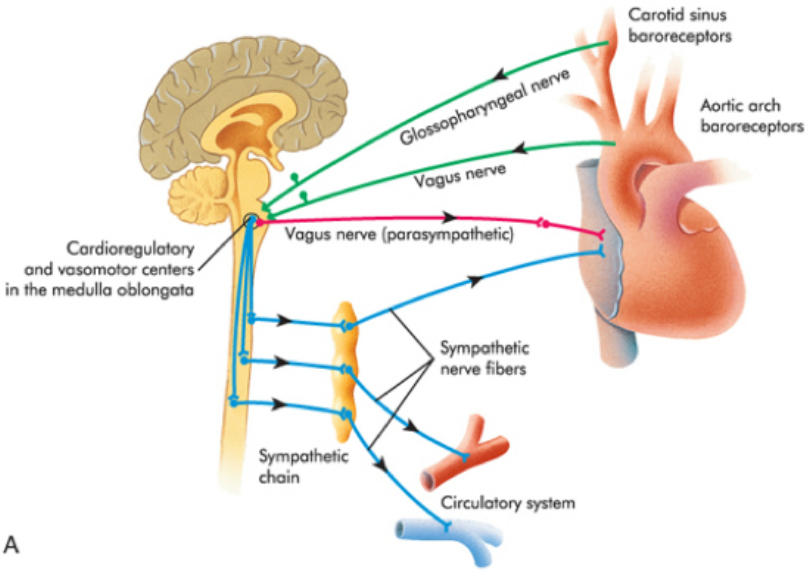
<u>Baroreceptor Reflex</u>

High BP reflex:

- Increased BP → increased stretch
  ↓
- Increased AP firing → increased parasympathetic + decreased sympathetic
  ↓
- Decreased HR & SV + vasodilation → decreased BP

Low BP reflex:

- Decreased BP → decreased stretch
  ↓
- Decreased AP firing → decreased parasympathetic + increased sympathetic
  ↓
- Increased HR & SV + vasoconstriction → increased BP



A

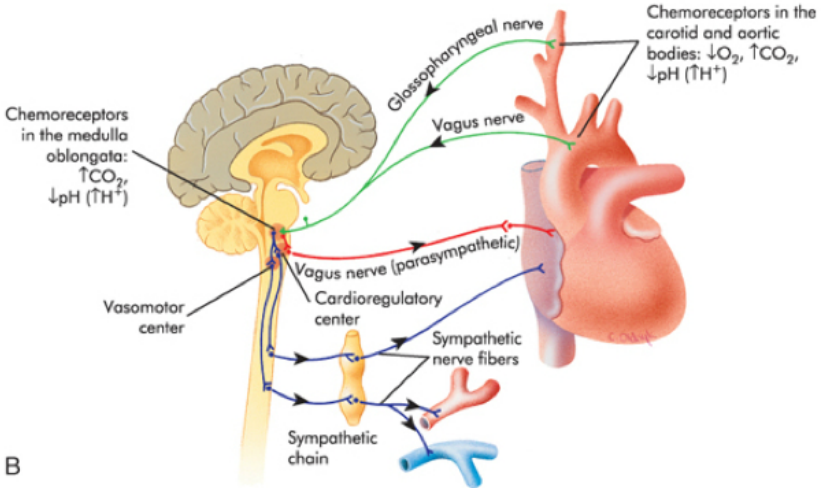
Chemoreceptor Reflex

Alkalosis/High O_2 reflex

- Decreased H+/P_{CO2} or increased P_{O2}
  ↓
- Increased AP firing → increased parasympathetic + decreased sympathetic
  ↓
- Decreased HR & SV + vasodilation → decreased BP

Acidosis/Low O_2 reflex

- Increased H+/P_{CO2} or decreased P_{O2}
  ↓
- Decreased AP firing → Decreased parasympathetic + Increased sympathetic
  ↓
- Increased HR & SV + vasoconstriction → increased BP



**Same chemoreceptors that control ventilation.

**Δ P_{O2} more significant than Δ pH or P_{CO2}

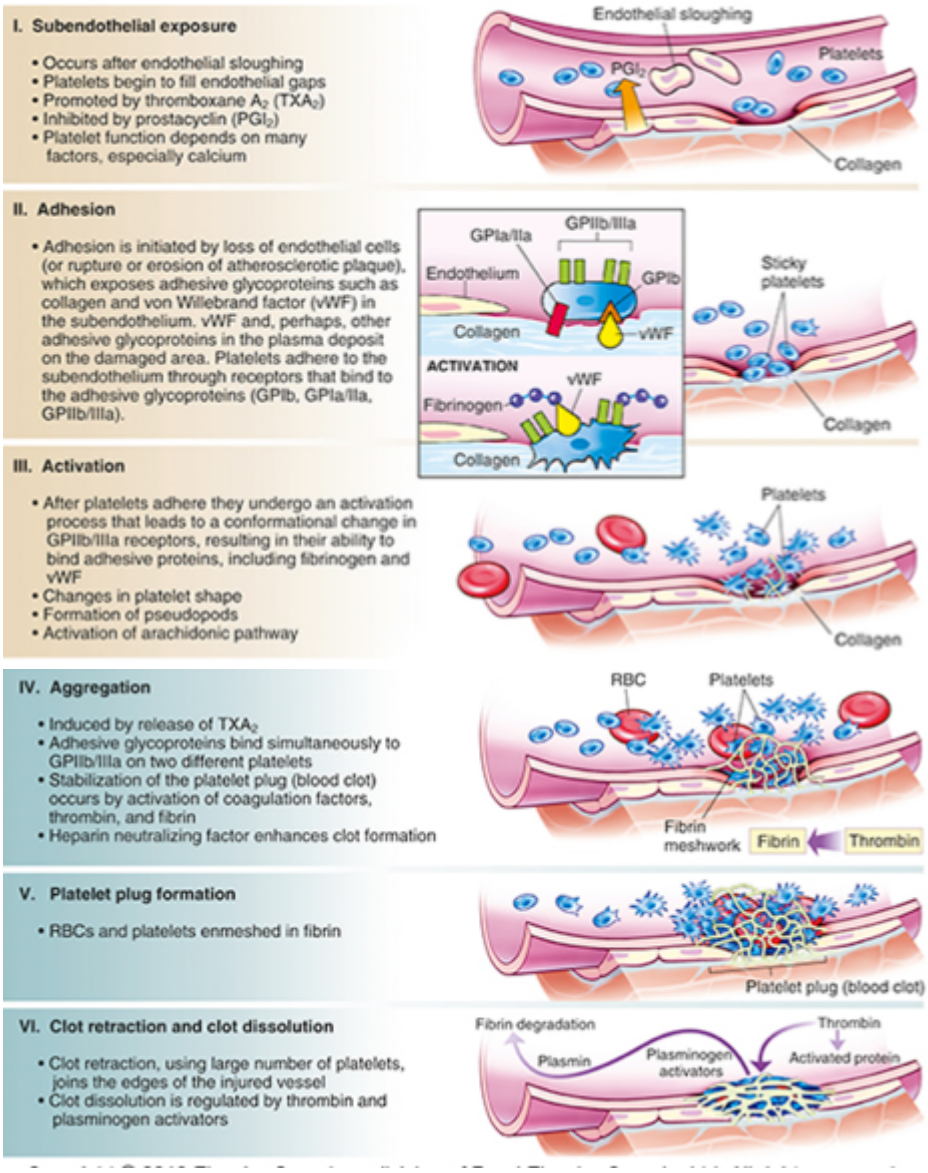
Orthostatic/Postural Hypotension

- Defective Baroreceptor Reflex → decreased BP upon standing up (~20mmHg S or -10mmHG D)
  - Normally: stand up → decreased venous return due to gravity → decreased BP
  - Rapid activation of baroreceptor reflex → increased SNS activity → increased BP
- Acute temporary factors
  - Ex: drugs, massive diuresis, stand up immobile → venous pooling
- Chronic primary or secondary
  - Ex: metabolic syndrome, cardiovascular autonomic neuropathy
- Prevention: raise slowly, calf contraction, vasoconstrictors

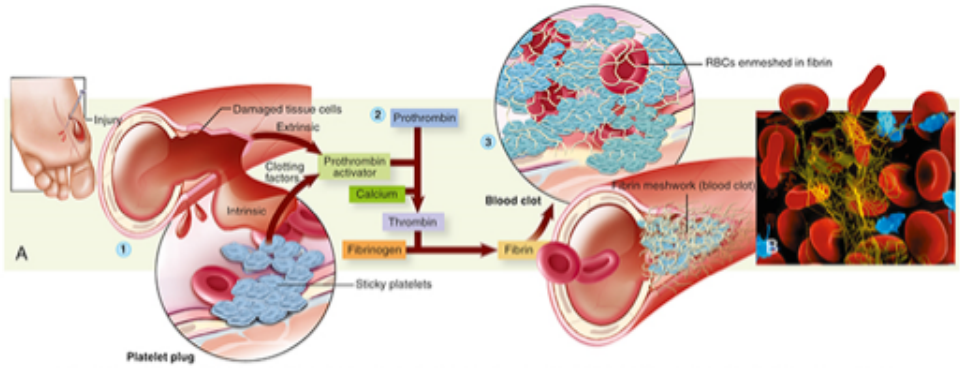
THROMBOEMBOLIC DISORDER DRUGS (Ch. 52)

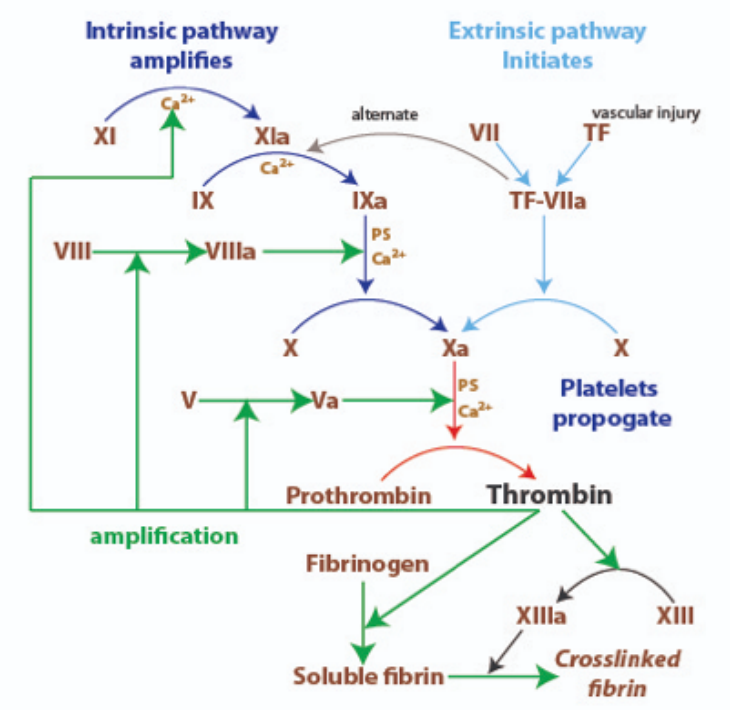
Hemostasis Review

Platelet plug formation

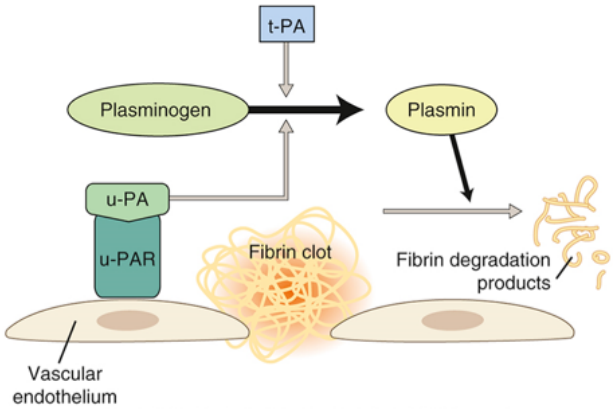


Coagulation Cascade



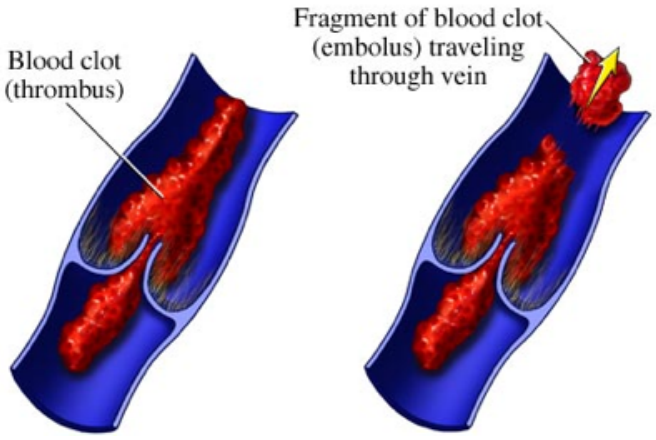


Fibrinolytic System



When a clot has formed, plasmin will help with the degradation of the clot.

Thrombosis



Thrombosis is the formation of the clot.

BACK TO PHARM

Drug Categories Overview

1. Anticoagulant drugs (ex. Warfarin, Heparin)
2. Antiplatelet drugs (ex. Aspirin, Clopidogrel)
3. Thrombolytic (fibrinolytic) drugs (ex. Alteplase)

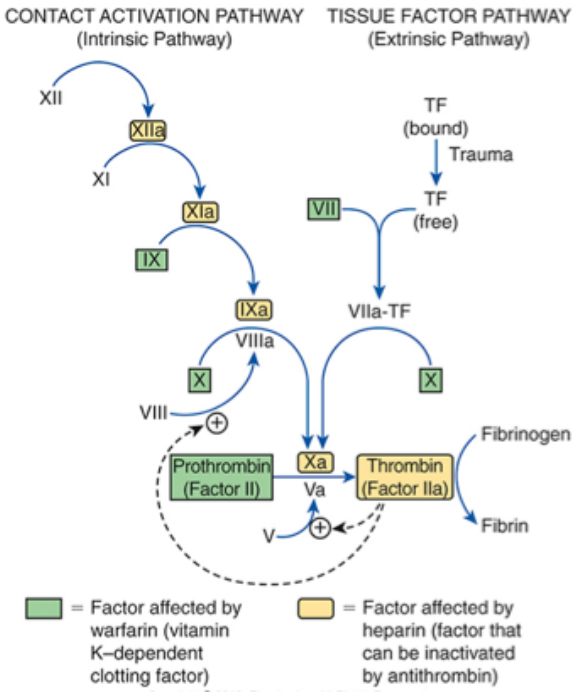
General Safety Alert: they all increase risks of bleeding

- Monitor BP, HR & mucous membrane for internal bleeding signs

Anticoagulants

1. Drugs that activate Antithrombin (ex. heparin)
2. Vitamin K antagonists (ex. warfarin)
3. Direct thrombin inhibitors (ex. dabigatran)
4. Direct factor Xa inhibitors (ex. Apixaban)

Common Action: decreased fibrin formation
Therapeutic Use: venous & arterial thrombosis prevention



Antithrombin Activators: Heparins & Derivatives

Comparison of Drugs That Activate Antithrombin

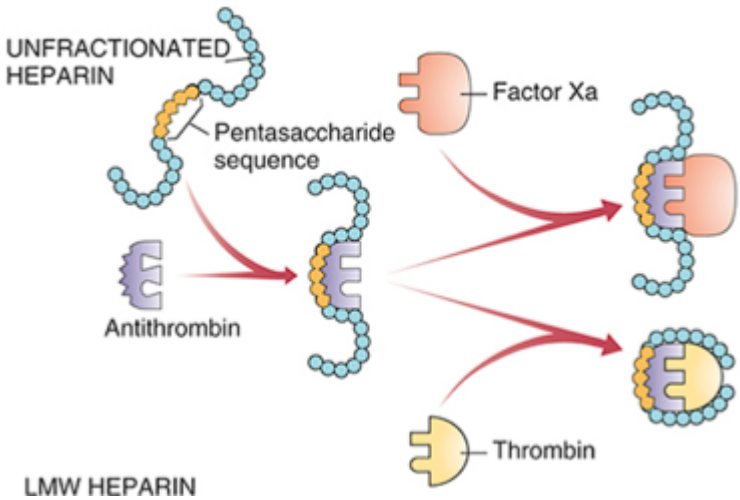
Property	Unfractionated Heparin	Low-Molecular-Weight Heparins	Fondaparinux
Molecular weight range	3000–30,000	1000–9000	1728
Mean molecular weight	12,000–15,000	4000–5000	1728
Mechanism of action	Activation of antithrombin, resulting in the inactivation of factor Xa and thrombin	Activation of antithrombin, resulting in preferential inactivation of factor Xa, plus some inactivation of thrombin	Activation of antithrombin, resulting in selective inactivation of factor Xa
Routes	IV, subQ	SubQ only	SubQ only
Nonspecific binding	Widespread	Minimal	Minimal
Laboratory monitoring	aPTT monitoring is essential	No aPTT monitoring required	No aPTT monitoring required
Dosage	Dosage must be adjusted on the basis of aPTT	Dosage is fixed	Dosage is fixed
Setting for use	Hospital	Hospital or home	Hospital or home

*The mechanism of action differs in selectivity: the unfractionated heparin has more widespread effects vs. others are more selective.

Heparin (unfractionated)

Kinetics

- Large polar molecule → no membrane crossing
- Subcut/IV admin → onset in minutes
- Plasma protein binding → variable activity
- Hepatic metabolism + renal excretion



Mechanism of action:

- The unfractionated heparin will bind & wrap around antithrombin. It can then inhibit factor Xa or thrombin.
- The end result: less fibrin formation

Main therapeutic uses:

- Anticoagulation during pregnancy
- When rapid anticoagulation required: ex. Massive DVT & pulmonary embolism

Main adverse effects:

- Possible hypersensitivity reactions (because it's a protein, and our body can produce an immune response against it)
- Hemorrhage (=10%)
- Spinal/epidural hematoma

    - Monitor neurologic impairment signs/symptoms
- Heparin-induced thrombocytopenia (HIT)
    - Monitor platelet count: < 100,000/mm^3 = discontinue

Nursing Capsule: Heparin Considerations

- High risk patients
    - Hemophilia, peptic ulcers, severe hypertension, threatened abortions
- Contraindications
    - Thrombocytopenia, uncontrollable bleeding & following eye, brain or spinal cord surgery
- Drug interaction: synergistic action with antiplatelet drugs (ex. aspirin)
- Heparin overdose antidote: protamine sulfate IV, 1mg/100 heparin units
- Dosage & administration
    - Dosage in units based on coagulation test results
    - No oral availability (too large and polar for absorption!!)
    - Dosage varies for usage: ex. Small for postoperative prophylaxis vs. large for open heart surgery

Nursing Capsule: Heparin Lab Monitoring

- Therapeutic objective = decrease thrombosis without increased bleeding
- Activated partial thromboplastin time (aPTT)
    - Measures time for blood clot formation
    - Normal value = 40 seconds
    - **Heparin therapy objective** = 60-80 seconds
    - Test every 4-6 hours initially → adjust dosage accordingly
    - Once optimal dosage achieved: test once daily
- Anti-Factor Xa Heparin Assay
    - New test: → increased accuracy
    - Measures Factor Xa activity → inversely proportional to heparin activity
    - Heparin therapy objective = 0.3-0.7 IU/mL
    - Drawback = cost

Low-Molecular Weight Heparins (LMWH)

Action:

- Preferential **inhibition of Factor Xa**
- Less inhibition of thrombin
- Fondaparinux = factor Xa inhibition ONLY

1st Line Tx for Thrombosis Prophylaxis & Therapy:

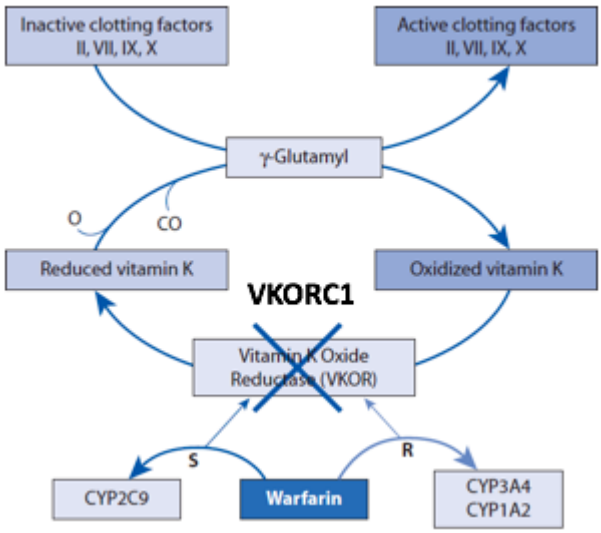
- Efficacy = unfractionated heparin
- Bleeding < heparin
- Other ADRs = heparin
- Less protein binding + longer half-life
- **No aPTT monitoring → allows home use** (huge advantage)

- Fixed dosage / subcutaneous administration

***Superior to Unfractionated Heparin on almost all counts**

Warfarin: Mechanism of Action

- Warfarin is a vitamin K oxidase inhibitor
- Inhibits clotting factor activation: VKORC1 activates vitamin K, which then in turn activates other clotting factors
- No impairment of existing activated factors
- Disadvantage : delayed action (days)
- Advantage: orally available
- Use: long-term thrombosis prophylaxis
- Kinetics:
    - 99% Albumin-bound (high risk of interaction with other protein bound drugs)
    - Mostly CYP2C9 metabolism
    - Urine excretion



History Capsule: Morbid Discovery

- Canadian farmer notices his cattle dying after eating spoiled clover
- Chemical analysis: spoiled clover contained high quantities of a warfarin-like chemical
- Warfarin used as rat poison. Believed to be too dangerous for human medicine
- Failed suicide attempt with warfarin triggered interest in medicinal use
- Clinical trials determined a narrow but safe therapeutic window existed

Warfarin: Toxicity & Interactions

Adverse reactions:

- Severe hemorrhage
    - Discontinue before surgical procedures
- Very teratogenic
    - Fetal hemorrhage & gross malformation
    - Enters breast milk

* The drugs with the most significant number of potential interactions!! Especially likely with other anticoagulant/antiplatelet drugs.

- Interactions = caution not contraindication

Drug Category	Interaction Mechanism	Examples
Increase Warfarin Effect	Albumin Displacement	Aspirin
	Inhibition of Warfarin Degradation	Acetaminophen Ketoconazole
Promote Bleeding	Platelet Aggregation Inhibition	Clopidogrel
	Inihibition of clotting factors/thrombin formation	Heparins Dabigatran
	Ulcer formation promotion	Aspirin
Decrease Warfarin Effect	Induction of Metabolism	Phenytoin
	Increase Clotting Factor Synthesis	Oral Contraceptives
	Decrease Warfarin Absorption	Cholestyramine

*drugs with the most interactions

Nursing Capsule: Warfarin Monitoring

- Prothrombin Time (PT) test:
  - Measures vitamin K-dependent clotting time
  - Normal value = 12 seconds
  - Warfarin objective: see table → adjust dosage accordingly
  - Frequent monitoring throughout therapy
  - Re-test for each drug interaction possibility
  - Home monitoring devices now available
  - Adequate monitoring decreases risks of hemorrhage

Condition Being Treated	INR[b]
Acute myocardial infarction[c]	2–3
Atrial fibrillation[c]	2–3
Valvular heart disease[c]	2–3
Pulmonary embolism	2–3
Venous thrombosis[d]	2–3
Tissue heart valves[c]	2–3
Mechanical heart valves	3–4.5
Systemic embolism	
Prevention	2–3
Recurrent	2–3

Nb. INR: international normalized ratio derived from PT test

Nursing Capsule: Warnings & Dosage

- Warnings/contraindications
  - Contraindications = same as heparins + pregnancy/lactation + liver impairment/alcoholism
  - Extreme caution = severe hypertension, gastric ulcers, hemophilia, threatened abortions
- Warfarin overdose antidote
  - Vitamin K PO or IV
  - If fails, use fresh whole blood, frozen-fresh plasma or other concentrates of vitamin K clotting factors
- Dosage
  - Individualized via trial-error + INR monitoring
  - Genetic considerations: VKORC1 & CYP2C9 polymorphisms
    - Genetic testings are recommended but not required by FDA
    - Can help reduce bleeding risks

Direct Thrombin Inhibitors

Therapeutic Use:

- Prevention & treatment of thromboembolisms/stroke for: atrial fibrillation patients, knee/hip replacements

Kinetics:

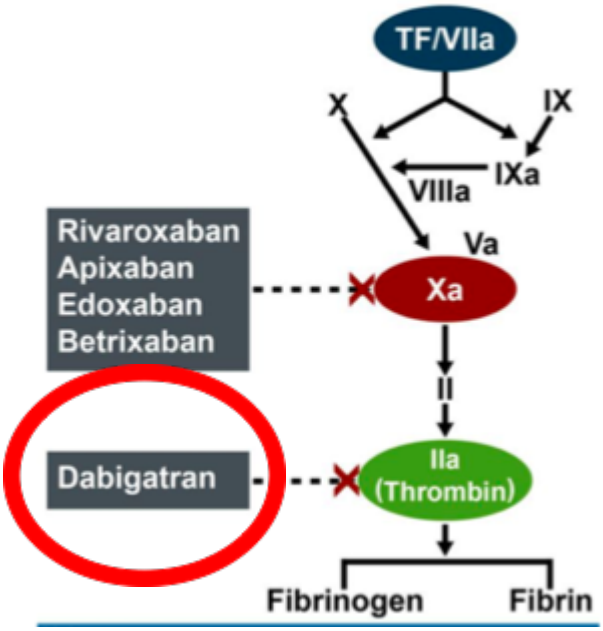
- Good oral absorption
- No plasma protein binding
- No P450 metabolism
- Renal elimination

Main adverse effects:

- Bleeding & GI disturbances
- P-Glycoprotein interactions

Advantages vs. Warfarin:

1. Rapid onset
2. No monitoring
3. Few interactions
4. Lower bleeding risk
5. Fixed dosage



Disadvantages:

1. New drug
2. No antidote
3. Shorter duration

Direct Factor Xa Inhibitors

- Same usage and advantages/disadvantages as Dabigatran
- Main differences = kinetics distribution & metabolism
    - They have protein binding while the thrombin inhibitors do not
- Avoid/caution with renal or hepatic impairments & during pregnancy

Kinetics:

- Good oral absorption
- 92-95% plasma protein binding
- Some CYP3A4 metabolism
- Renal elimination

Main adverse effects:

- Bleeding & spinal hematoma
- CYP2A4 & P-Glycoprotein interactions

Drugs:

- Rivaroxaban
- Apixaban
- Edoxaban
- Betrixaban

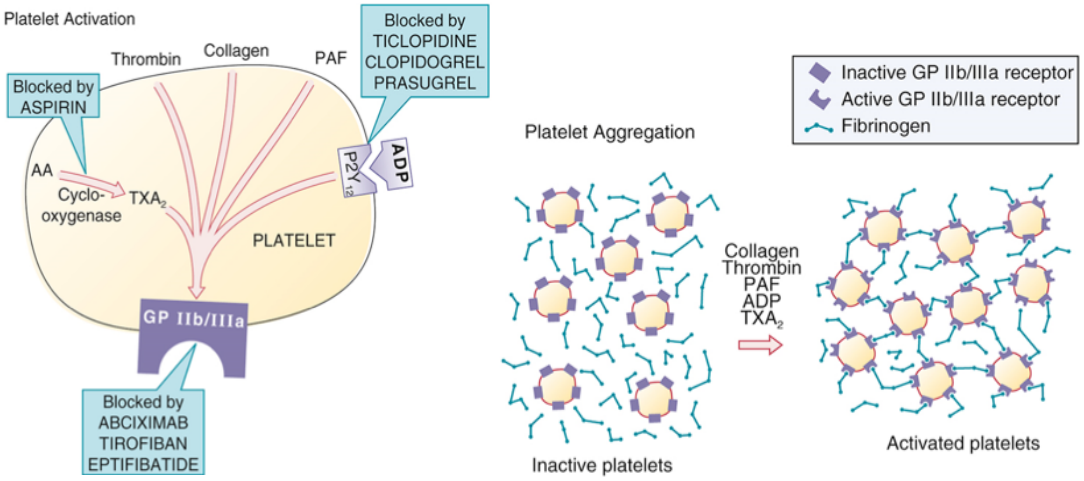
Oral Anticoagulants Summary (Table 52-6, p. 616)

Properties of Oral Anticoagulants

	Warfarin [Coumadin]	Rivaroxaban [Xarelto]	Apixaban [Eliquis]	Edoxaban [Savaysa]	Dabigatran Etexilate [Pradaxa, Pradax ◆]
Mechanism	Decreased synthesis of vitamin K–dependent clotting factors	Inhibition of factor Xa	Inhibition of factor Xa	Inhibition of factor Xa	Direct inhibition of thrombin
Indications					
Atrial fibrillation	Yes	Yes	Yes	Yes	Yes
Heart valve replacement	Yes	No	No	No	No
Knee or hip replacement	Yes	Yes	No	No	Yes
Onset	Delayed (days)	Rapid (hours)	Rapid (hours)	Rapid (hours)	Rapid (hours)
Duration	Prolonged	Short	Short	Short	Short
Antidote available	Yes (oral/parenteral vitamin K)	No	No	No	No
Drug-food interactions	Many	Few	Few	Few	Few
INR testing needed	Yes	No	No	No	No
Dosage	Adjusted based on INR	Fixed	Fixed	Fixed	Fixed
Doses/day	One	One	Two	One	Two
Clinical experience	Extensive	Limited	Limited	Limited	Limited
Advantages, summary	Decades of clinical experience Precise dosage timing not critical, owing to long duration Antidote available for overdose	Rapid onset Fixed dosage No blood tests needed Less bleeding and hemorrhagic stroke Few drug-food interactions	Same as rivaroxaban	Same as rivaroxaban	Same as rivaroxaban
Disadvantages, summary	Delayed onset Blood tests required No fixed dosage Many drug-food interactions	Dosing on time is important, owing to short duration No antidote to overdose Limited clinical experience	Same as rivaroxaban	Same as rivaroxaban	Same as rivaroxaban *plus* GI disturbances are common

Antiplatelet Drugs

- Best against arterial thrombosis
  - (anticoagulants = best against vein thrombosis)
- Diagram below:
  - Aspirin can block COX enzyme inhibiting the formation of TXA2 → inhibiting GP protein activation
  - Directly inhibit the GP protein activation
  - Block the ADP receptor called $P2Y_{12}$ receptor → inhibits platelet aggregation



Antiplatelet Drugs

Properties of the Major Classes of Antiplatelet Drugs

	Aspirin, a Cyclooxygenase Inhibitor	$P2Y_{12}$ Adenosine Diphosphate (ADP) Receptor Blockers	Protease-Activated Receptor-1 (PAR-1) Antagonists	Glycoprotein (GP) IIb/IIIa Receptor Blockers
Representative drug	Aspirin	Clopidogrel [Plavix]	Vorapaxar [Zontivity]	Tirofiban [Aggrastat]
Mechanism of antiplatelet action	Irreversibly inhibits cyclooxygenase, and thereby blocks synthesis of TXA_2	Irreversibly blocks receptors for ADP[a]	Reversibly blocks the protease-activated receptor-1 (PAR-1) expressed on platelets	Reversibly blocks receptors for GP IIb/IIIa
Route	PO	PO	PO	IV infusion
Duration of effects	Effects persist 7–10 days after the last dose	Effects persist 7–10 days after the last dose[a]	Effects persist 7–10 days after the last dose	Effects stop within 4 hr of stopping the infusion
Cost	$3/month	$87/month	$320/month	$1000/course

Notice the last column is IV infusion, and the last row about cost.

Aspirin - Antiplatelet Action

Indication:

- *Ischemic stroke* (to reduce the risk of death and nonfatal stroke)
- *TIAs* (to reduce the risk of death and nonfatal stroke)
- *Chronic stable angina* (to reduce the risk of MI and sudden death)
- *Unstable angina* (to reduce the combined risk of death and nonfatal MI)
- *Coronary stenting* (to prevent reocclusion)
- *Acute MI* (to reduce the risk of vascular mortality)
- *Previous MI* (to reduce the combined risk of death and nonfatal MI)
- *Primary prevention of MI* (to prevent a first MI in men and in women age 65 and older)

MI prevention benefit vs. GI bleeding risk analysis to determine if Aspirin should be administered

Optimal Dosage:

- Initial acute MI treatment = 325mg/day
- Maintenance & chronic prevention: 81mg/day

$P2Y_{12}$ ADP Receptor Antagonists

Clopidogrel

- Inhibits ADP-stimulated platelet aggregation by blocking the $P2Y_{12}$ ADP receptor
- Prodrug → CYP2C19 activation
- Poor metabolizers contraindications → switch to other ADP-antagonist
- Main use = coronary artery stent blockage prevention

	$P2Y_{12}$ Adenosine Diphosphate (ADP) Receptor Blockers
Representative drug	Clopidogrel [Plavix]
Mechanism of antiplatelet action	Irreversibly blocks receptors for ADP[a]
Route	PO
Duration of effects	Effects persist 7–10 days after the last dose[a]
Cost	$87/month

Main Adverse Effects

- Bleeding & rare cases of thrombotic thrombocytopenic purpura
- Interactions: CYP2C19 inhibitors
- Proton pump inhibitors consensus statement:
  - PPI + clopidogrel for GI bleeding high risk patients (interaction at the CYP2C19 enzyme)
  - Clopidogrel alone if no particular GI bleeding risk

Glycoprotein IIb/IIIa Antagonists

- "Super Aspirin" → most effective antiplatelet drugs
- Antagonism of GP IIb/IIIa inhibits all pathways
- Short term use only in emergency situations due to cost
- Adverse effects = other antiplatelets
- Bleeding risk >> other antiplatelets
- Decrease ischemic complications in ACS
- Decrease reocclusion risk following balloon or laser angioplasty

Application
Acute coronary syndromes (ACS)
Percutaneous coronary intervention[a] (PCI) following treatment for ACS
PCI without prior treatment for ACS

	Glycoprotein (GP) IIb/IIIa Receptor Blockers
Representative drug	Tirofiban [Aggrastat]
Mechanism of antiplatelet action	Reversibly blocks receptors for GP IIb/IIIa
Route	IV infusion
Duration of effects	Effects stop within 4 hr of stopping the infusion
Cost	$1000/course

Thrombolytic Drugs

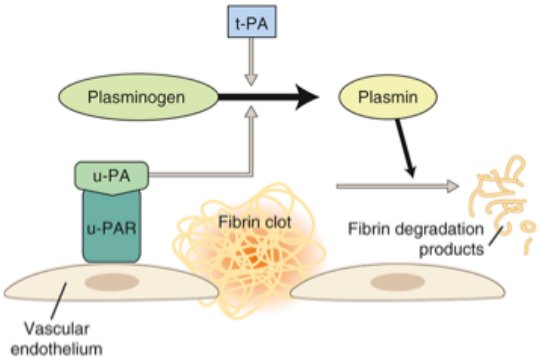
Properties of Thrombolytic (Fibrinolytic) Drugs

	Alteplase (tPA)	Tenecteplase	Reteplase
Brand name	Activase, Cathflo Activase	TNKase	Retavase
Description	A compound identical to human tPA	Modified form of tPA with a prolonged half-life	A compound that contains the active sequence of amino acids present in tPA
Source	All three drugs are made using recombinant DNA technology		
Mechanism	All three drugs promote conversion of plasminogen to plasmin, an enzyme that degrades the fibrin matrix of thrombi		
Indications			
Acute MI	Yes	Yes	Yes
Acute ischemic stroke	Yes	No	No
Acute pulmonary embolism	Yes	No	No
Clearing a blocked central venous catheter	Yes	No	No
Adverse effect: Bleeding	With all three drugs, bleeding is the primary adverse effect		
Half-life (min)	5	20–24	13–16
Dosage and administration for acute MI	*Intravenous:* 15-mg bolus, then 50 mg infused over 30 min, then 35 mg infused over 60 min	*Intravenous:* Single bolus based on body weight (see text)	*Intravenous:* 10-unit bolus 2 times, separated by 30 min

*Note the differences in half-life: alteplase has the shortest half-life.

Alteplase (Recombinant tPA)

- Digest fibrin → thrombolysis
- Degrade fibrinogen & clotting factors → increased bleeding risks



Therapeutic Use:

- Acute MI / acute ischemic stroke / acute PE
- Administration: sooner the better!
- IV infusions only / very short duration

Bleeding = major adverse effects:

- Can destroy clots of recently healed vessels → severe internal bleeding
- Antidote = IV aminocaproic acid + blood replacement
- Super contraindication: patients with a history of intracranial hemorrhage (ICH)

Hemophilia Medications (Ch. 54)

Hemophilia

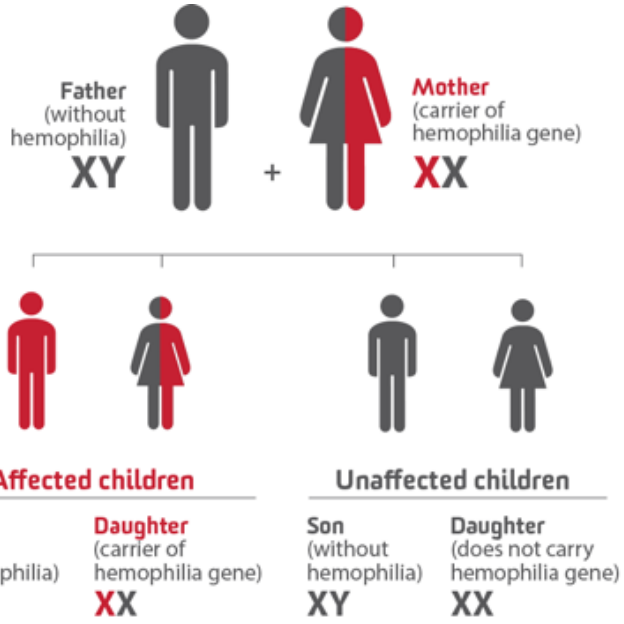
- Hemophilia A: most common type of hemophilia. 8 out of 10 people with hemophilia have hemophilia A > people with hemophilia A do not have enough clotting factor VIII (factor *)
- Hemophilia B: is also known as Christma disease and a less common type of hemophilia. People with hemophilia B do not have enough clotting factor IX (factor 9). It is caused by a deficiency in clotting factor 9.

Clinical Classification of Hemophilia Severity

Disease Parameter	Disease Severity		
	Severe	Moderate	Mild
Clotting factor level (VIII or IX)	Less than 1% of normal	Between 1% and 5% of normal	Between 6% and 49% of normal
Bleeding tendency	Can bleed with very mild injury	Can bleed with moderate injury	Can bleed with severe injury, surgery, or invasive procedures
Bleeding frequency	May bleed once or twice a week	May bleed once a month	May never have a bleeding episode
Occurrence of joint bleeding	Frequent	Less frequent	Infrequent, but can occur in response to severe injury

Hemophilia: Inheritance

- X-linked recessive disease
- Severity of hemophilia depends on mutations



Nursing Capsule: Hemophilia Therapy Overview

Ideal specialist team:

- Hematologist + orthopedist + dietician + psychologist
- Physical & occupational therapist + genetic counselor
- Infectious disease specialist + social worker + nurse coordinator

Cornerstone = replacement therapy

- Factor VIII (hemophilia A) or Factor IX (hemophilia B) or desmopressin (mild)
- Adjunct = antifibrinolytic drugs (ex. Aminocaproic acid)
- Good prognosis but lifelong therapy → treatment = very costly (60-150k/year)

Bleeding-related pain management

- Mild → acetaminophen
- Severe → opioid
- Avoid Aspirin & other NSAIDs

Immunization

- Normal vaccination schedule is recommended in hemophilic children
  - Monitor closely for signs of bleeding
- Hepatitis A & B vaccines for both the patient & family members administering clotting factors

<u>Factor VIII & IX Concentrates</u>

Therapeutic Use:

- Hemophilia A (VIII) & B (IX) treatment
- Plasma-derived (cheaper) or recombinant (safer - less allergic reactions)
- 3rd generation recombinant (ex. Adavate) = treatment of choice

Dosage & Administration

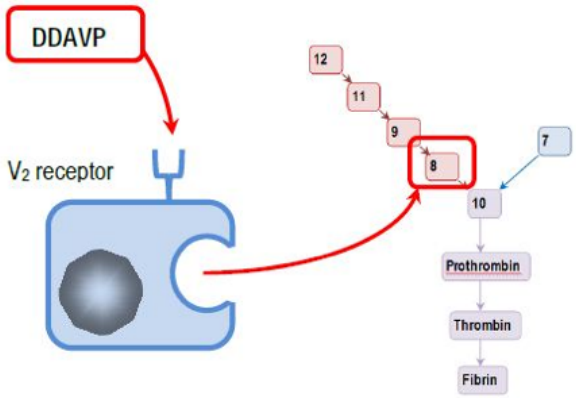
- On demand - to stop a bleeding
  - Slow IV push over 5-10min
  - Dosage depends on site & severity
  - Calculate based on % of activity target & patient body weight
- Prophylactic therapy
  - Mostly for severe hemophilia in kids
  - Goal = maintain % factor VIII above 1%
  - At home infusions 3-4x/week (VIII) or 2x/week (IX)
  - Central venous access devices can be installed

Safety Alert

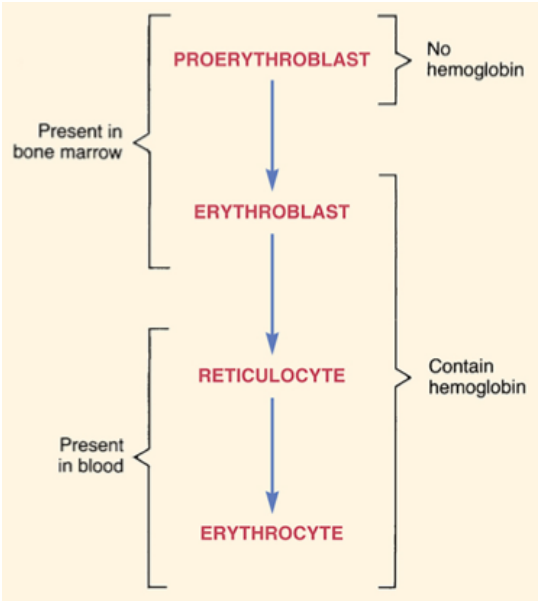
- Mild to severe allergic reactions
  - Mild → antihistamines
  - Severe → subcutaneous epinephrine

<u>Desmopressin (DDAVP)</u>

- Analog of Vasopressin/ADH
- Adverse effects: fluid retention/hyponatremia
- Used only for mild hemophilia A prophylaxis & treatment
- Releases stored Factor VIII
- Cheaper & safer than factor replacement (no risk for allergic reactions)
- Administration = intranasal or IV



DRUGS FOR ANEMIC DEFICIENCIES (Ch. 55)



RBC Development

Necessary ingredients for proper RBC development:

1. Healthy bone marrow
2. Erythropoietin → stimulate RBC maturation
3. Iron → hemoglobin synthesis
4. Vitamin B12 → DNA synthesis
5. Folic acid → DNA synthesis

Anemia = decrease in RBC #, size or hemoglobin

Deficiency in any of the above → anemia

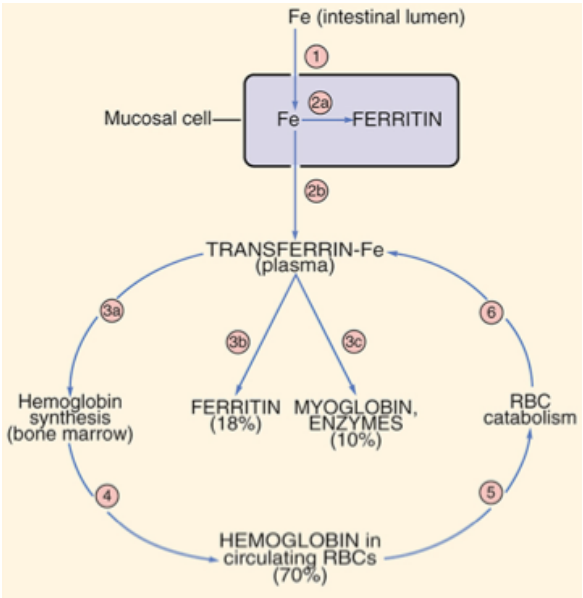
Marrow dysfunction → anemia

- Reticulocyte is the monitoring point.
    - When there is a case of anemia or risk of anemia, we want to look at the reticulocyte count. Why? Because it's a better measure of the development of RBC. If we only look at the amount of erythrocytes (active RBCs), at that precise moment the amount of RBCs might be healthy, but you're amount of reticulocytes might be low, indicating you will have anemia in a few days or months.

*Review hematology pathophysiology lecture if necessary

Iron Physiology

- Most common nutritional deficiency worldwide
- Necessary for hemoglobin, myoglobin & some enzymes
- Intestinal absorption rate varies with need ~2-20%
- Ferritin = storage / transferrin = plasma transport
- Physiologic excretion = very low
- Iron loss → **blood donation, hemorrhage & menses**



Individual Characteristic	Recommended Dietary Allowance (RDA)
Male	11 mg/day
Female	18 mg/day
Pregnant Female	27 mg/day (must use supplements)

Iron deficiency

Causes	Consequences	Diagnosis
1. **Blood volume expansio**n (ex. Pregnancy, puberty) 2. **Chronic blood loss** (ex. GI bleeding, menses) Mostly increased in demand Decreased uptake = very rare	**1. Iron deficiency anemia** a. Microcytic & hypochromic b. Fatigue & skin pallor c. Severe = tachycardia & angina 2. Impaired myoglobin synthesis 3. Impaired enzyme synthesis 4. Impaired child development 5. Impaired cognition	**Hallmarks:** 1. microcytic/hypochromic RBCs 2. Absence of aggregated ferritin **Lab Tests to confirm:** ● Decreased RBCs & reticulocyte count ● Decreased hemoglobin & hematocrit values ● Decreased serum iron content ● Increased serum iron-binding capacity

Ferrous Iron Salts

Indications: Iron deficiency anemia treatment + prevention

- All equivalent efficacy & toxicity
- Ferrous sulfate = preferred choice because cheaper

Main Adverse Effects:

- GI disturbances (dose-dependent) → tolerance & colored stool
    - Ex: nausea, diarrhea/constipation, heartburn
- Teeth staining
- Iron poisoning in children/kids = leading poisoning fatality
    - Main symptoms = acidosis & shock
    - Antidotes = gastric lavage or iron chelating agents can
- Drug interactions: antacids & tetracyclines decreases absorption / vitamin C increases absorption

Parenteral Iron: Iron Dextran

- Indications: patients for whom oral iron is inefficient/impossible
    - Ex: GI diseases or severe blood loss

Nursing Capsule: Iron Deficiency Guidelines

Assessments:

- Determine cause of iron deficiency to optimize intervention
- Monitor reticulocyte & hemoglobin levels for therapeutic success/failure
- Avoid therapeutic combinations with other iron, folic acid or vitamin B12 medications

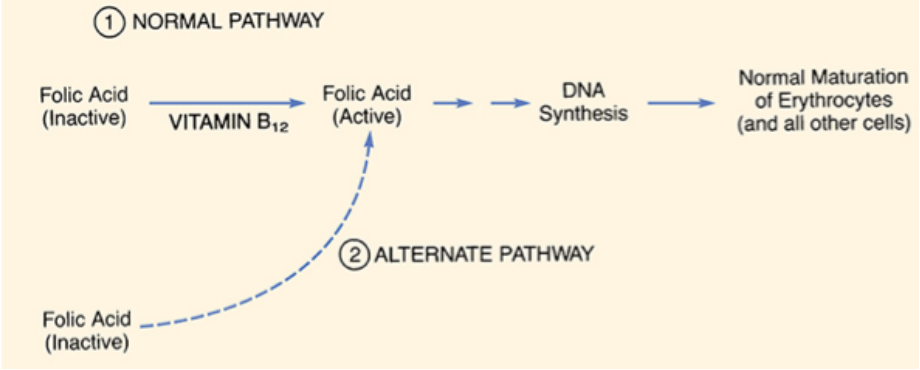
Dosage & administration considerations:

- Oral iron salts = best between meals to maximize absorption
    - With meals only during initiation or with large doses to minimize GI distress
    - Optimal dosage = 65mg 3x/day for a total of 200mg
- Parenteral iron dextran = complex dosage equation with body weight & severity of anemia
- Safety alert: fatal anaphylactic reactions with parenteral
    - Test dose before full-blown administration → monitor for 15min
    - IV administration has lower anaphylaxis risk than IM
    - Epinephrine & reanimation equipment readily available

Therapy duration: until hemoglobin levels are normal ~1-2 months

Vitamin B12 Physiology

- Main utility = folic acid activation
- Absorption at distal ileum requires intrinsic factor → mostly stored in the liver
- Very slow excretion → daily requirements are minuscule
- Deficiency takes years to develop



*Note: alternate pathway when high levels of folic acid. So if you have B12 deficiency, it can be overridden if you have high levels of folic acid via the alternate pathway.

Vitamin B12 Deficiency

Causes:

- Impaired absorption
    - Ex. GI diseases, lack of intrinsic factor
- Insufficient diet = very rare

Diagnosis:

- Megaloblast detection
- Test of plasma B12 levels
- B12 absorption test

Consequences:

→ Affects mostly highly dividing cells

- **Megaloblastic (pernicious) anemia**
  - Pernicious = old connotation when no Tx available
  - Macrocytic (large) RBC
  - Systemic Hypoxia, heart failure & dysrhythmias
- **Nervous System Injuries**
  - Demyelination of neurons
  - Long-term deficiency = permanent damage
  - Unrelated to folic acid or DNA
- GI disturbances
- Decreased WBC & platelets

Cyanocobalamin (B12 supplement)

- Drug of choice for all B12 deficiencies
- May produce hypokalemia: RBC synthesis requires potassium

Dosage and administration:

- Oral
  - Mild to moderate deficiency patients
  - Even if lack of intrinsic factor as ~1% is still absorbed → very high dosage
- Parenteral
  - Best for patients with severe deficiency → neurologic damage
  - IM or subcutaneous only, NEVER IV
- Intranasal
  - Good alternative to parenteral injections

Nursing Capsule: Vitamin B12 Deficiency Guidelines

Moderate B12 deficiency:

- Only manifestation = megaloblasts, NO neuronal damage or WBC decrease
- Manage via B12 supplements

Severe B12 deficiency:

- Disruptions of all blood cells + GI disturbances + neuronal injuries
- **Treatment protocol**: IM B12 + folic acid injection + blood replacement + platelet transfusion
- **Monitor success**: megaloblasts disappear + reticulocyte count increases
  - Need to see both. If you only see megaloblasts disappear with a decrease in reticulocyte count, that means he RBCs are being destroyed.
- Neurologic recovery is proportional to duration of deficiency

Long-term therapy:

- Patients with B12 malabsorption + intrinsic factor deficiency
- Monthly injections or very large oral doses

Folic Acid Physiology

- Necessary for DNA synthesis
- Alternative pathway bypasses need for vitamin B12
- Unlike B12, deficiency develops rapidly due to daily loss
- Extensive enterohepatic recycling decreases folate loss
- RDA for adults = 400 mcg/day; 600 mcg for pregnant women

*N.B. B12 deficiency does not equal folate deficiency

Vitamin B_{12} Deficiency Versus Folic Acid Deficiency

	Vitamin B_{12} Deficiency	Folic Acid Deficiency
Usual cause	Vitamin B_{12} malabsorption from lack of intrinsic factor	Low dietary folic acid
Primary hematologic effect	Megaloblastic anemia	Megaloblastic anemia
Neurologic effect	Damage to brain and spinal cord	None[a]
Diagnosis	Low plasma vitamin B_{12}; low B_{12} absorption (Schilling test)	Low plasma folic acid
Treatment (usual route)	Cyanocobalamin (PO or IM)	Folic acid (PO)
Usual duration of therapy	Lifelong	Short term

[a]Folic acid deficiency early in pregnancy can cause neural tube defects in the fetus.

Folic Acid Deficiency

Causes:

- Alcoholism
  - Poor diet
  - Enterohepatic folate recycling decreases
- Sprue
  - Malabsorption syndrome
- Very rare: drug-induced

Consequences:

- Similar to B12 deficiency except no neuronal injuries
- Potential increase in colorectal cancer & atherosclerosis
- Neural tube defect
  - Deficiency early during pregnancy
  - Avoid this via folate supplements

Diagnosis:

- Megaloblastic anemia with high B12 levels

Folic Acid Supplements

- Pteroylglutamic acid = inactive folic acid → rapidly activated upon absorption
- Already active form are no longer effective and more expensive
- Indications:
  - Folic acid deficiency megaloblastic anemia treatment & prophylaxis
  - Initial severe vitamin B12 megaloblastic anemia therapy

- Adverse effects:
    - None short-term
    - Increased colorectal cancer & atherosclerosis risks long-term

Nursing Capsule: Folic Acid Deficiency Guidelines

- Intervention should match the cause
    - Ex. poor diet → adjust diet, don't take supplements (except pregnancy!)
    - Malabsorption → folate supplementation
- Administration: mostly PO, rarely injected
- Prophylactic supplements: only for soon to be pregnant, pregnant or lactating women
- Severe deficiency management:
    - Initially: IM injection of B12 + folic acid → combination fastens recovery
    - Continue with oral folate only
    - Monitor success: same as with B12

HEMATOPOIETIC AGENTS (Ch. 56)

Hematopoietic Growth Factors (HGF)

HGF = naturally occurring hormones regulating proliferation & differentiation of blood cells
Also called Colony-Stimulating Factors (CSF)

Therapeutic applications:

- Post-chemotherapy platelet & WBC regeneration
- Boost bone marrow transplant recovery
- Boost RBC synthesis in chronic renal failure (CRF) patients

Nursing advice:

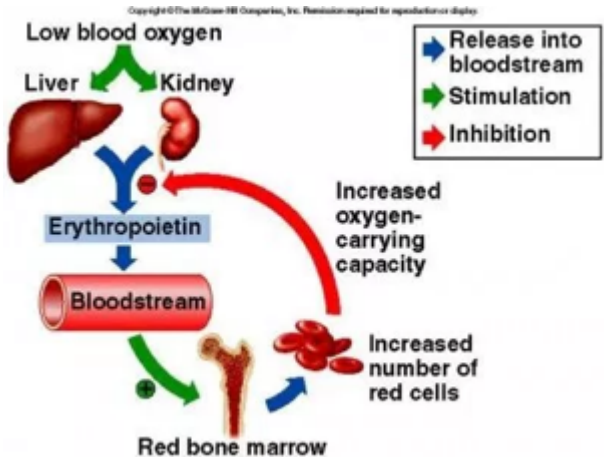
- These agents are usually contraindicated in patients with myeloid (blood) cancer

Nomenclature for Hematopoietic Growth Factors

Biologic Name	Pharmacologic Names	
	Generic Name	Brand Name
ERYTHROPOIETIC GROWTH FACTORS		
Erythropoietin	Darbepoetin alfa	Aranesp
	Epoetin alfa	Epogen, Procrit, Eprex ♣
LEUKOPOIETIC GROWTH FACTORS		
Granulocyte colony-stimulating factor (G-CSF)	Filgrastim	Neupogen
	Pegfilgrastim	Neulasta
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	Sargramostim	Leukine
THROMBOPOIETIC GROWTH FACTOR		
Interleukin-11	Oprelvekin	Generic only

Erythropoietin (EPO)

- Primary function: promote RBC maturation
- Alternative to blood transfusions
- Inefficient without vitamin B12 + folate + iron
- Other functions:
  - Angiogenesis modulation
  - Cell-injury apoptosis inhibition → maintain cellular integrity



Epoietin Alfa (EPO)

- Parenteral injections only → decreases transfusion requirements
- Indications:
  - Anemia in chronic renal failure (CRF) → but no quality of life improvement!
  - Chemotherapy-induced anemias: palliative purposes only
  - AIDS patients on zidovudine (AZT)
  - Elevate RBC count prior to surgery: only if anticipate significant hemorrhage
- Adverse effects:
  - No significant allergic reactions or interactions
  - Hypertension in CRF patients due to hematocrit increase
  - Serious cardiovascular events
    - Ex. heart failure, cardiac arrest, stroke, MI
    - Greater risk when hemoglobin rises fast

Darbepoetin Alfa (long-acting EPO)

- Longer half-life (49h vs. 24h) than Epoietin Alfa
- Decreases # of injections
- Efficacy & toxicity profile = Epoietin Alfa
- Indications:
  - Anemia associated with CRF
  - Anemia associated with chemotherapy

Nursing Capsule: EPO Considerations

- Safety-alert - minimizing serious cardiovascular events in CRF patients
  - Dosage should be lowest for effective RBC elevation
  - Decrease dosage if hemoglobin increase > 1g/dL in 2 weeks
  - Temporarily hold treatment if hemoglobin > 11g/dL
- Warnings
  - Contraindicated for all cancer patients on a curative/remission therapy
  - Must be combined with anticoagulant for preoperative RBC elevation
- Monitoring
  - Measure hemoglobin levels at baseline + 2x/week until achieved target
  - Blood chemistry, iron levels & complete blood count should be done routinely

Leukopoietic Growth Factors (LGF)

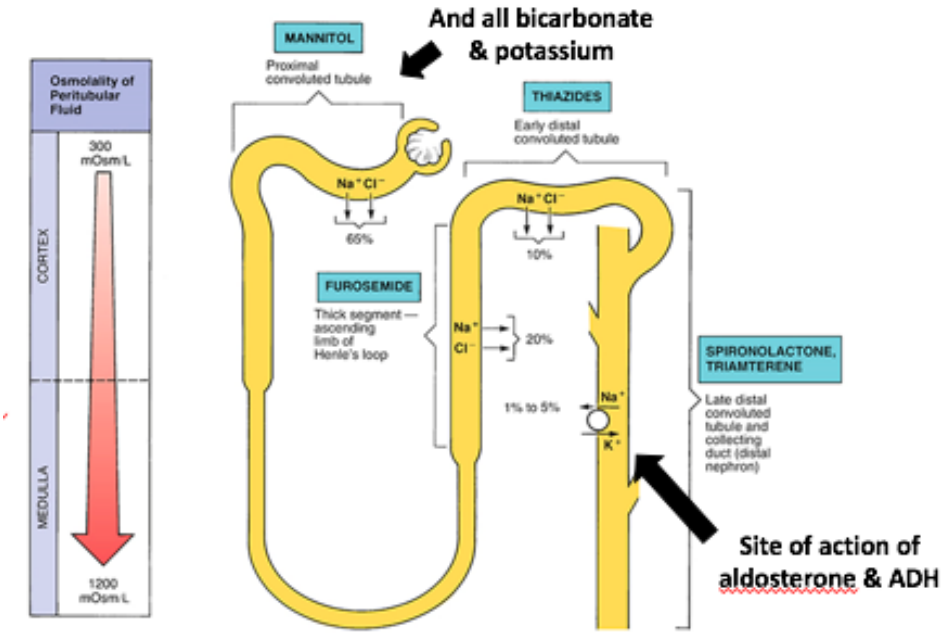
- LGFs stimulate white blood cell (leukocytes) production
- Monitor blood count 2x/week during therapy to avoid leukocytosis & thrombocytosis

	Filgrastim (G-CSF)	Sargramostim (GM-CSF)
Physiology	• Released in response to inflammation • ↑ Neutrophil synthesis + Phagocytic & Cytotoxic	Same as Filgrastim but for macrophages, neutrophil & eosinophil
Therapeutic Use	• ↓ infection risk during chemotherapy • ↓ neutropenia in bone marrow transplant (BMT) patients • ↑ Pre-BMT hematopoietic stem cell (HSC) harvest • Congenital neutropenia therapy (↓ infection)	• Accelerate BMT recovery • ↑ failed BMT survival time • ↑ neutrophil recovery + ↓ infections in acute myeloid leukemia patients
Administration	Degraded in GIT → **Parenteral administration only.**	
Adverse Effects	• Short term: Almost none & no interactions • **Bone Pain**: usually mild, treatable with NSAIDs • **Leukocytosis**: Excessive WBC ↑ with high dosage	Similar to Filgrastim Possible **Leukocytosis & Thrombocytosis**

Worse Than Beer & Coffee: Diuretics (Ch. 41)

Kidney Nephrons Review

- Clearance = GF + TS - TR
    - How much is evacuated from the body
- Filtration = 125ml/min = 180L/day
- Reabsorption: active transport (requires ATP energy + requires proteins)
- Secretion: pumps in the PCT



Diuretics Overview

- Diuretics increased clearance via decreased NaCl reabsorption
- Diuresis proportional to amount blocked
    - Ex. Furosemide > Thiazide > Spironolactone (refer back to the picture above for the % excreted by each)
- Small blockage → large consequences
- Daily output = +1.8L urine/1% blockade
    - (for every 1% of sodium blocked for reabsorption = 1.8L urine produced)

Main adverse effects for all diuretics:

- Hypovolemia
- Acid-base imbalances
- Electrolyte imbalances

Loop Diuretics: Furosemide

- Diuresis even if GFR is low (ex. Severe renal impairment)
- Very powerful → use only if necessary
    - Ex. pulmonary edema + congestive heart failure (CHF)

- Edema or HTN when other diuretics fail
- Major source of interactions in elderly

Main adverse effects:

- Severe dehydration + NaCl loss
- Hypotension
- Hypokalemia
- Ototoxicity (rare)
    - Risk with aminoglycoside (Abx)
- Possible teratogen
- Interaction with digoxin
- Hypokalemia → increased digoxin toxicity
- Combine with K+ sparing diuretics decrease toxicity

Loop Diuretics: Routes, Time Course, and Dosage

Drug	Route	Time Course		Dosage (mg)	Doses/Day
		Onset (min)	Duration (hr)		
Furosemide [Lasix]	Oral	Within 60	6–8	20–80	1–2
	IV or IM	Within 5	2	20–40	1–2
Ethacrynic acid [Edecrin]	Oral	Within 30	6–8	50–100	1–2
	IV	Within 5	2	50	1–2
Bumetanide [Burinex ♣, generic only in United States]	Oral	30–60	4–6	0.5–2	1
	IV	Within a few	0.5–1	0.5–1	1–3
Torsemide [Demadex]	Oral	Within 60	6–8	5–20	1
	IV	Within 10	6–8	5–20	1

<u>Thiazides: Hydrochlorothiazide</u>

- Unlike loop diuretics: ineffective when GFR is low (< 15-20mL/min)
- Main indications:
    - Essential hypertension (1st choice drug)
    - Edema associated to mild-moderate heart failure
- Main adverse effects:
    - = loop diuretics EXCEPT ototoxicity
    - Interactions = same as loop (dig, NSAIDs, lithium & antihypertensive drugs)
    - K-sparing diuretics decrease toxicity

Thiazides and Related Diuretics: Dosages and Time Course of Effects

Generic Name	Brand Name	Time Course		Optimal Oral Adult Dosage (mg/day)
		Onset (hr)	Duration (hr)	
THIAZIDES				
Chlorothiazide	Diuril	1–2	6–12	500–1000
Hydrochlorothiazide	Microzide	2	6–12	12.5–25
Methyclothiazide	Enduron	2	24	2.5–5
RELATED DRUGS				
Chlorthalidone	Thalitone	2	24–72	50–100
Indapamide	Lozide ◆, generic only in the United States	1–2	Up to 36	2.5–5
Metolazone	Generic only	1	12–24	2.5–20

K+ Sparing: Spironolactone

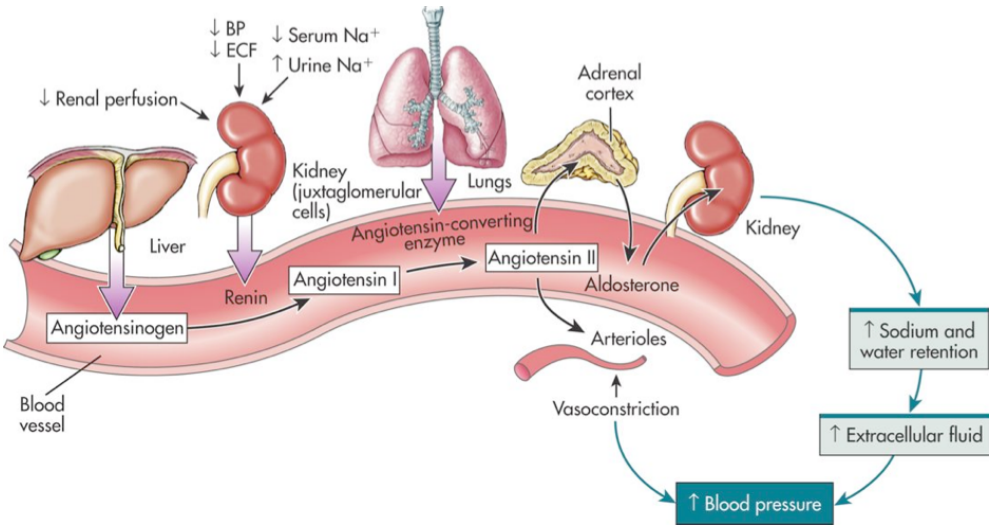
- **Aldosterone Antagonist**:
  - Decrease synthesis of Na/K transporters
  - Hormonal action = delayed onset
- Effects: increase urine output + decrease K+ loss
- Main therapeutic uses:
  - Counter Thiazide/Furosemide toxicity
  - Heart failure → aldosterone block = protective
- Triamterene action:
  - Direct Na+/K+ inhibition
  - Protein action = fast onset
- Main adverse effects:
  - Hyperkalemia
  - Endocrine irregularities (ex. Abnormal menses, impotence, hirsutism) because it also acts on hormones.
  - Thyroid & testes tumors long-term use
  - Interaction with other K+ sparing drugs (ex. ACE inhibitors/blockers)

RAAS Agents (Ch. 44)

PATHO REVIEW

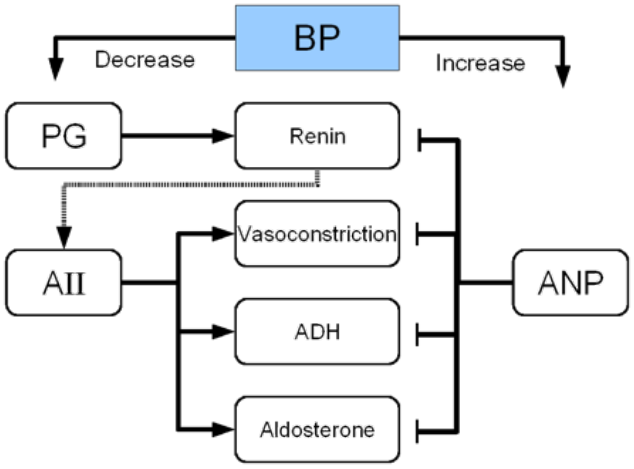
Renin-Angiotensin-Aldosterone System (RAAS) Review

- Very efficient system to raise BP
- Takes time to act
- Energy costly



Natriuretic Hormones (NH)

- Ex. ANP, BNP, CNP, urodilatin → require K+, Ca^{2+}, Mg^{2+} for proper function
- anti-RAAS effects → increase diuresis + vasodilation + decrease aldosterone + decrease SNS
- NH dysfunction → pressure-natriuresis shift → HT
- Mimic drug used for heart failure Tx



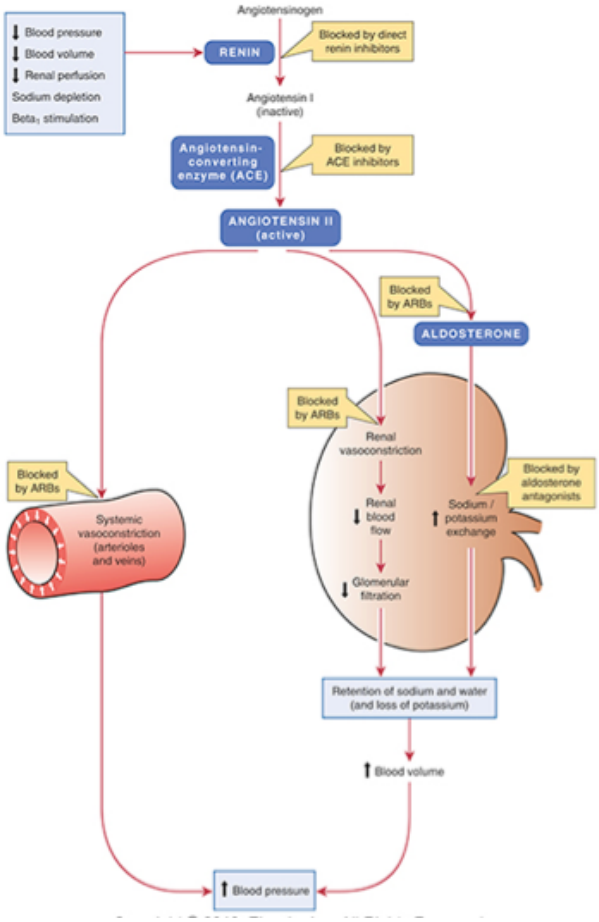
BACK TO PHARM

RAAS Agents Overview

Keep in mind that some tissues are able to produce angiotensin locally vs. the RAAS is the systemic production of Angiotensin II

- Local Angiotensin II production
  - Independent of main system
  - Synthesis via non-ACE pathways
  - ACE inhibitors do not block RAAS 100%

Indications	ACE Inhibitors	ARBs	Aldosterone Antagonists	DRI
Hypertension	Yes	Yes	Yes	Yes
Heart Failure	Yes	Yes	Yes	
Diabetic Nephropathy	Yes	Yes		
Cardiovascular Events Prophylaxis	Yes	Yes		
Myocardial infarction	Yes			

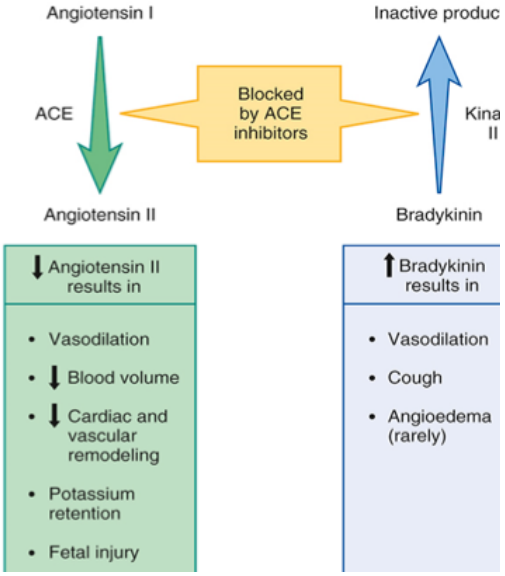


ACE Inhibitors (ACE-I)

- Mechanism of Action: blocks the conversion of angiotensin I to angiotensin II.
- Has other purposes, such as converting bradykinin into an inactive product. So if ACE is blocked, there will be a build up of bradykinin. Some of the adverse effects of ACE-I is related to this build up.

Kinetics:

- Almost all administered orally
- Captopril = only ACE-I with short half-life
- Almost all prodrugs → liver failure = decreased efficacy
- All excreted in kidneys → kidney failure = increased toxicity



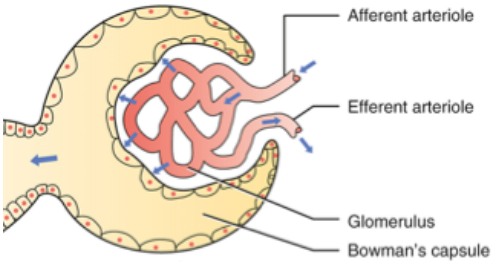
E Inhibitors: Approved Indications and Adult Dosages

eneric ame	Brand Name	Approved Indications	Starting Dosage	Usual Maintenance Dosage
nazepril	Lotensin	Hypertension	10 mg once/day	20–80 mg/day in 1 or 2 doses
ıptopril	Capoten	Hypertension	25 mg 2 or 3 times/day	25–50 mg 2 or 3 times/day
		Heart failure	6.25–12.5 mg 3 times/day	50 mg 3 times/day
		LVD after MI	12.5 mg 3 times/day	50 mg 3 times/day
		Diabetic nephropathy	25 mg 3 times/day	25 mg 3 times/day

ACE-I: Therapeutic Uses

1. Hypertension
   - Drug of choice for most types of HTN
   - Proved to decrease HTN-related cardiovascular mortality
   - Initial BP decreases proportionally to decrease RAAS angiotensin II
   - Prolonged BP decreases due to local angiotensin II decrease

2. Heart Failure
   - Drug of choice: several benefits on heart function
   - Overall improvement of symptoms & increased survival
   - May reverse pathologic hypertrophy



3. Nephropathy
   - Slows down renal damage/nephropathy onset
   - Works via decreased GFR

4. Myocardial Infarction
   - Decreased mortality & HF development

5. Diabetic Retinopathy
   - Prevention/slow-down onset only in T1DM patients without HTN, nephropathy or retinopathy

6. CVE Prevention
   - Decrease risk of MI, stroke & mortality in HIGH RISK patients only!!
   - High risk = CVE history + another risk factor
     - Ex. smoking, high cholesterol, HTN, etc.

ACE-I: Adverse Effects

Adverse Effects	Nursing Considerations
1st dose hypotension	• Minimize via small initial dose • Discontinue other diuretics 2-3 days prior • Monitor BP after 1st done • Hypotensive patients in supine position
Cough	• 10% of patients → discontinue if too severe • Increased risk in elderly, women & asian patients (high accumulation of bradykinin in these individuals)

Hyperkalemia	● Rare → educate patient to avoid K+ supplements
Renal Failure	● Contraindicated in patients with bilateral artery stenosis
Fetal Injury	● Teratogenic during 2nd & 3rd trimester ● Discontinue ASAP if pregnant ● Monitor developing fetus if exposed
Neutropenia	● Educate patients to report signs of infection immediately (ex. Fever, sore throat) ● Increased risk in renal impaired patients

*1st dose hypotension: ACE-I act on the RAAS system, made to increase BP. What happens when you start a patient on ACE-I, there's going to be a rebound effect. The body will react by stopping its response and the overdrive it has on the RAAS system. The body kind of shuts off and lets the drug do the work. Eventually, the body will adjust to it and hypotension will no longer occur.

ACE-I: Safety Alert & Drug Interactions

Safety Alert: Angioedema

- Affects = 1% of patients
- Caused by excessive bradykinin accumulation
- Early signs/Sx = giant edema of tongue, lips or eyes
- Tx = epinephrine injection
- Discontinue ACE inhibitors forever

Interacting Drug	Effect
Diuretics	Increased 1st dose hypotension
Antihypertensive agents	Additive hypotension
Drugs increase potassium (ex. K+ sparing diuretics)	Hyperkalemia Use only if necessary & monitor potassium levels
Lithium	Increased lithium accumulation → monitor!!
NSAIDS (ex. Aspirin, Ibuprofen)	Antagonistic hypertensive effect

Angiotensin II Receptor Blockers (ARB)

ACE-I block production vs. ARB = block action

- Similar effects → similar indications
- ARB advantages: less hyperkalemia & decrease in coughing
- ARB disadvantage: efficacy < ACE inhibitors → 2nd choice drug
    - Why? The ARBs still need to compete for the receptors with angiotensin II that are being produced, so not all the receptors will be blocked. While ACE-I, ALL angiotensin II is blocked.

All available PO

- Adverse effects: **angioedema risks**, fetal injury, renal failure
- Drug interactions: additive effect with antihypertensive drugs

Angiotensin II Receptor Blockers: Approved Indications and Adult Dosages

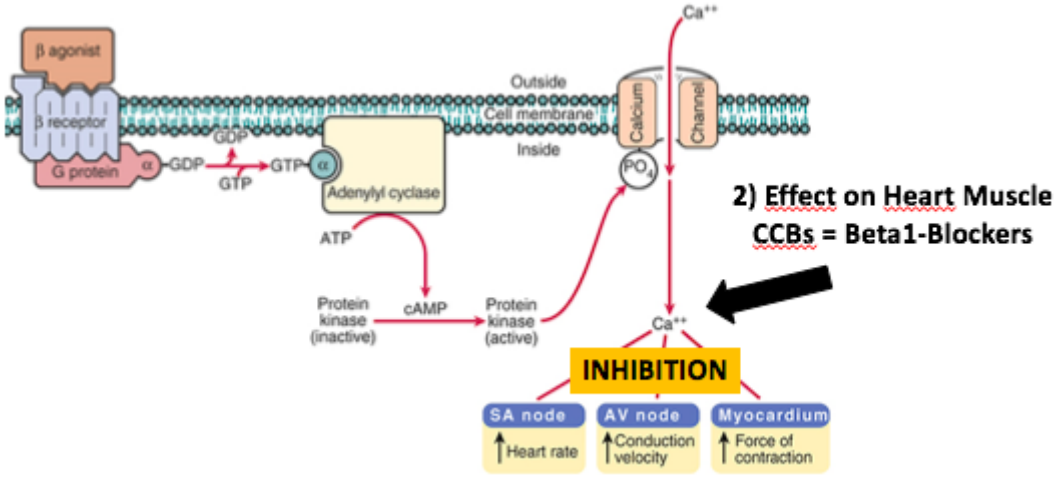
Generic Name	Brand Name	Approved Indications	Initial Dosage	Maintenance Dosage
Azilsartan	Edarbi	Hypertension	40–80 mg once/day	80 mg once/day
Losartan	Cozaar	Hypertension	25–50 mg once/day	25–100 mg/day in 1 or 2 doses
		Stroke prevention[b]	50 mg once/day	50–100 mg once/day
		Diabetic nephropathy[c]	50 mg once/day	100 mg once/day

Calcium-Channel Blockers (Ch. 45)

Calcium-Channels Physiology

1. Effect on vascular smooth muscle (VSM): decreases calcium-induced contractions → vasodilation
2. Effect on heart muscle CCBs = beta1-blockers

- When the beta receptors are activated, it activates the G-protein cascade. Then the ultimate result is the production of cAMP, which then opens the calcium channel, calcium comes into the heart and then the heart increases the rate of conduction, contraction, etc.
- The beta1-blockers basically halt this cascade.



Calcium-Channel Blockers (CCB) Overview

Calcium Channel Blockers: Classification, Sites of Action, and Indications

Classification	Sites of Action	Indications		
		Hypertension	Angina	Dysrhythmias
DIHYDROPYRIDINES				
Nifedipine [Adalat CC, Nifediac, Nifedical, Procardia]	Arterioles	✓	✓	
Amlodipine [Norvasc]	Arterioles	✓	✓	
Clevidipine [Cleviprex]	Arterioles	✓[b]		
Felodipine [Plendil, Renedil ♣]	Arterioles	✓		
Isradipine [DynaCirc CR]	Arterioles	✓		
Nicardipine [Cardene SR]	Arterioles	✓	✓	
Nimodipine [Nymalize, Nimotop ♣]	Arterioles			
Nisoldipine [Sular]	Arterioles	✓		
PHENYLALKYLAMINE				
Verapamil [Calan, Covera-HS ♣, Verelan]	Arterioles/heart	✓	✓	✓
BENZOTHIAZEPINE				
Diltiazem [Cardizem, Dilacor XR, Tiazac, others]	Arterioles/heart	✓	✓	✓

- Vascular specific CCB: Nifedipine - acts on arterioles only → vasodilation effect
- Non-specific CCB: Verapamil - acts on arterioles and the heart (both #1 & 2 as mentioned above)

Non-Specific CCB: Verapamil

- Direct effects = vasodilation + decreases SA/AV node conduction & contractility
- Indirect effects = rebound baroreceptors reflex increases SA/AV node conduction & contractility
    - This is caused by the vasodilation, decrease in node conduction & contractility causing a sudden drop in BP, so your body reacts with a rebound baroreceptor reflex to bring up your BP.
- Net effect = vasodilation → **decreases BP + increases coronary perfusion**

Kinetics:

- PO or IV administration
- Onset = 30min / peak = 5 hours
- Extensive hepatic metabolism

Adverse Effects:

- Common: constipation, headaches, edema
- Exacerbate cardiac dysrhythmias & failures
- Elderly patients: chronic eczematous eruptions

Drug Interactions:

- Digoxin → additive AV block effect
- Beta-blockers → additive effects

- Grapefruit juice → decreases metabolism

Toxicity Management:
- Severe hypotension or AV block/bradycardia
- Gastric lavage to remove verapamil
- Calcium gluconate counters inotropic + vasodilation (not AV block!!)
- IV norepinephrine counters hypotension
- Atropine helps for conduction block

Vascular-Specific CCB: Nifedipine
- Direct effects = vasodilation → decreased BP + increased coronary perfusion
- Indirect effects = rebound baroreceptor reflex increases SA/AV node conduction & contractility
- Indirect effect limited to immediate-release formulation —> safety alert!
- Blunted in sustained-release formulation → preferred (much much safer)
- **Net effect = decreases BP + increases HR & contractility**

Kinetics:
- PO or IV administration
- Extensive hepatic metabolism
- IR: onset = seconds / peak = 30min
- SR: onset = 20min / peak = 60 hours

Adverse Effects:
- Common: headache, edema
- Elderly patients: chronic eczematous eruptions

Difference vs. Verapamil
- Little cardiac effects and constipation
- Reflex tachycardia → prevent with beta-blocker

Toxicity:
- High dose Nifedipine has effects on heart
    - it has a much higher affinity for calcium channels on the smooth muscle vessels than on the heart. But if you give a high dose, all the smooth muscle calcium channels are taken and the remaining Nifedipine floating around will go bind on the calcium channels of the heart.
- Management = Verapamil management

Verapamil vs. Nifedipine Summary

Comparisons and Contrasts Between Nifedipine and Verapamil

Property	Drug	
	Nifedipine	Verapamil
DIRECT EFFECTS ON THE HEART AND ARTERIOLES		
Arteriolar dilation	Yes	Yes
Effects on the heart		
Reduced automaticity	No	Yes
Reduced AV conduction	No	Yes
Reduced contractile force	No	Yes
MAJOR INDICATIONS		
Hypertension	Yes	Yes
Angina pectoris (classic and variant)	Yes	Yes
Dysrhythmias	No	Yes
ADVERSE EFFECTS		
Exacerbation of		
AV block	No	Yes
Sick sinus syndrome	No	Yes
Heart failure	No	Yes
Effects secondary to vasodilation		
Edema (ankles and feet)	Yes	Yes
Flushing	Yes	Yes
Headaches	Yes	Yes
Dizziness	Yes	Yes
Reflex tachycardia	Yes	No
Constipation	No	Yes
DRUG INTERACTIONS		
Intensifies digoxin-induced AV block	No	Yes
Intensifies cardiosuppressant effects of beta blockers	No	Yes
Often combined with a beta blocker to suppress reflex tachycardia	Yes	No

Vasodilators (Ch. 46)

Vasodilator Pharmacology

- Selectivity determines effects:
  - Arterioles → increased CO & decreased heart workload
  - Veins → decreased CO & decreased heart workload
- Therapeutic uses
  - Hypertension
  - Angina pectoris
  - HF
  - MI
  - Many others with risk of increased BP
- Adverse effects
  - Postural/orthostatic hypotension → falls!!!
  - Reflex tachycardia via baroreceptor reflex → counter with beta-blockers
  - Blood volume expansion via RAAS → counter with diuretics

Category	Examples	Chapter	Site of Vasodilation
RAAS Agents	Captopril / Losartan / Aliskiren	44	Arterioles + Veins
Organic Nitrates	Nitroglycerin	51	Vein specific
CCB	Nifedipine / Verapamil	45	Arterioles specific
Alpha-Blockers	Prazosin	18	Arterioles + Veins
Indirect alpha-blockers	Clonidine / Reserpine	19	
Others	Hydralazine / Minoxidil Nitroprusside	46	Arterioles specific Arterioles + Veins

Hydralazine

- Arteriole specific vasodilation → decreased BP + increased CO
- Advantage: minimal postural hypotension

- Indications
  - Essential HTN: not preferred agent anymore, there are safer drugs now
  - Hypertensive crisis: incremental parenteral doses
  - Heart failure: decreased afterload short-term

- Kinetics
  - PO: onset = 45mins / duration = 6 hours
  - Parenteral: onset = 10mins / duration 2-4h

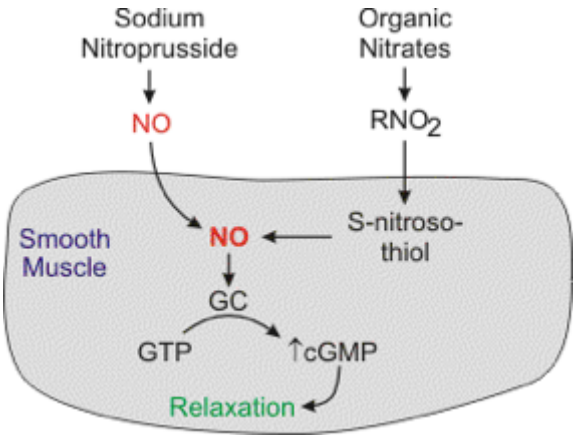
- Metabolism:
  - Acetylation (phase II)
  - Watch out for genetic individual variations

- Adverse effects:
  - Severe reflex tachycardia
  - Blood volume expansion
  - Risk of lupus-like syndrome

- Drug interactions:
  - Antihypertensives → additive effects

Sodium Nitroprusside

- Arteriole and vein vasodilation
- Nitrous Oxide is a substrate for a molecule that promotes muscle relaxation
- Advantage: fast onset & minimal postural hypotension
- IV infusions → adjust to desired BP
- Liver metabolism of cyanide groups



- Indications:
    - Hypertensive emergency = DBP > 120
    - Increased risk of organ damage (MI, ICH,HF, renal failure)
    - Nitroprusside → rapid BP decrease until oral medication onset

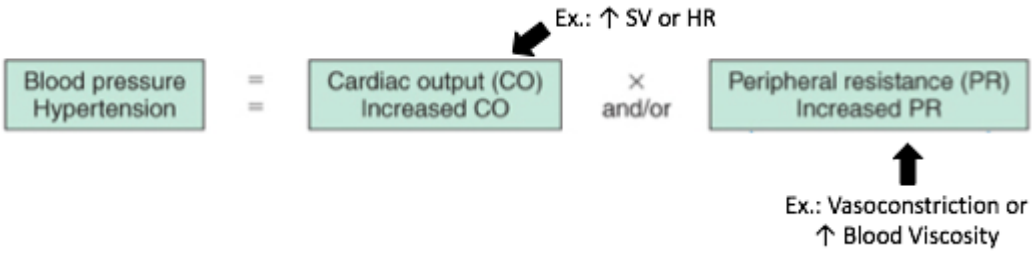
- Adverse effects:
    - Rapid administration → excessive hypotension
    - Cyanide poisoning → increased risk with liver disease
        - To metabolize NO, it's combined with a carbon atom, creating cyanide.
    - Thiocyanate toxicity → increased risk when admin **>** 3 days → monitor!

Drugs for Hypertension (Ch. 47)

PATHO REVIEW

Hypertension (HTN)

- Sustained BP > 130mmHg systolic or > 80 mmHg diastolic
- 33% of 20+ years old & 66% of 60+ years old
- Primary (essential) HTN = 90-95%
- Secondary HTN = 5-10%
    - Identifiable primary cause (often hemodynamics disorder)
- HTN increases risk of multiple organ diseases



Secondary HTN

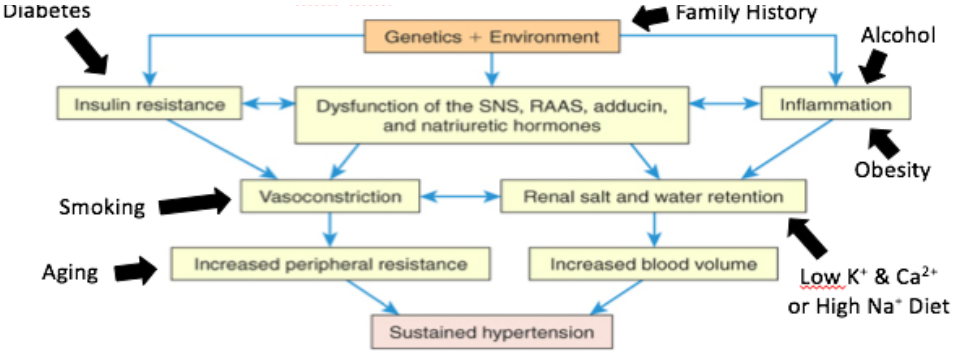
1. Renal disorders (ex. Adrenal tumor → increases RAAS)
2. Endocrine disorders (ex. Increased aldosterone/GH/catecholamines/etc.)
3. Vascular disorders (ex. arteriosclerosis)
4. Pregnancy-induced (unknown mechanism)
5. Neurologic disorders (ex. Brain tumor → increased intracranial BP → increased systemic BP)
6. Acute stress (ex. Increased corticosteroids & adrenaline)
7. Drug-induced (ex. Oral contraceptives, glucocorticoids, etc)

All of them cause increase TPR or CO → increased BP / must treat underlying disease

*review table 32-3 (only overview, no need to know by heart)

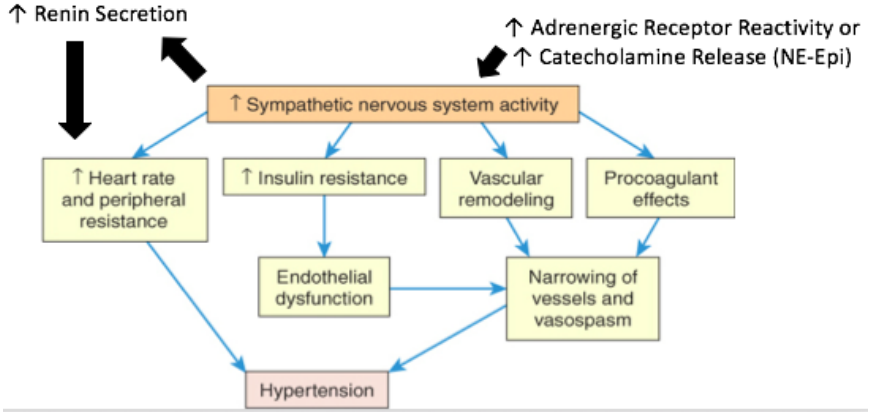
Primary HTN: Risk Factors

- Multifactorial
- Nicotine = vasoconstrictor
- Alcoholics (3+/day) > abstainers > moderate (2-4/week)
- Diet: low K+ & Ca^{2+} → increased Na+ retention

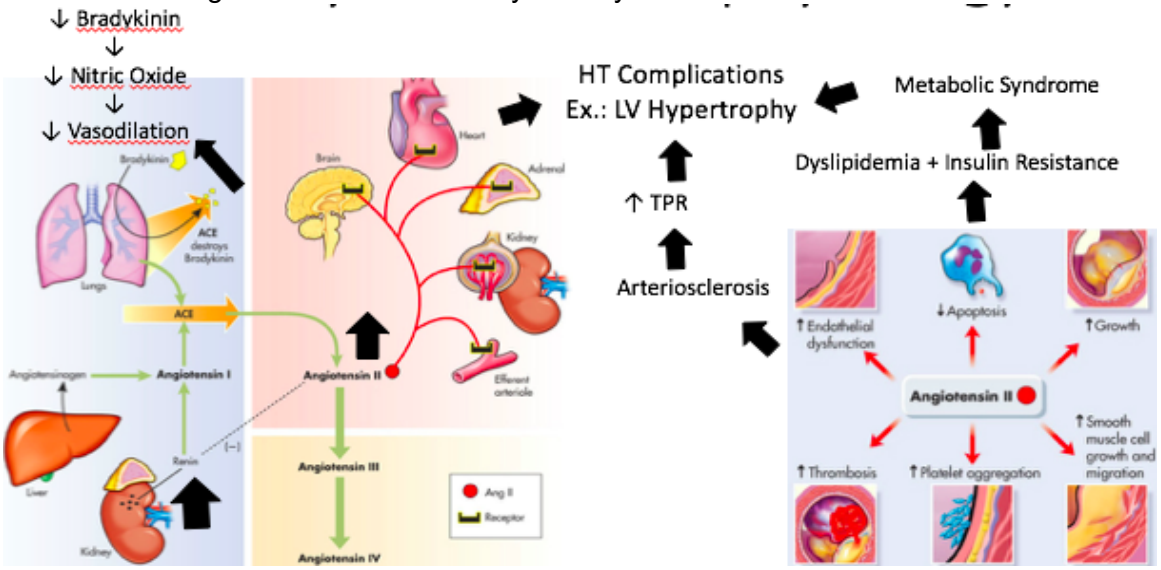


Primary HTN: Pathophysiology

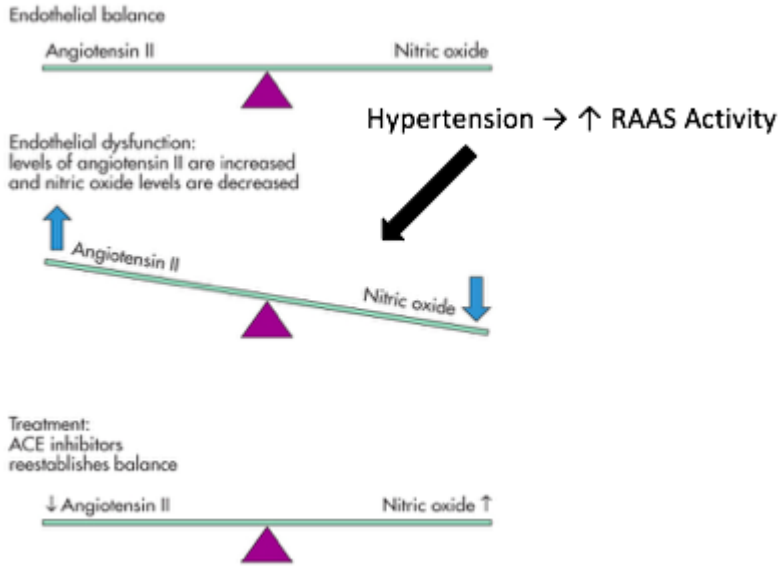
1. Sympathetic nervous system (SNS) hyperactivity



2. Renin-angiotensin-aldosterone system dysfunction



RAAS Continued



Hypertension Complications

- Vascular remodeling (VR) = smooth muscle hypertrophy & hyperplasia + tunica fibrosis
- Chronic HTN → VR → decreased blood flow to target organs → organ damage & complications
    - Target organs: eyes, brain, kidneys, heart
    - Ex. myocardial hypertrophy & ischemia, stroke, renal failure, retinal sclerosis
- Malignant hypertension
    - Stage 3 HT → 180+/140+ (rapid progressive HTN)
        - Increased cerebral artery BP → cerebral edema → Tissue dysfunction & death → encephalopathy
    - Renal failure, stroke, heart failure, retinopathy

BACK TO PHARM

Chronic Hypertension Management

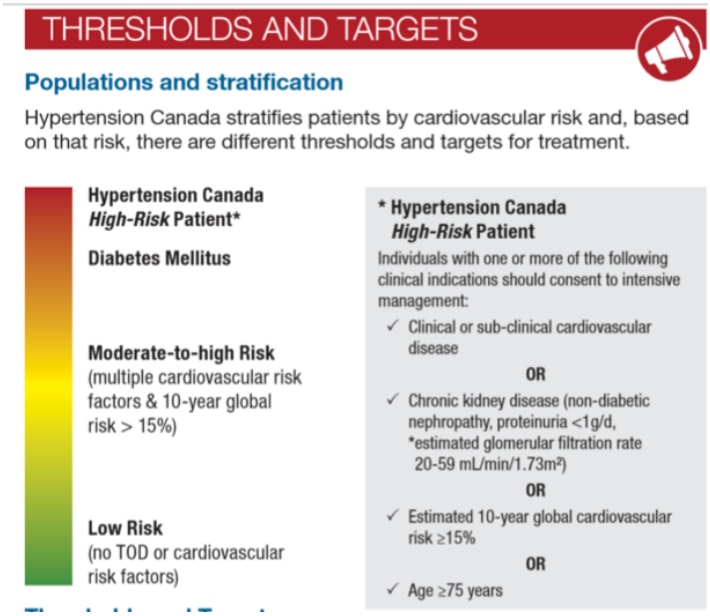
Basic Considerations

Therapeutic goals:

1. SBP/DBP below 130-80 mmHg
2. Maintain or improve quality of life

Interventions:

1. Lifestyle modifications
2. Antihypertensive drugs



Benefits of decreased BP

- Decreases morbidity / increases lifespan
- Decreases stroke 35-40%
- Decreases MI 20-25%
- Decreases HF 50+%

Patient Evaluation:

1. Assess cause & risk factors
2. Tx of cause if possible (ex. cushing's)
3. Intervene on risk factors if possible
4. Perform diagnostic tests

Recommended HTN tests:

- Electrocardiogram (ECG)
- Cholesterol & triglycerides
- Electrolytes (Ca^{2+}, Na+, K+)
- Hemoglobin & hematocrit
- Urine analysis: creatine, glucose, urea concentrations

Thresholds and Targets

In patients with documented hypertension, attaining blood pressure targets is vital to prevent cardiovascular and cerebrovascular complications.

Blood pressure thresholds for initiation of antihypertensive therapy and treatment targets in adults:

Patient Population	BP threshold for initiation of antihypertensive therapy		BP treatment target	
	SBP mmHg	DBP mmHg	SBP mmHg	DBP mmHg
Hypertension Canada High-Risk Patient*	≥ 130	N/A	< 120	N/A
Diabetes mellitus**	≥ 130	≥ 80	< 130	< 80
Moderate-to-high Risk (TOD or CV risk factors)**	≥ 140	≥ 90	< 140	< 90
Low Risk (No TOD or CV risk factors)**	≥ 160	≥ 100	< 140	< 90

* BP treatment threshold and target based on AOBP measurements
**BP treatment thresholds and targets refer to non-AOBP measurements performed in office.

Health Behaviour Recommendations

Objective	Recommendations	Application
Weight Reduction	Healthy BMI (18.5-25) and waist circumferance (Males <102cm & Females <88cm) Encourage multidisciplinary approaches	Prevention of HTN for normotensive individuals
Increased Physical Activity	30-60 mins/day of moderate intensity dynamic exercises 4-7 days /week (Ex.: walking, cycling, swimming)	
Moderate Alcohol Consumption	No more thn 2 drinks/day Males < 14 drinks/week Females < 9 drinks /week	Management of HTN for hypetensive patients
Healthy Diet (DASH)	↑ Fruits, veggies, dietary fibers ↓ meat, dairy and saturated fats	
Relaxation Therapies	Individualized cognitive behavior interventions success ↑ with relaxation techniques	If stress = important factor of elevated BP
Smoking Cessation	Smoke-Free Environment Cessation pharmaco & psychotherapy	Global cardiovascular risk reduction strategy

Lifestyle Modifications

Modification	Approximate SBP reduction	
Weight loss	5-20 mmHg/10kg	Increases antihypertensive Rx efficacy

Adoption of DASH diet	8-14 mmHg	
Exercise (endurance)	4-9 mmHg	And prevents onset!!
Dietary sodium restriction	2-8 mmHg	= 2000mg sodium/day MAX
Stress reduction	4-5 mmHg	yoga/meditation/social support
Moderate alcohol consumption	2-4 mmHg	= 0.5-1 ounce/day MAX (1 ounce = 2 glasses of wine)
Smoking cessation		
Potassium & calcium intake		= 4700mg potassium/day = 1000mg calcium/day

- Individual behaviour modification = modest
- **Combination of behaviour modification = significant!!**

(14!!) Antihypertensive Drug Classes (Table 47-2 p.516)

Diuretics	Sympatholytics	RAAS Suppressants	Others
Thiazides and Related Diuretics	**Beta Blockers**	**ACE Inhibitors**	**Direct-Acting Vasodilators**
Chlorothiazide	Acebutolol (has ISA)	Benazepril	Hydralazine
Chlorthalidone	Atenolol	Captopril	Minoxidil
Hydrochlorothiazide	Betaxolol	Enalapril	**Calcium Channel Blockers**
Indapamide	Bisoprolol	Fosinopril	Amlodipine
Methyclothiazide	Metoprolol	Lisinopril	Diltiazem (non-DHP)
Metolazone	Nadolol	Moexipril	Felodipine
Loop Diuretics	Nebivolol	Perindopril	Isradipine
Bumetanide	Penbutolol (has ISA)	Quinapril	Nicardipine
Ethacrynic acid	Pindolol (has ISA)	Ramipril	Nifedipine
Furosemide	Propranolol	Trandolapril	Nimodipine
Torsemide	Timolol	**Angiotensin II Receptor Blockers**	Nisoldipine
Potassium-Sparing Diuretics	**Alpha$_1$ Blockers**	Azilsartan	Verapamil (non-DHP)
Amiloride	Doxazosin	Candesartan	
Spironolactone	Prazosin	Eprosartan	
Triamterene	Terazosin	Irbesartan	
	Alpha/Beta Blockers	Losartan	
	Carvedilol	Olmesartan	
	Labetalol	Telmisartan	
	Centrally Acting Alpha$_2$ Agonists	Valsartan	
	Clonidine	**Direct Renin Inhibitor**	
	Guanabenz	Aliskiren	
	Guanfacine	**Aldosterone Antagonists**	
	Methyldopa	Eplerenone	
	Adrenergic Neuron Blockers	Spironolactone	
	Reserpine		

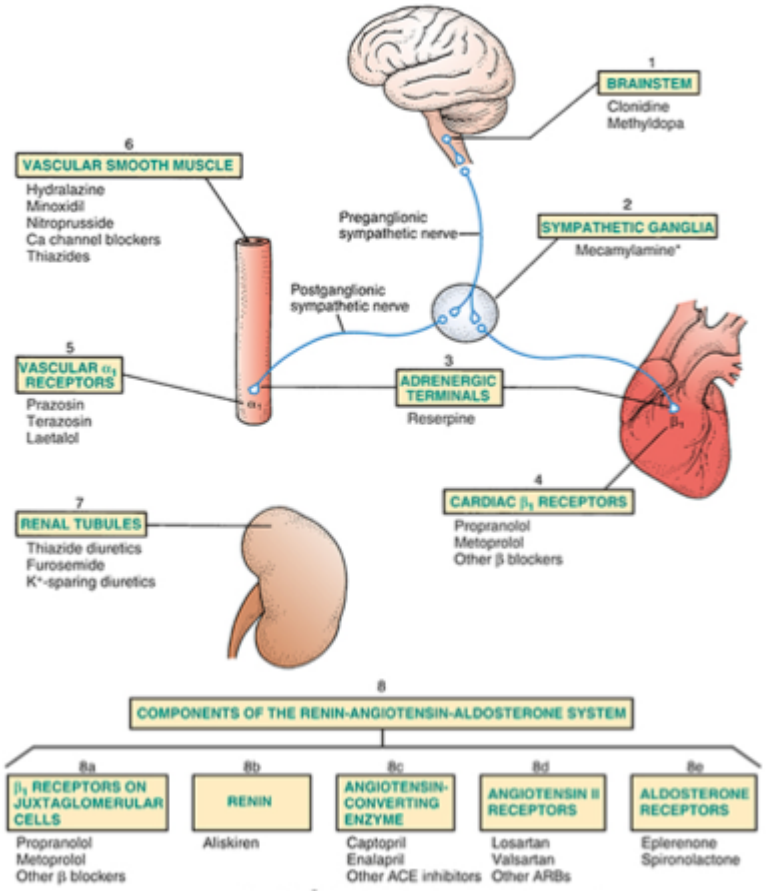
Several combination formulations include a thiazide + [Beta-blocker, ACE inhibitor or ARB]

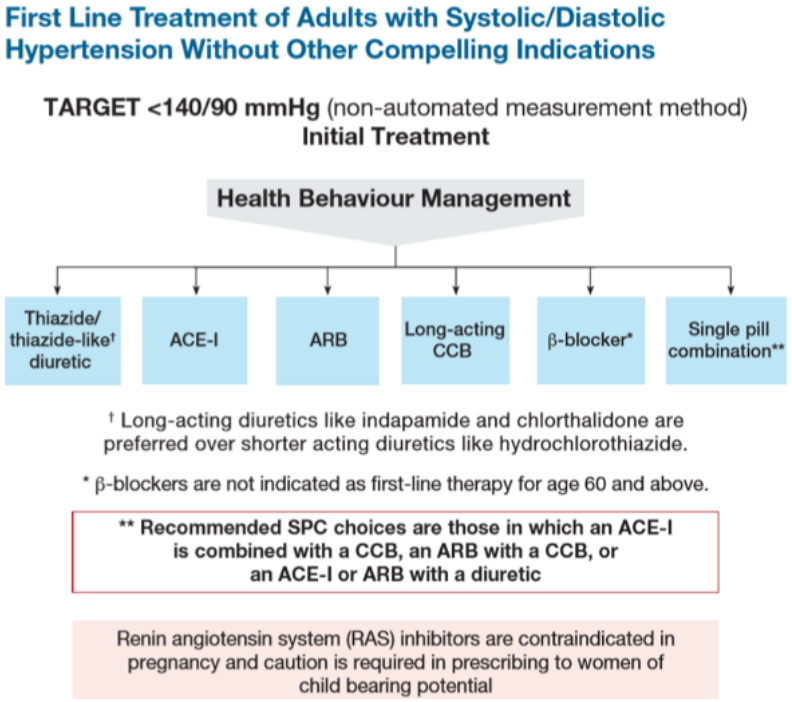
Antihypertensive Drug Therapy

We have already covered them all individually

You are expected to know them very well!!

Site of Drug Action*	Representative Drug	Drug Effects
1. Brainstem	Clonidine	Suppression of sympathetic outflow decreases sympathetic stimulation of the heart and blood vessels.
2. Sympathetic ganglia	Mecamylamine†	Ganglionic blockade reduces sympathetic stimulation of the heart and blood vessels.
3. Adrenergic nerve terminals	Reserpine	Reduced norepinephrine release decreases sympathetic stimulation of the heart and blood vessels.
4. Cardiac beta$_1$ receptors	Metoprolol	Beta$_1$ blockade decreases heart rate and myocardial contractility.
5. Vascular alpha$_1$ receptors	Prazosin	Alpha$_1$ blockade causes vasodilation.
6. Vascular smooth muscle	Hydralazine	Relaxation of vascular smooth muscle causes vasodilation.
7. Renal tubules	Hydrochlorothiazide	Promotion of diuresis decreases blood volume.
Components of the renin-angiotensin-aldosterone system (8a to 8e)		
8a. Beta$_1$ receptors on juxtaglomerular cells	Metoprolol	Beta$_1$ blockade suppresses renin release, resulting in (1) vasodilation secondary to reduced production of angiotensin II and (2) prevention of aldosterone-mediated volume expansion.
8b. Renin	Aliskiren	Inhibition of renin suppresses formation of angiotensin I, which in turn decreases formation of angiotensin II and thereby reduces (1) vasoconstriction and (2) aldosterone-mediated volume expansion.
8c. Angiotensin-converting enzyme (ACE)	Captopril	Inhibition of ACE decreases formation of angiotensin II and thereby prevents (1) vasoconstriction and (2) aldosterone-mediated volume expansion.
8d. Angiotensin II receptors	Losartan	Blockade of angiotensin II receptors prevents angiotensin-mediated vasoconstriction and aldosterone-mediated volume expansion.
8e. Aldosterone receptors	Eplerenone	Blockade of aldosterone receptors in the kidney promotes excretion of sodium and water and thereby reduces blood volume.





HTN Therapy with Comorbidities

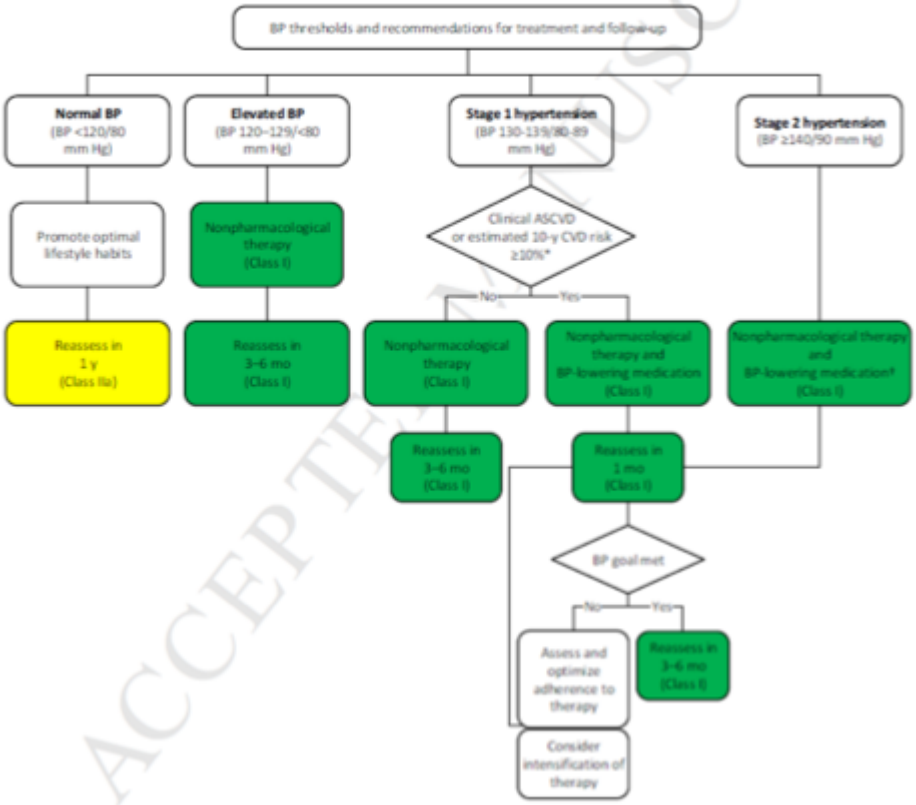
Classes of Antihypertensive Drugs Recommended for Initial Therapy of Hypertension in Patients With Certain High-Risk Comorbid Conditions

	Heart Failure	Recurrent Stroke Prevention	High Risk of CAD	Post–Myocardial Infarction	Diabetes	Chronic Kidney Disease
Recommended Drug Classes for Treatment of HTN	• ACE inhibitor • Aldosterone antagonist • ARB • Beta blocker • CCB • Diuretic	• ACE inhibitor • Diuretic	• ACE inhibitor • Beta blocker • CCB • Diuretic	• ACE inhibitor • Aldosterone antagonist • Beta blocker	• ACE inhibitor • ARB • Beta blocker • CCB • Diuretic	• ACE inhibitor • ARB

HTN Therapy: Intervention Algorithm

1. Lifestyle modifications
2. Add 1st antihypertensive Rx
3. Substitution or addition of 2nd antihypertensive
4. Substitution or addition of 3rd antihypertensive, etc.

Figure 4. Blood Pressure (BP) Thresholds and Recommendations for Treatment and Follow-Up



Combination Therapy

To achieve optimal blood pressure targets:

- Multiple drugs are often required to reach target levels, especially in patients with Type 2 diabetes.
- Replace multiple antihypertensive agents with single pill combination therapy.
- Single pill combinations or monotherapy should be considered for initial antihypertensive therapy.
- Low doses of multiple drugs may be more effective and better tolerated than higher doses of fewer drugs.

- Reassess patients with uncontrolled BP at least every two months.
- The combination of ACE inhibitors and ARBs should not be used.
- In high-risk patients in whom combination therapy is being considered, an ACE inhibitor plus a long-acting dihydropyridine CCB is preferable to an ACE inhibitor plus a thiazide or thiazide-like diuretic.

Suspected Resistant Hypertension

- Consider white coat hypertension and non-adherence.
- Diuretic therapy should be considered if not already prescribed or contraindicated.
- β-Blockers, when used in addition to ACE inhibitors or ARBs, have not been shown to have a clinically important effect on BP.
- Monitor creatinine and potassium when combining potassium sparing diuretics, ACE inhibitors and/or ARBs.
- Consider referral to a hypertension specialist if BP is still not controlled after treatment with three antihypertensive medications.

HTN Therapy: Multidrug Regimen Rules

1. Use drugs from different classes
    a. Increases efficacy (synergy interaction)
    b. Decreases necessary dosage → decreases toxicity
    c. Counter adverse reactions (ex. Vasodilator + beta-blocker decreases reflex tachycardia)
2. Start with low dosage
    a. HTN is not immediate threat
    b. Decreases risk of baroreceptor reflexes and toxicity
3. Gradually step-down medication
    a. After 1 year of good BP control only
    b. Lifestyle modifications can sustain BP regulation with smaller doses/# of drugs
    c. Monitor BP regularly when discontinuing an agent

Possible Reasons for Poor Response to Antihypertensive Therapy

- **Inaccurate measurement**
- **Suboptimal Treatment Regimens**
  - Dosage too low
  - Inappropriate combinations of antihypertensive agents
- **Poor Adherence**
  - Dietary
  - Physical activity
  - Medication
- **Associated Conditions**
  - Obesity
  - Tobacco use
  - Excessive alcohol consumption
  - Sleep apnea
  - Chronic pain
- **Drug Interactions**
  - Nonsteroidal anti-inflammatory drugs
  - Oral contraceptives
  - Corticosteroids and anabolic steroids
  - Cocaine
  - Amphetamines
  - Erythropoietin
  - Cyclosporine, tacrolimus
  - Licorice
  - Over-the-counter dietary supplements
  - Oral decongestant use (pseudoephedrine)
  - Monoamine oxidase inhibitors, certain selective serotonin reuptake inhibitors
- **Secondary Hypertension**
  - Renal insufficiency
  - Renovascular disease
  - Primary hyperaldosteronism
  - Thyroid disease
  - Pheochromocytoma and other rare endocrine causes
  - Obstructive sleep apnea

Individualizing HTN Drug Therapy

- Comorbidities requiring to avoid certain antihypertensives
    - Hyperkalemia → K+ sparing diuretics
    - Asthma → Beta2-blockers
    - AV heart block → CCBs
    - Diabetes & renal disease → thiazides (GFR rate is not sufficient enough)
    - (review table 47-5 p.522 for more examples)

- Special populations
    - African Americans
        - Increased HTN incidence + early onset
        - Monitoring & lifestyle = crucial
        - Diuretics & CCBs = best Rx

        - ACE-I & beta-blockers efficacy < whites
        - Still used if comorbid condition indicates it
    - Children & adolescents
        - No specific contraindications
        - Lower dosage
    - Elderly
        - Increased postural hypotension risk → avoid beta-blockers
        - Use low doses & gradual/incremental increase

Adherence Promotion

#1 chronic hypertension failure = lack of adherence to regimen

WHY?

- Chronic, slow, gradual progression with no Sx for most of development
- Difficult to justify use of Rx & prove efficacy
- Present vs. future complications

How to increase adherence:

- Patient education → future risk, current goals, etc.
- Self-monitoring → teach patients to record and follow their BP
- Minimize side-effects → encourage reporting, adjust regimen when possible
- Collaborative relationship → involve patient in choice of goals, program creation, etc.
- Simplifying regimen → minimum # of drugs with minimum # of administration/day
- Other measure → include family & friend to create support network!

HTN During Pregnancy

Most common pregnancy complication → 10% of pregnancies

Chronic HTN:

- HTN present before week 20
- Severe HTN (160+/110+) → treat
- Mild HTN → risks > benefits
- Avoid teratogens!!
    - Ex. ACE-I, ARBs & DRIs

Preeclampsia (PE):

- High BP + proteinuria after 20th week
- Low dose aspirin or L-arginine before week 16 decreases PE risk
- Late term mild PE: labor inductions
- Early mild PE: controversial… no evidence
- Severe PE: immediate labor induction = best
- If wait:
    - Labetolol to decrease BP

- Magnesium sulfate (antiseizure) to decrease epilepsy

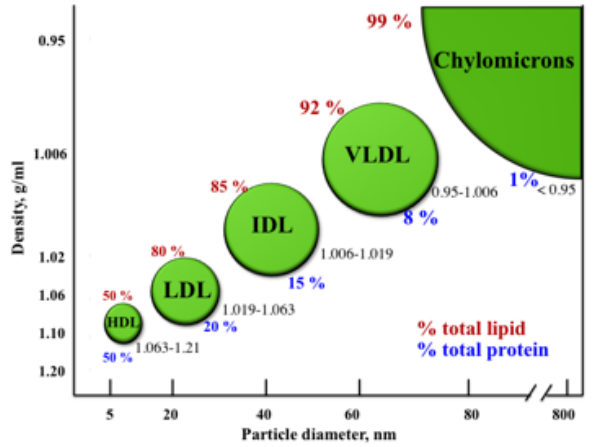
Atherosclerosis Prophylaxis (Ch. 50)

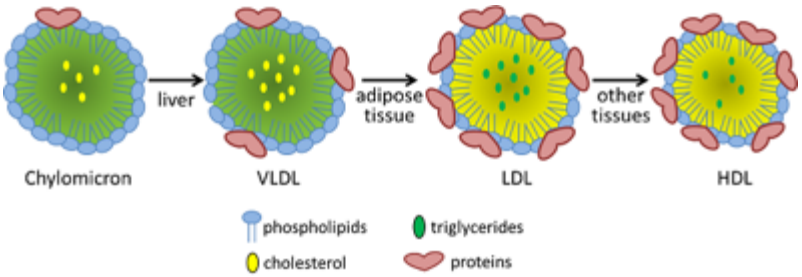
Cholesterol & Lipoproteins

- HDL is healthy
- LDL is bad
- The ratio of cholesterol is what is important. We do need some LDL, but it's when we have too much that it starts to have an effect.

Properties of the Plasma Lipoproteins That Affect Atherosclerosis

Lipoprotein Class	Major Core Lipids	Apolipoproteins	Transport Function	Influence on Atherosclerosis
VLDL	Triglycerides	B-100, E, others	Delivery of triglycerides to nonhepatic tissues	*Probably contribute* to atherosclerosis
LDL	Cholesterol	B-100	Delivery of cholesterol to nonhepatic tissues	*Definitely contribute* to atherosclerosis
HDL	Cholesterol	A-I, A-II, A-IV	Transport of cholesterol from nonhepatic tissues back to the liver	*Protect* against atherosclerosis





- LDL resembles a capsule carrying other cholesterol.

Cholesterol Screening

Adults:

- Screen every 5 years after 20
- Samples taken after fasting
- Measure
  - Total cholesterol
  - LDL cholesterol
  - HDL cholesterol
  - Triglycerides (TG)

Statin Benefit Groups as Defined by the 2013 ACC/AHA Blood Cholesterol Guidelines

Individuals with clinical atherosclerotic cardiovascular disease (ASCVD)
Individuals with primary elevations of LDL cholesterol (LDL-C) ≥190 mg/dL
Individuals 40 to 75 years of age with diabetes with LDL-C 70 to 189 mg/dL
Individuals without clinical ASCVD or diabetes who are 40 to 75 years of age with LDL-C 70 to 189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher

Kids:

- Screen between 9-11 & 18-21
- Familial history: screen between 2-8
- Lifestyle modifications if elevated cholesterol
- No lipid-lowering Rx until adults

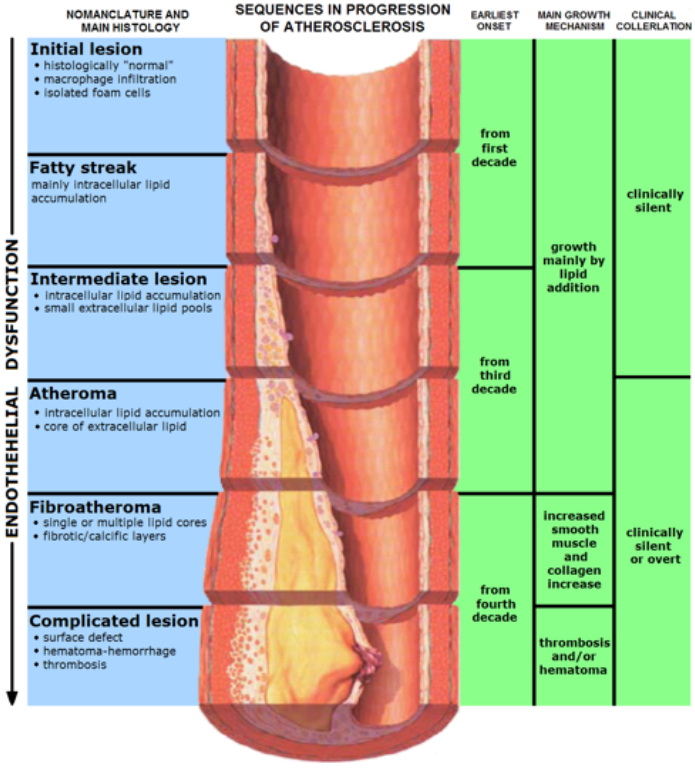
NCEP Classification of Cholesterol Levels for Children and Adolescents[a]

Category	Total Cholesterol (mg/dL)	LDL Cholesterol (mg/dL)
Acceptable	<170	<110
Borderline	170–199	110–129
Elevated	≥200	≥130

PATHO REVIEW

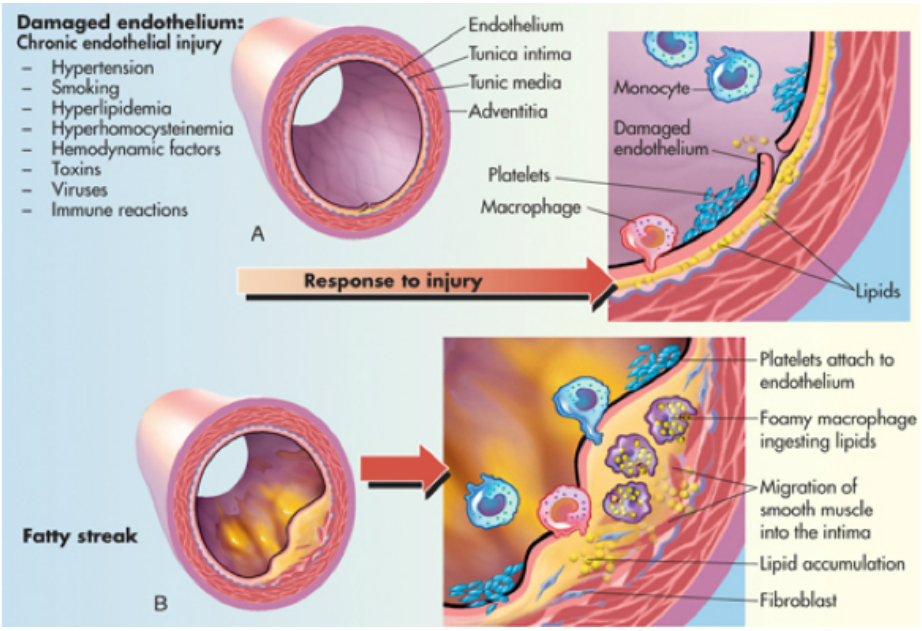
Atherosclerosis

- Accumulation of lipid-filled macrophage (foam cells) within artery wall → plaque formation = artery wall thickens
- Gradual pathologic process causing varying degrees of ischemia and complications
- Mostly clinically silent

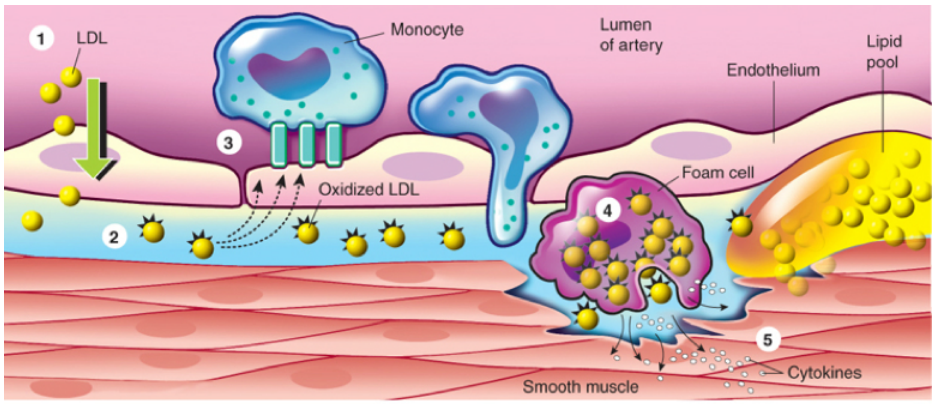


Atherosclerosis: Pathophysiology

- Damaged endothelium → inflammation + decreases anticoagulants & vasodilation → increases macrophage
- Macrophage invasion → increases ROS & LDL → increases smooth muscle cell → fatty streak



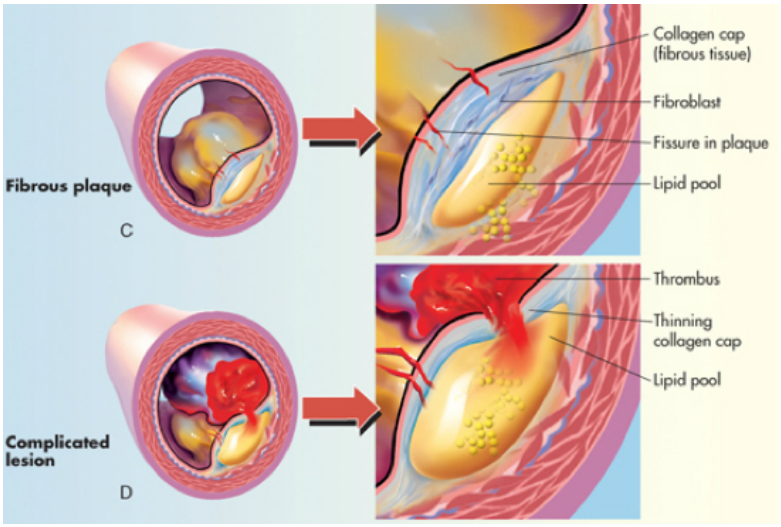
- LDL infiltration → inflammation → oxidative stress → oxidized-LDL
- Endothelial toxicity + smooth muscle hyperplasia + increased macrophage adhesion
- Increased inflammation



Increased foam cells → fatty streaks + inflammation → Smooth muscle cells collagen production → fibrous plaque

November 7th, 2019
William Archambault

Unstable plaques → increased rupture risk
Rupture = complicated plaque
Platelet adhesion → thrombus formation



Management:

- Decrease risk factors
- Plaque stabilisation
- Complication management

<u>Atherosclerosis: Management</u>

- Decrease risk factors → lifestyle changes
- Plaque stabilization → anticoagulants + anti-lipids
- Complication management → perfusion of ischemic areas

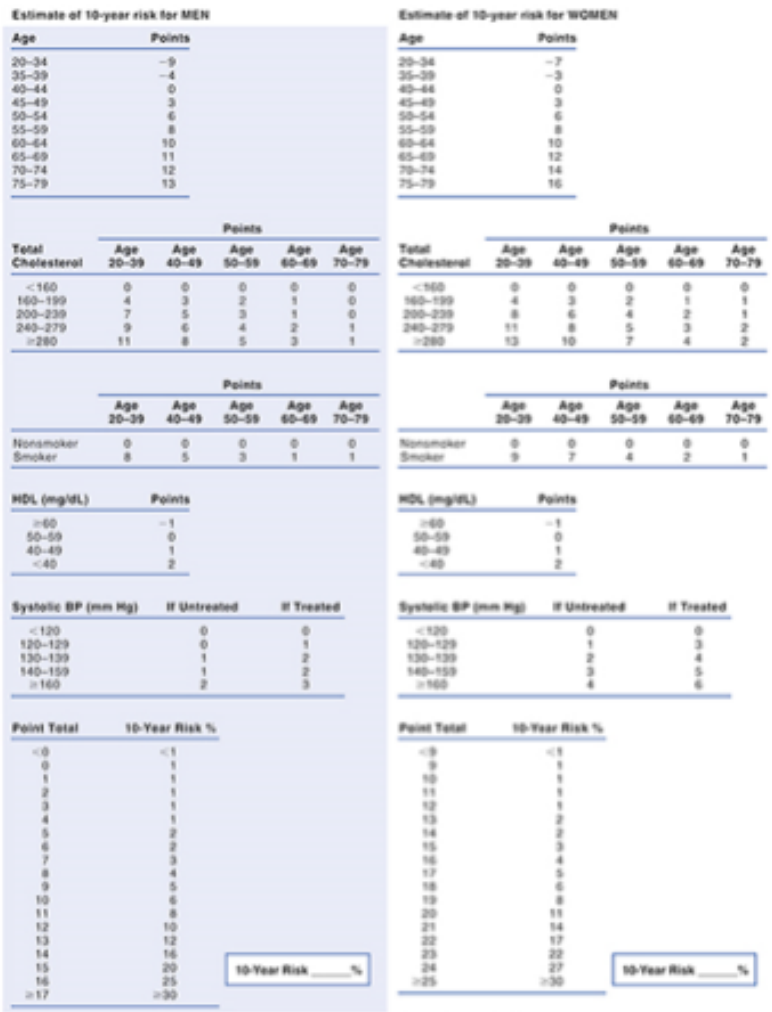
BACK TO PHARM

<u>ASCVD Risk Assessment</u>

Framingham risk prediction score - 10 year ASCVD risk

N.b. All dyslipidemias are independent risk factors

ASCVD risk equivalents (10-year risk of major CVE > 20%)



Estimate of 10-year risk for MEN

Age	Points
20–34	−9
35–39	−4
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	11
70–74	12
75–79	13

Total Cholesterol	Points Age 20–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79
<160	0	0	0	0	0
160–199	4	3	2	1	0
200–239	7	5	3	1	0
240–279	9	6	4	2	1
≥280	11	8	5	3	1

	Points Age 20–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dL)	Points
≥60	−1
50–59	0
40–49	1
<40	2

Systolic BP (mm Hg)	If Untreated	If Treated
<120	0	0
120–129	0	1
130–139	1	2
140–159	1	2
≥160	2	3

Point Total	10-Year Risk %
<0	<1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥17	≥30

10-Year Risk _____%

Estimate of 10-year risk for WOMEN

Age	Points
20–34	−7
35–39	−3
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	12
70–74	14
75–79	16

Total Cholesterol	Points Age 20–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79
<160	0	0	0	0	0
160–199	4	3	2	1	1
200–239	8	6	4	2	1
240–279	11	8	5	3	2
≥280	13	10	7	4	2

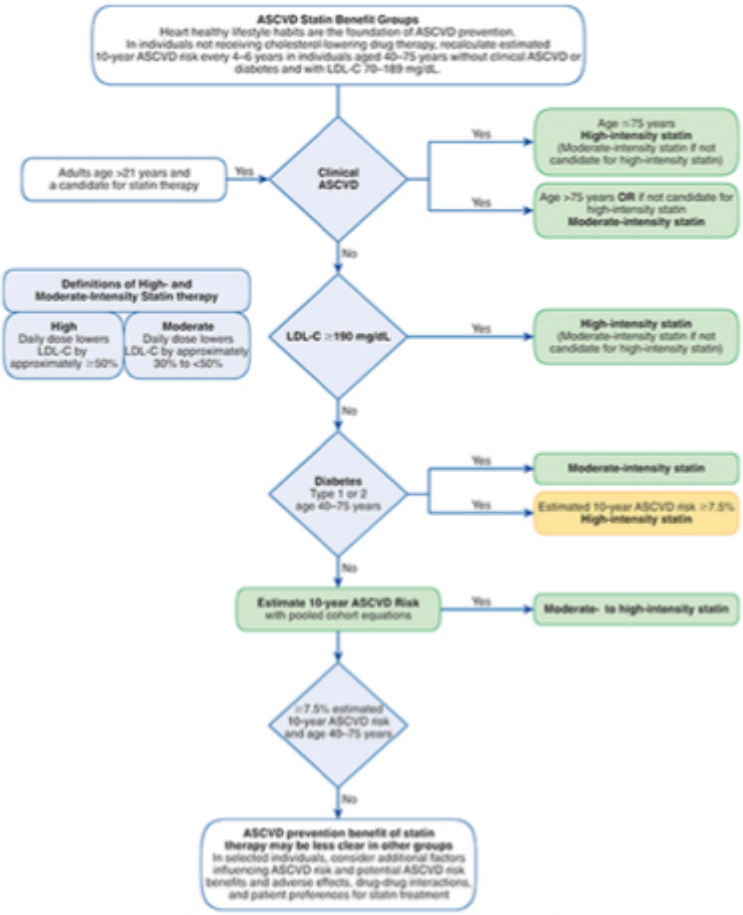
	Points Age 20–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dL)	Points
≥60	−1
50–59	0
40–49	1
<40	2

Systolic BP (mm Hg)	If Untreated	If Treated
<120	0	0
120–129	1	3
130–139	2	4
140–159	3	5
≥160	4	6

Point Total	10-Year Risk %
<9	<1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥30

10-Year Risk _____%



See Figures 50-3 (p.573) & 50-4 (p.574)

<u>High LDL Cholesterol Treatment</u>

- Therapeutic lifestyle changes (TLC) or TLC + drug therapy

Drug Therapy:

- Better for prevention/slow ASCVD onset
- Poor for atherosclerosis regression

High-, Moderate-, and Low-Intensity Statin Therapy

High-Intensity Therapy	Moderate-Intensity Therapy	Low-Intensity Therapy
Daily dose lowers LCL-C on average by ≥ 50%	Daily dose lowers LDL-C on average by ~30% to <50%	Daily dose lowers LDL-C on average by <30%
Atorvastatin: 40–80 mg Rosuvastatin: 20 mg	Atorvastatin: 10 mg Rosuvastatin: 10 mg Simvastatin: 20–40 mg Pravastatin: 40 mg Lovastatin: 40 mg	Simvastatin: 10 mg Pravastatin: 10–20 mg Lovastatin: 20 mg

TLC:

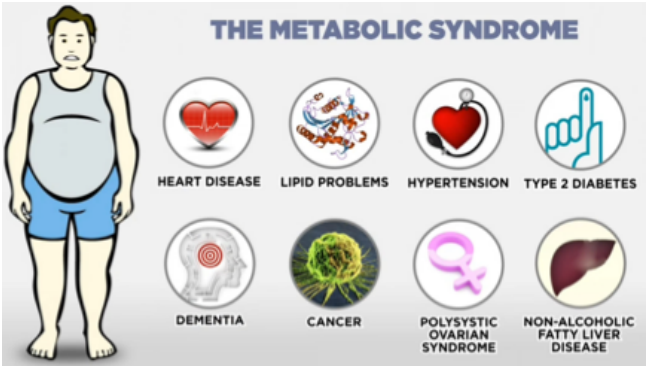
1. Diet
    a. Low saturated fats & cholesterol
    b. High soluble fibers & plant stanols (cholesterol-lowering)
2. Exercise
    a. Physical activity increases HDL & lowers LDL
    b. Duration (30-60mins) more important than intensity
3. Smoking cessation
    a. Smoking increases LDL & lowers HDL
4. Weight loss
    a. Especially metabolic syndrome patients

<u>Secondary Treatment Targets</u>

Treatments:

- Weight loss & physical activity
- Goals: decrease ASCVD & T2DM

High TG = independent ASCVD risk factor
Treat via statins + fibrates



A Closer Look At The Criteria For The Diagnosis Of Metabolic Syndrome[1]

Risk Factor	Criteria
Obesity	Waist circumference, which is geographic and ethnic specific U.S. men >102 cm, U.S. women >88 cm
Dyslipidemia (TG)	Triglycerides >150 mg/dL or being treated for elevated triglycerides
Dyslipidemia (HDL)	Elevated HDL cholesterol Male <40 mg/dL, female <50 mg/dL
Hyperglycemia	Fasting plasma glucose >100 mg/dL or being treated for hyperglycemia
Hypertension	Systolic blood pressure >130 mmHg and/or diastolic blood pressure >85 mmHg, or being treated for hypertension

*Metabolic syndrome puts you at increased risk of multiple diseases

<u>Plasma-Lipid Management Drugs</u>

- Statins = most effective & safe
- LDL decrease = therapeutic effect / HDL increase = beneficial side-effect
- Others are more specific to certain dyslipidemia

Drugs Used to Improve Plasma Levels of LDLs, HDLs, and Triglycerides

	HMG-CoA Reductase Inhibitors (Statins)[a]	Bile Acid Sequestrants	Fibrates	Ezetimibe	Monoclonal Antibody (PCSK9) Inhibitors
Results of Treatment					
Effect on LDL	↓ 21%–63%	↓ 15%–30%	↓ 6%-10%, but may increase if TGs are high	↓ 19%	↓ 63%–71%
Effect on HDL	↑ 5%–22%	↑ 3%–5%	↑ 10%–20%	↑ 1%–4%	↑ 6%
Effect on TG	↓ 6%–43%	↓ or no change	↓ 20%–50%	↓ 5%–10%	↓ 11%–16%
Clinical Trial Results	Reduced major coronary events, stroke, ASCVD deaths, and total mortality	Reduced major coronary events and ASCVD deaths	Reduced major coronary events	Impact on coronary events and mortality has not been established	Reduced major coronary events and stroke

HMG-CoA Reductase Inhibitors: Statins

- Reduction of LDL, HDL and TGs are the 3 main beneficial actions + atherosclerosis plaque stability

HMG-CoA Reductase Inhibitors: Selected Aspects of Clinical Pharmacology

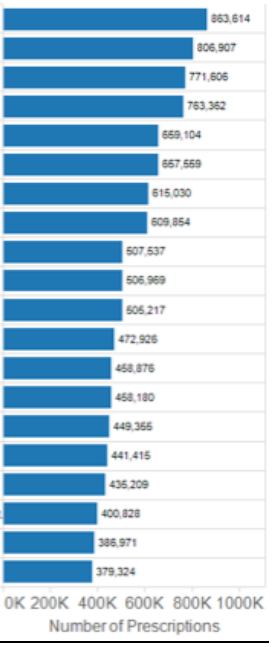
Drug	% Change in Serum Lipids[a]			Effect of CYP3A4 Inhibitors on Statin Levels[b]	Effect of Renal or Hepatic Impairment on Statin Levels
	LDL-C	HDL-C	TGs		
Atorvastatin [Lipitor]	↓ 25–60	↑ 5–15	↓ 15–50	Moderate ↑	No change with renal disease; significant ↑ with hepatic impairment
Fluvastatin [Lescol, Lescol XL]	↓ 20–40	↑ 2–11	↓ 10–25	None	No change with renal disease; possible ↑ with hepatic impairment
Lovastatin [Altoprev, Mevacor]	↓ 20–40	↑ 5–10	↓ 5–25	Significant ↑	↑ with significant renal impairment; no change with hepatic impairment
Pitavastatin [Livalo]	↓ 40–45	↑ 6–8	↓ 15–30	Little or none	↑ with significant renal impairment; little or no change with hepatic impairment
Pravastatin [Pravachol]	↓ 20–40	↑ 1–15	↓ 10–25	None	Potential ↑ with either renal or hepatic impairment
Rosuvastatin [Crestor]	↓ 30–60	↑ 3–20	↓ 10–40	None	↑ levels with severe renal impairment or hepatic dysfunction
Simvastatin [Zocor]	↓ 25–50	↑ 7–15	↓ 8–40	Significant ↑	Potential ↑ with severe renal or hepatic impairment

Top Prescribed Drugs (US, 2014)

Lipitor & Zocor = if combined, by far the most prescribed class of drug!!

2014 Top 20 Prescription Medications by Volume

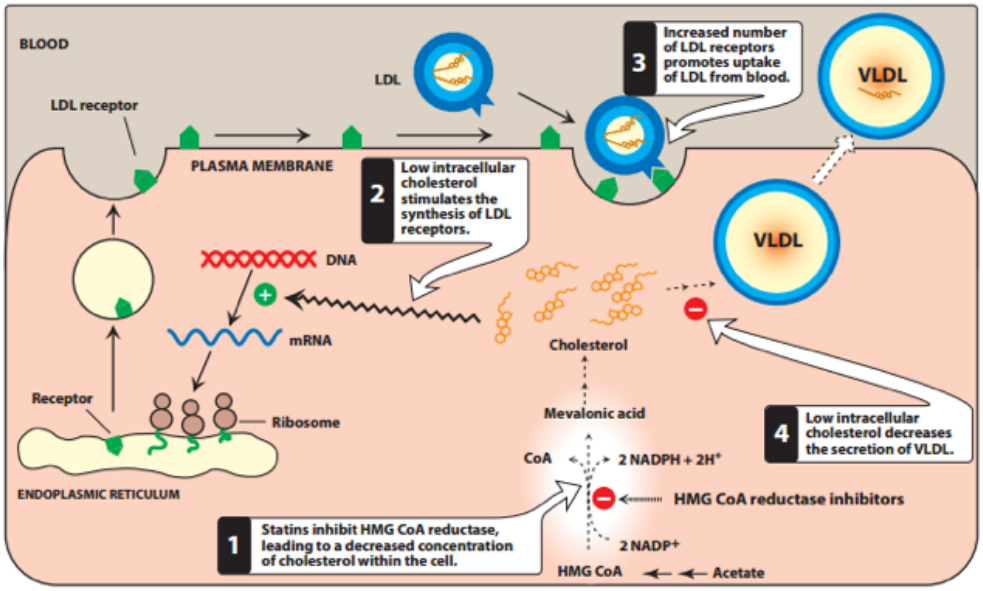
Brand Name	Drug Name	Therapeutic Category	Number of Prescriptions
PRINIVIL	LISINOPRIL	ANTIHYPERTENSIVES	863,614
SYNTHROID	LEVOTHYROXINE	THYROID AGENTS	806,907
VICODIN	HYDROCODONE/ACETAMINOPHEN	ANALGESICS - OPIOID	771,606
LIPITOR	ATORVASTATIN	ANTIHYPERLIPIDEMICS	763,362
ZOCOR	SIMVASTATIN	ANTIHYPERLIPIDEMICS	659,104
NORVASC	AMLODIPINE	CALCIUM CHANNEL BLOCKERS	657,559
PRILOSEC	OMEPRAZOLE	ULCER DRUGS	615,030
AMOXIL	AMOXICILLIN	PENICILLINS	609,854
FLONASE	FLUTICASONE	ALLERGIC RHINITIS	507,537
FORTAMET	METFORMIN	ANTIDIABETICS	506,969
ZITHROMAX	AZITHROMYCIN	ANTIBIOTIC	505,217
MICROZIDE	HYDROCHLOROTHIAZIDE	DIURETICS	472,926
ZOLOFT	SERTRALINE	ANTIDEPRESSANTS	458,876
SINGULAIR	MONTELUKAST	ANTIASTHMATIC/BRONCHODILATOR	458,180
XANAX	ALPRAZOLAM	ANTIANXIETY AGENTS	449,365
NEURONTIN	GABAPENTIN	ANTICONVULSANTS	441,415
PERCOCET	OXYCODONE/ACETAMINOPHEN	ANALGESICS - OPIOID	435,209
ADDERALL	AMPHETAMINE/DEXTROAMPHETA	ATTENTION DEFICIT HYPERACTIVITY DISORDER	400,828
VITAMIN D	VITAMIN	VITAMINS	386,971
DELTASONE	PREDNISONE	CORTICOSTEROIDS	379,324



Statins: Mechanism of Action

In hepatocytes:

1. HMG CoA inhibition
2. Decrease in cholesterol synthesis
3. Hepatocytes will increase LDL receptor synthesis
4. Decrease blood LDL levels



Statins: Therapeutic Uses

- Hypercholesterolemia: decreased LDL levels by 60%
- CV prevention: decreased risk proportional to LDL decrease
- Diabetes: refer to Canadian Guidelines
- Several promising uses under study:
  - Alzheimer's disease
  - Renal disease
  - Multiple sclerosis
  - Some cancers, etc.

- Kinetics:
  - PO administration
  - Some metabolized by CYP3A4 (interactions!)
  - Rosuvastatin - reduce dose in Asian population

HMG-CoA Reductase Inhibitors: FDA-Approved Indications

Indication	Atorvastatin [Lipitor]	Fluvastatin [Lescol, Lescol XL]
Primary hypercholesterolemia	✓	✓
Homozygous familial hyperlipidemia	✓	
Heterozygous familial hypercholesterolemia in adolescents	✓	
Mixed dyslipidemia	✓	✓
Primary dysbetalipoproteinemia	✓	
Primary prevention of coronary events	✓	
Secondary prevention of CV events	✓	✓
Increasing HDL cholesterol in primary hypercholesterolemia	✓	
Slowing progression of coronary atherosclerosis		✓

Statins: Adverse effects

- Generally safe and well tolerated
- Serious effects = hepatotoxicity & myopathies → rare / benefits outweigh risks

Myopathy/Rhabdomyolysis:

- 5-10% patients → muscle ache/tenderness
  - Monitor for blood creatinine kinase increase
  - Fatal rhabdomyolysis = 10x CK increase (very rare)
- Risk factor:
  - Advanced age
  - Low vitamin D & coenzyme Q levels
  - Comorbidities
  - Rosuvastatin > other statins (but still very rare)

Hepatotoxicity:

- Less than 0.5% of patients but still a risk
- Pre-treatment baseline LFT
- Serum transaminase levels increase 3x → discontinue

Others:

- New onset diabetes → unclear causation
- Confusion & memory loss → unclear evidence
- Slight increase cataract risk → uncommon mechanism

Drug interactions:

- Increased adverse effects risk with other lipid-lowering drugs → monitoring frequency increases
- CYP3A4 inhibitors/inducers alter concentration of lovastatin, simvastatin & atorvastatin

Nursing Capsule: Statins

Dosage & administration:

- Cholesterol synthesis increases at night
- Once daily evening administration increases efficacy

HMG-CoA Reductase Inhibitors: Preparations, Dosage, and Administration

Drug	Dosage	Administration With Regard to Meals	Dosage Changes in Special Populations	Preparations
Atorvastatin [Lipitor]	*Initial:* 10 mg at bedtime *Maximum:* 80 mg at bedtime	Take without regard to meals	No changes needed	*Lipitor (tablets):* 10, 20, 40, 80 mg
Fluvastatin [Lescol, Lescol XL]	*Initial:* 20–40 mg at bedtime *Maximum, Lescol:* 40 mg twice a day *Maximum, Lescol XL:* 80 mg at bedtime	Take without regard to meals	Reduce dosage for severe renal impairment	*Lescol (capsules):* 20, 40 mg *Lescol XL (extended-release tablets):* 80 mg
Lovastatin [Altoprev, Mevacor; generics]	*Initial:* 20 mg *Maximum:* 40 mg twice daily or 80 mg at bedtime	Take immediate-release tablets with evening meal to increase absorption. Take extended-release tablets at bedtime.	Reduce dosage for severe renal impairment	*Altoprev (extended-release tablets):* 20, 40, 60 mg *Mevacor and generics (tablets):* 10, 20, 40 mg
Pitavastatin [Livalo]	*Initial:* 2 mg once daily at any time of day *Maximum:* 4 mg once daily	Take without regard to meals	Reduce dosage for moderate to severe renal impairment	*Livalo (tablets):* 1, 2, 4 mg
Pravastatin [Pravachol; generics]	*Initial:* 40 mg at bedtime *Maximum:* 80 mg at bedtime	Take without regard to meals	Reduce dosage for moderate to severe renal impairment	*Pravachol and generics (tablets):* 10, 20, 40, 80 mg
Rosuvastatin [Crestor]	*Initial:* 5–20 mg at bedtime *Maximum:* 40 mg at bedtime	Take without regard to meals	Reduce dosage for severe renal impairment Reduce dosage in Asian patients	*Crestor (tablets):* 5, 10, 20, 40 mg
Simvastatin [Zocor; generics]	*Initial:* 10–20 mg at bedtime *Maximum:* 40 mg/day	Take without regard to meals	Reduce dosage for severe renal impairment	*Zocor and generics (tablets):* 5, 10, 20, 40, 80 mg

Drug selection:

- Atorvastatin or Simvastatin for LDL decrease > 40%
- Choose statin without CYP3A4 when possible
- Atorvastatin or Fluvastatin for kidney disease patients
- 6 statins available in generic form → cheaper $$

Use in pregnancy = contraindicated:

- Teratogenic risk > benefits (9 month break doesn't increase ASCVD risk much)
- Cholesterol = crucial for hormone & cell membrane synthesis → crucial fetal development

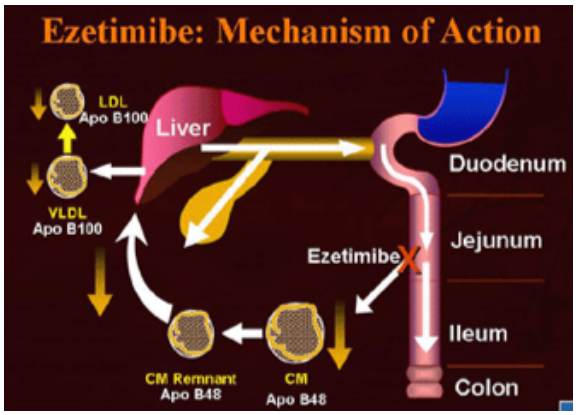
Ezetimibe

- Inhibition of cholesterol absorption → decreases blood total cholesterol, LDL & apoB

Therapeutic use:

- Adjunct to statins and TLC for cholesterol lowering

- No evidence of clinical improvement or ASCVD risk decrease

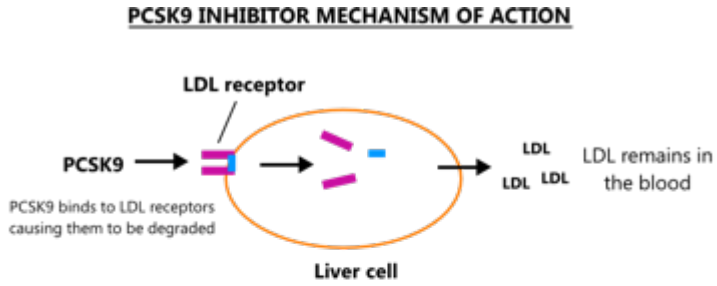


Kinetics:
- PO administration
- Eliminated in bile

Adverse effects:
- No GI related effects
- Potential cases of hepatitis, rhabdomyolysis & pancreatitis

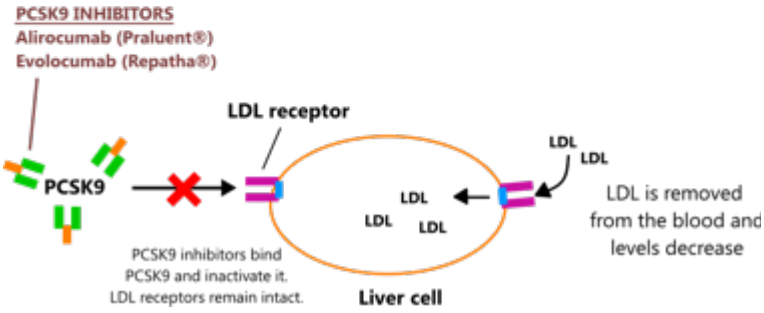
Drug interactions:
- Increased statins toxicity → monitor serum transaminase
- Avoid combination with fibrates → increases risk of gallstones
- Avoid combination with sequestrants → decreases absorption
- Cyclosporine → increases ezetimibe levels
- Caution with hepatic impaired patients

<u>PCSK9 Inhibitors: Aliro or Evolocumab</u>
- New class of drugs
- Benefits not completely known
- Appear to be relatively mild compared to statins



Therapeutic use:
- Adjunct to TLC + statins for total cholesterol decrease

Kinetics:
- Subcutaneous administration
- Half-life = 11-20 hours

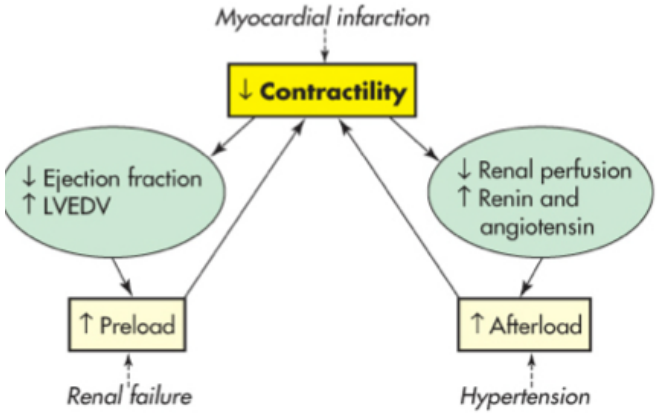


Adverse effects:
- Hypersensitivity reactions
- Risk of anti-PCSK9 inhibitor antibodies production

Drug Interactions:
- None known to this day

Heart Failure Drugs (Ch. 48)

PATHO REVIEW

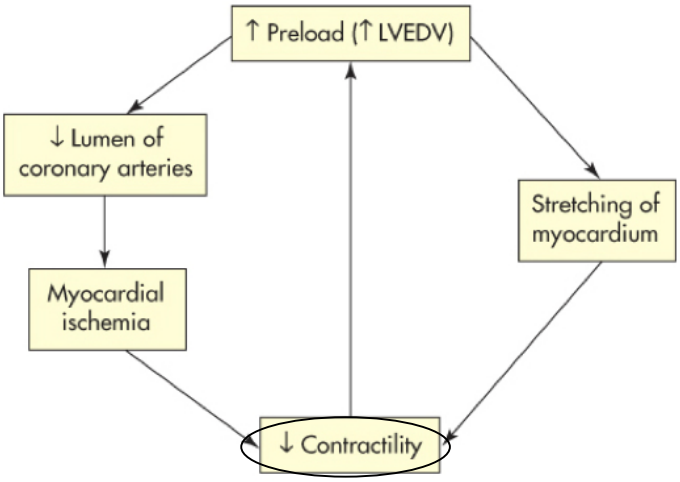


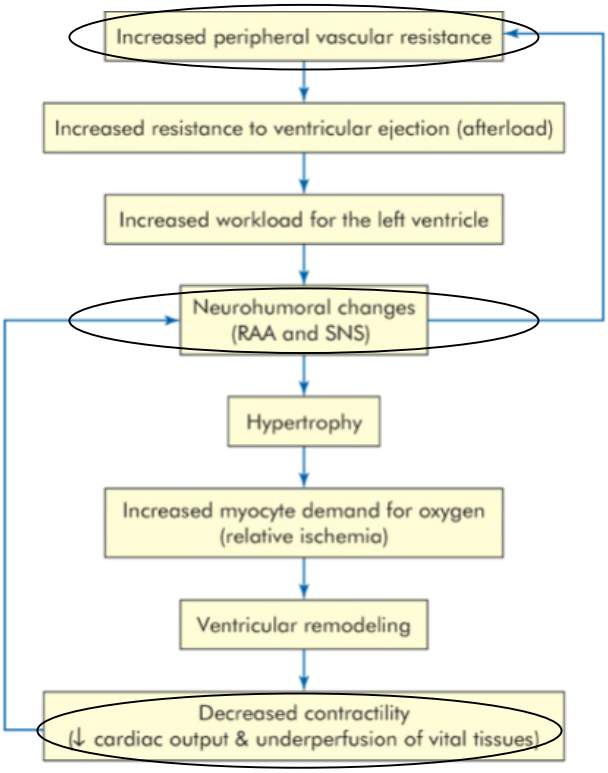
Heart Failure (HF)

- Heart dysfunction → decreased CO < systemic needs
- Congestive HF = left heart failure (LHF)
  - Systolic = HF + decreased ejection fraction (<40%)
- Heart fails to perform its job. It's like a heart attack for the rest of the body.
- Dx: decreased CO + markers of other heart disorders
- Tx:
  - Vasodilators → decrease preload and afterload
  - Diuretics → decrease preload
  - Inotropic drugs → increase contractility
  - ACE inhibitors → decrease preload and afterload
  - Specific to heart disease at origin

Systolic HF

- Heart disease → decreased contractility → decreased SV → decreased CO





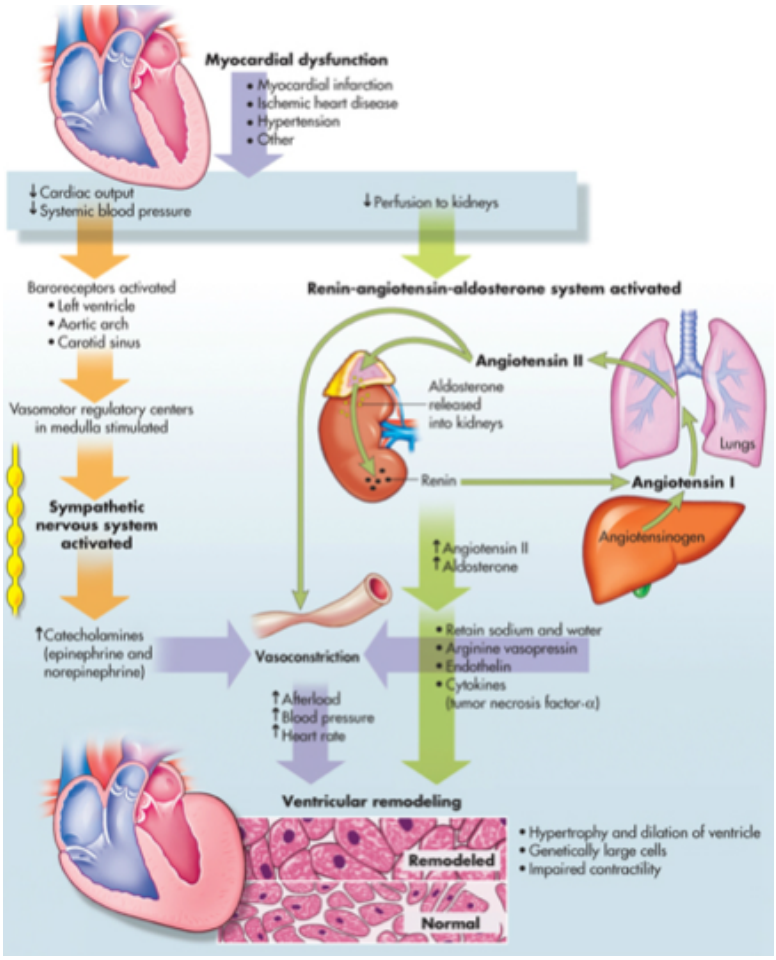
Systolic HF: Key Processes

RAAS & SNS

- Increased catecholamines → myocardial toxicity + hypertrophy
- Increased angiotensin II → increased aldosterone & vasopressin (ADH)
- Ventricular remodeling + increased BP + fibrosis & TPR

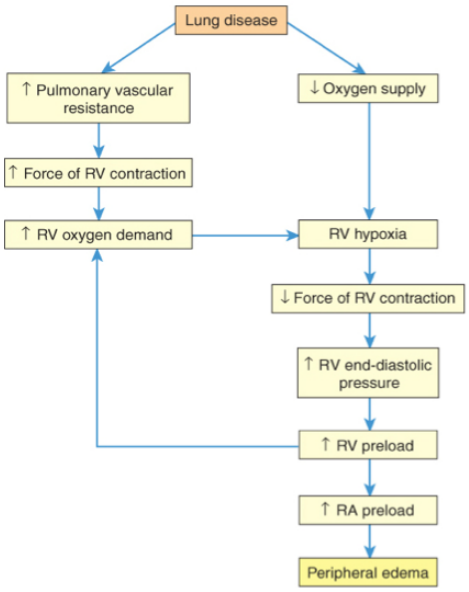
Others:

- Decreased calcium regulation → decreased contractility + arrhythmias
- Diabetes → micro & macrovascular complications → HF



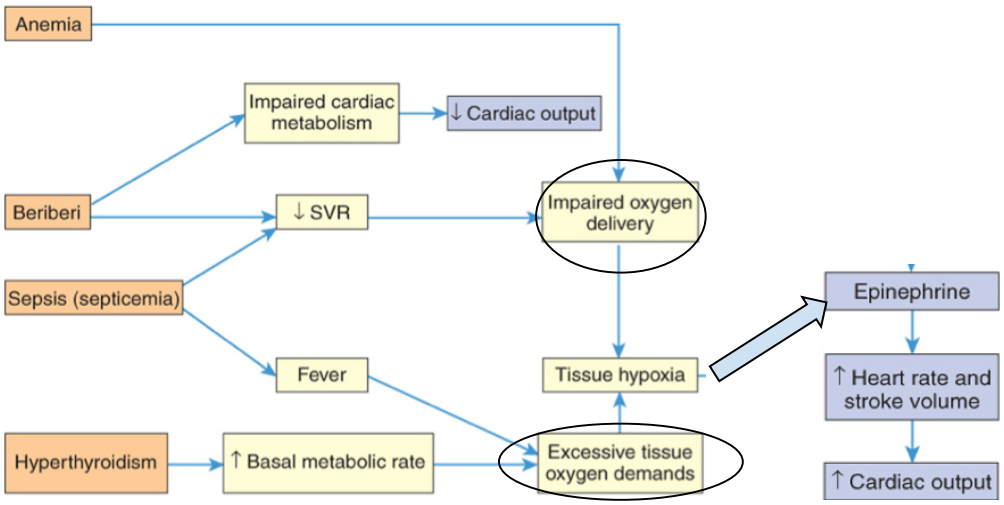
Right Heart Failure

- Decreased right heart CO
- Causes:
  - LHF → increased pulmonary BP
  - Increased pulmonary resistance → decreased CO
  - COPD → see cor pulmonale



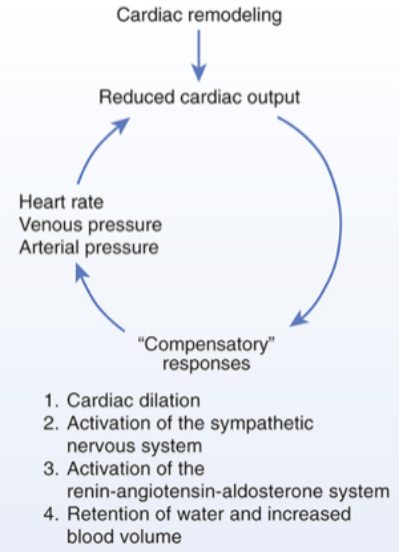
High Output Failure

- Perfusion failure despite increased CO

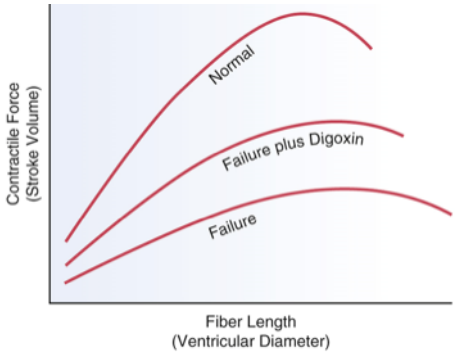


BACK TO PHARM

Heart Failure Vicious Cycle



- The reduced cardiac output sets in motion a bunch of compensatory mechanisms →
- The compensatory mechanisms are trying to counteract and increase the CO. The problem is, even if the body was able to increase the CO, because of the improper remodeling, this would only last a short amount of time. Compensatory mechanisms are very energy demanding.
- Main signs & symptoms
  - Fatigue
  - Short of breath
  - Tachycardia
  - Fluid retention → weight gain
  - Pulmonary edema



- Imagine the heart fibre similar to an elastic. So the harder you pull, the bigger the recoil. Initially, if you stretch the muscle fibre, you'll get an increase in stroke volume (increase in slope).
- There's a point where this relationship breaks (the dip at the end of the curve). If you stretch the fibre so much, causing damage, the recoil will decrease.

HF Classification & Stages

ACC/AHA Stage	NYHA Functional Classification
A At high risk for HF but without structural heart disease or symptoms of HF	
B Structural heart disease but without symptoms of HF	I Asymptomatic
C Structural heart disease with prior or current symptoms of HF	II Symptomatic with moderate exertion
	III Symptomatic with minimal exertion
D Advanced structural heart disease with marked symptoms of HF at rest despite maximal medical therapy. Specialized interventions (e.g., heart transplant, mechanical assist device) required	IV Symptomatic at rest

Heart Failure Drugs

- Routine HF Therapy:

Prototype Drugs

Drugs for Heart Failure

Diuretics

Hydrochlorothiazide
Furosemide

Inhibitors of the Renin-Angiotensin-Aldosterone System

Captopril (ACE inhibitor)
Losartan (angiotensin II receptor blocker)
Entresto (angiotensin receptor neprilysin inhibitor)
Eplerenone (aldosterone antagonist)

Beta Blockers

Metoprolol

Inotropic Agents

Digoxin (a cardiac glycoside)
Dopamine (a sympathomimetic)

Vasodilators

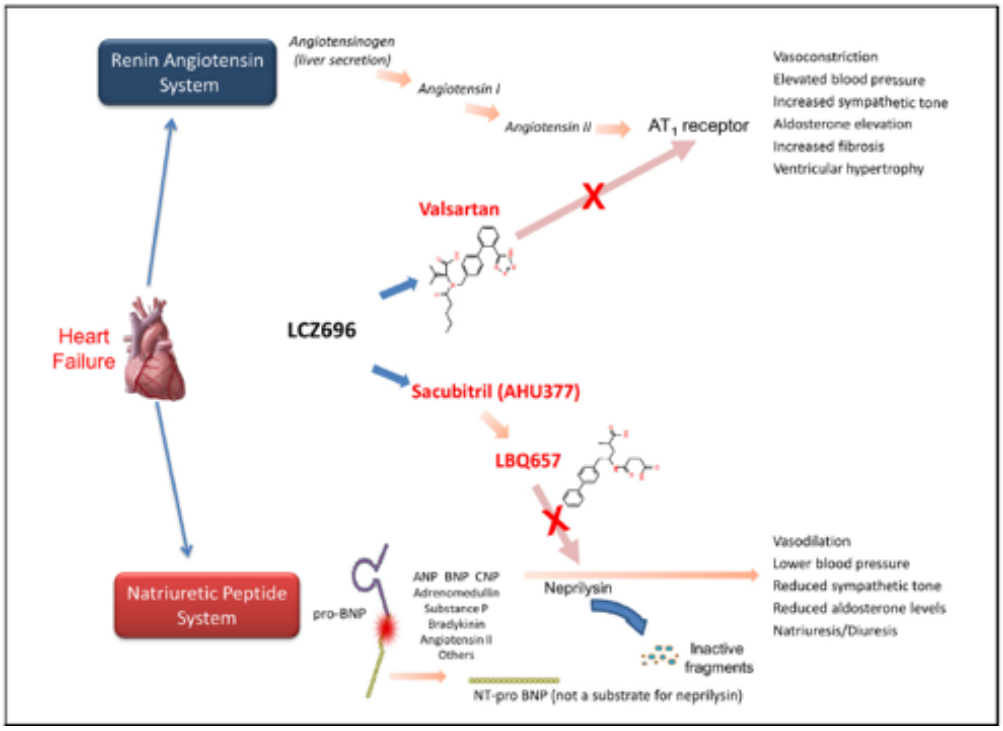
Isosorbide dinitrate plus hydralazine

Main HF Drugs

Drug Class	Diuretics	RAAS inhibitors	Beta-Blockers
General comments	1st-line HF Rx Sx reduction only No ↑ survival	ACE Inhibitors = Best choice for HF ARBs if ACE-I not tolerated	Protect from excessive SNS & Dysrhythmias Start with very low dosage
Beneficial Effects	↓ Blood volume ↓ all of the following: • Cardiac dilation • Pulmonary edema • Venous & Arterial BP	**ACE Inhibitors** Hemodynamic benefits ↑ Kinin → favorable cardiac remodeling **Angiotensin II Receptor Blockers** Equivalent to ACE-I except kinin ↑ **Aldosterone Antagonists** ↑ survival especially in symptomatic patients on ACE-I + Beta-blocker regimen	↑ LV ejection ↑ Exercise endurance ↓ HF progression ↑ Survival
Drug Examples	**Thiazide** Best if GFR is high **Loop Diuretics** Best for severe HF **K+-Sparing** Prevent digoxin toxicity		HF Approved Beta-blockers: **Carvedilol** **Bisoprolol** **SR-Metoprolol**

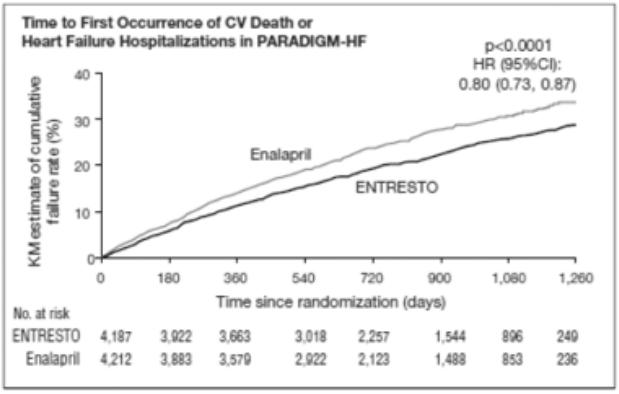
ARB + Neprilysin Inhibitor (ARNI)

- Block angiotensin receptor + increased natriuretic peptides (ANP, BNP)



- Study ended early due to overwhelming advantage of Entresto
- Superior to Enalapril for class II-IV HF:
  - Decreased hospitalization & overall + CV mortality
  - Over time, the gap grew bigger, confirming that Entresto decreases mortality +++

Figure A



Digoxin

Positive Inotropic Agent:

- Increases contractility of the heart
- Alters mechanical & electrical heart activity
- Narrow TI → serious dysrhythmias risk
- Potential increase in female mortality

Indications: HF & Dysrhythmias

- Alleviates HF symptoms but no increase in survival
- 2nd line drug for HF

Kinetics:

- PO or IV administration

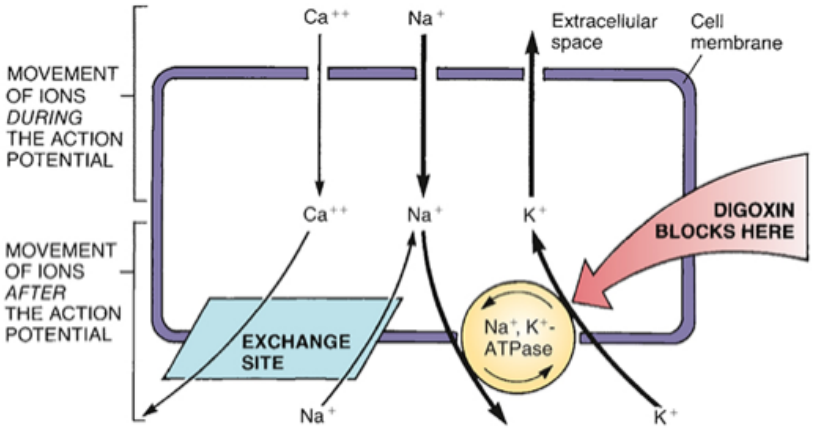
- Very lipid-soluble + 23% albumin-bound
- Almost 100% renal elimination
- Half-life = 1.5 days → 6 days to plateau
- Onset = 30min vs. 5min
- Peak = 4-6h vs. 1-4h

Plasma Digoxin Monitoring:

- Optimal range = 0.5-0.8 ng/mL
- Toxicity increase > 1ng/mL
- Substantial interpatient variability

Digoxin: Mechanism of Action

- Directly blocks the Na+/K+ ATPase pump: K+ levels rise outside the cell, and Na+ levels will rise inside the cell.
- Indirectly blocks at the Ca^{2+}/Na+ exchange site → increases myocyte calcium concentration → **increased contractility**
    - Because in the direct method there is an increase in intracellular Na+, the exchange site will stop pumping Na+ into the cell, to prevent rising levels even more.



Digoxin competes with potassium because they have the same binding site.

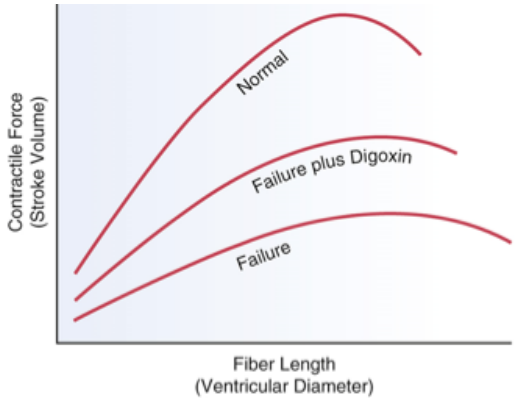
- Hypokalemia → increased digoxin action → toxicity
    - Because K+ levels are lower, Digoxin will bind more easily, it outnumbers K+
- Hyperkalemia → decreased digoxin action → Tx failure
    - K+ outnumbers Digoxin and will bind more easily than Digoxin.
- Must keep [K+] between 3.5-5 mEq/L

Digoxin: Benefits

Hemodynamic benefits:

- Increased cardiac output
- Decreased sympathetic tone → decreased HR & afterload
- Decreased renin release → decreased BP & blood volume

- Increased urine output → decreased BP & edema



Neurohormonal Benefits:

- Initiated at lower dose han inotropy
- Also caused by Na+/K+ ATPase inhibition
- Decreased renin release (decreased fluid retention)
- Increased baroreceptor reflex signalling (decreased SNS tone)

Electrical Effects - Beneficial or Toxic depending on Tx:

- SA node → decreased automaticity (HR)
- AV node → decreased conduction (HR)
- Purkinje fibers → increased automaticity/ectopic heart beats
- Ventricular myocytes → increased automaticity/ectopic heart beats
  ****Yet, no increased survival for HF patients****

<u>Digoxin: Cardiac Dysrhythmias</u>

- Rare if kept in therapeutic range
- Can trigger any type of dysrhythmias
- AV block + escape beats = most common
- Ventricular flutter/fibrillation = most dangerous

Management:

1. Withhold digoxin & diuretics
2. Monitor K+ levels
    a. Administer K+ if low levels
3. Antidysrhythmic drug administration (ex. Lidocaine)
4. If AV block/bradycardia → atropine
5. Severe toxicity → Fab antibody antidote
    a. Very expensive Tx (3-4000$ per injection!!)

Predisposing Factors:

1. Hypokalemia (ex. Diuretics, vomiting, diarrhea)
2. Elevated digoxin levels

   a. Individualization of dose = crucial
3. Heart disease
   a. Toxicity probability is proportional to severity

Digoxin: Other Adverse Effects

- GI ADRs: anorexia, nausea & vomiting
- CNS ADRs: fatigue & visual disturbances

GI/CNS ADRs tend to precede dysrhythmias. Teach patients to use them as warning signs.

Patient Education

- Explain all the toxicity related to digoxin
- Instruct patients to:
  - Take digoxin exactly as prescribed
  - Take K+ supplements/diuretics as prescribed

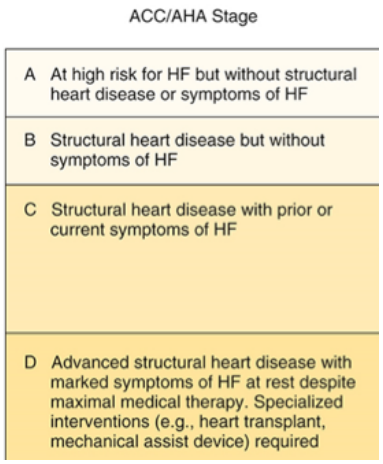
Many drug interactions with digoxin:

Interaction Type	Drug Exampes	Effect
Dynamic	Loop & Thiazide Diuretics	↑ K+ loss → Dysrhytmias
	Beta-blockers / Verapamil	↓ Contractility & HR
	Sympathomimetics	↑ Contractility & HR
Kinetics	Cholestyramine / Neomycin	↓ Absorption or Bioavailability
	Aminoglycosides / Antacids / Omeprazole	↑ Absorption or Bioavailability
	Captopril / Atorvastatin / Verapamil	↓ Excretion or ↑ Distribution or both

Nursing Capsule: Stage A, B & D HF Management

Stage A - asymptomatic

- HF onset risk reduction:
  - Decrease smoking & alcohol
  - Regulate blood glucose & dyslipidemia if present
  - ACE-inhibitor or ARB for diabetic or HTN patients



Stage B - structural heart disease

- Prevent symptomatic HF development
  - Stage A recommendations
  - ACE-I + beta-blocker for patients with decreased ejection fraction

Stage D - advanced HF despite maximal Tx

- Heart transplant = best hope
  - LV mechanical assist can increase life until transplant
  - Regulate fluid retention with diuretics → source of most Sx
  - Avoid ACE-inhibitors or beta-blockers in stage D → worsen state

Nursing Capsule: Stage C HF management

Stage C - structural + functional HF

- Goals = Sx alleviation + increased quality of life + slow cardiac dysfunction + prolong lifespan

Drug therapy

- 1st line = diuretics + ACE-inhibitors + beta-blockers
- Can add digoxin only if Sx management suboptimal with above options
- Can add aldosterone antagonists in moderate to severe HF with well functioning kidneys

Drugs to avoid

- CCBs
- NSAIDs
- Antidysrhythmic drugs - to not amplify the changes in HR

Device therapy

- Implanted cardioverter-defibrillator & cardiac resynchronization pacemakers can decrease mortality

Exercise training

- Recommended in stable patients → improve clinical status & quality of life

Treatment evaluation

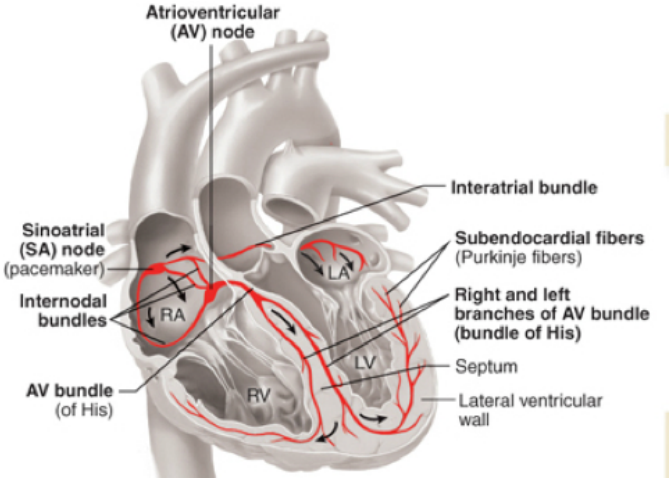
- Based on Sx & physical findings → decrease edema, increase physical endurance, increase sleep & sexual functions
- Decreased BNP levels in blood = survival
- Ejection fraction assessment is not a good measure of success

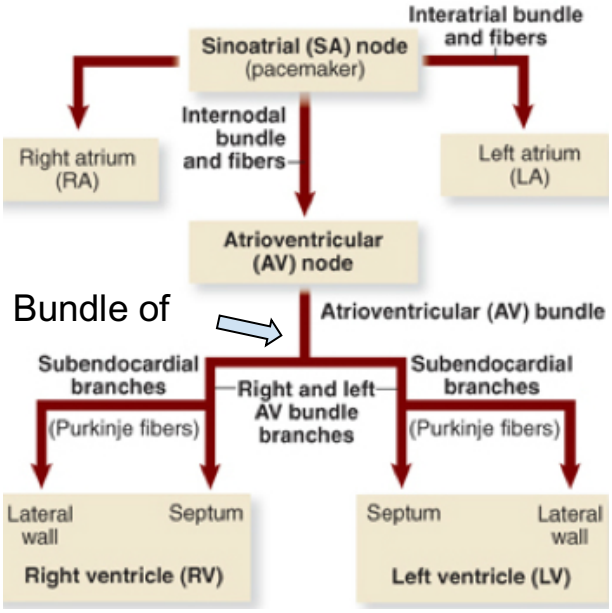
Antidysrhythmic Drugs (Ch. 49)

PATHO REVIEW

Heart Electrical System

- Inside to outside depolarization

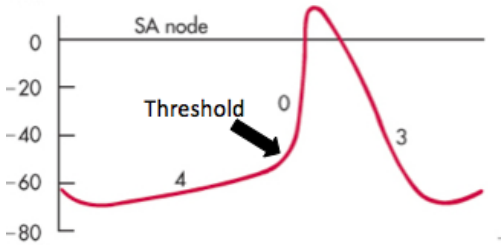




Cardiac Action Potentials

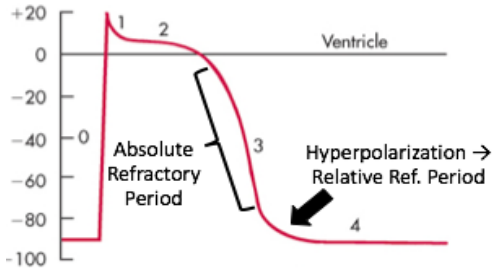
SA node action potential

- 0 = depolarization → T-type Ca^{2+} channels
- 3 = repolarization → K+ leak channels
- 4 = resting potential → leak (funny) Na+ channels & Ca^{2+} channels (calcium clock)



Ventricular action potential

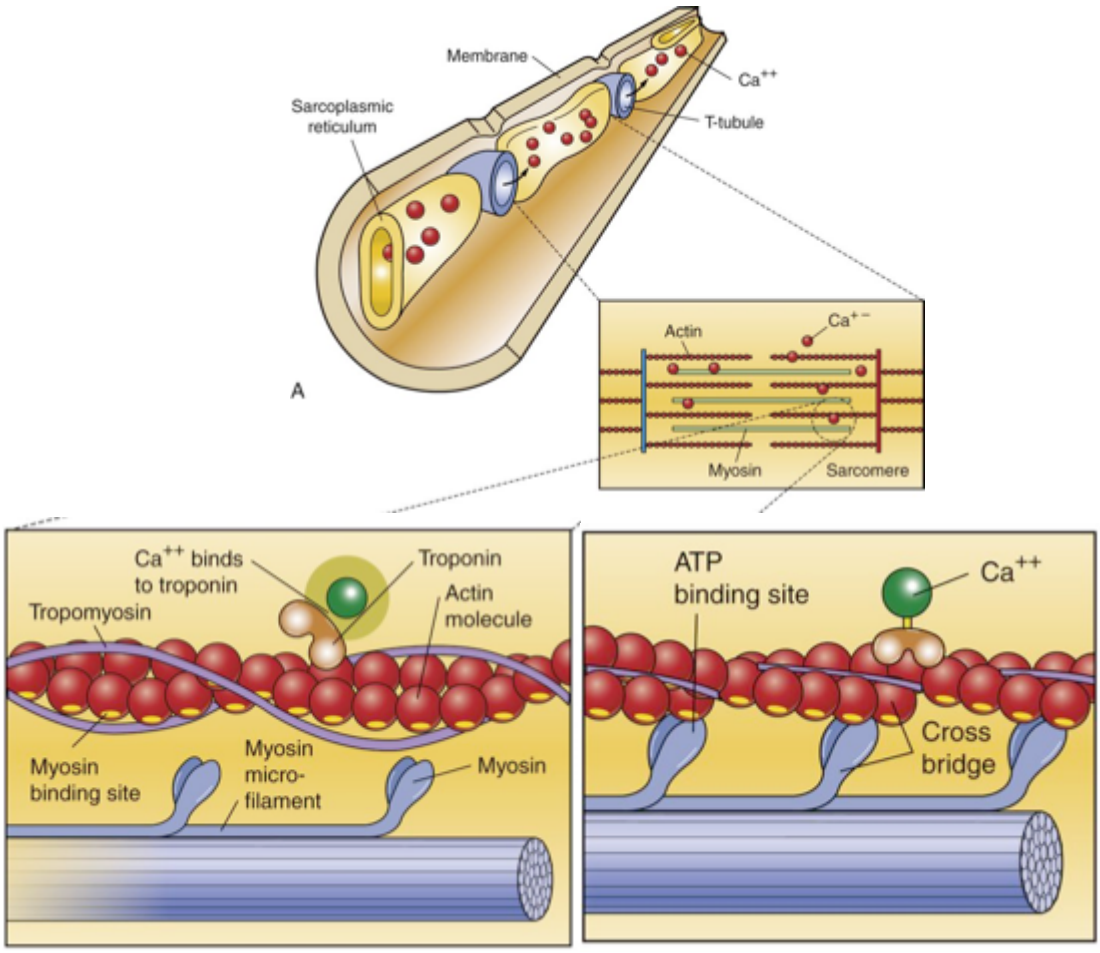
- 0 = depolarization → Na+ channels open
- 1= early repolarization → Na+ channels closure + T-type Ca^{2+} channels open
- 2 = plateau → L-type Ca^{2+} channels
- 3 = repolarization → K+ leak channels
- 4 = resting potential → back to normal



Calcium & Heart Contractions

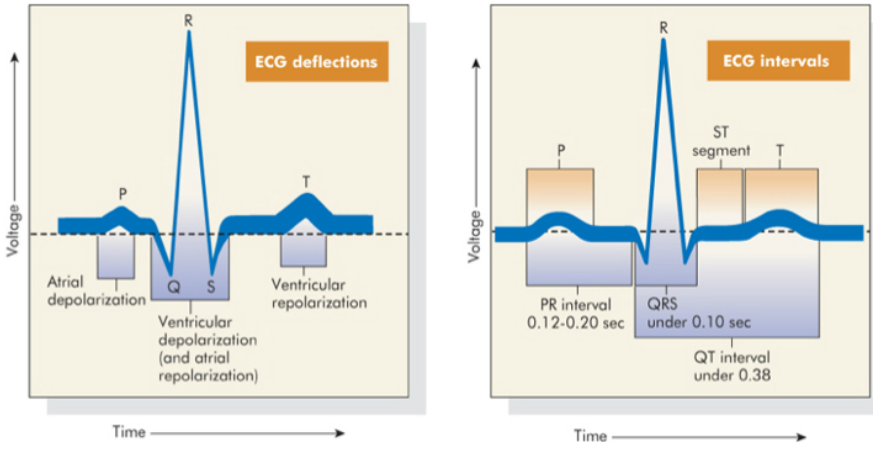
Contraction strength is proportional to calcium concentration

1. Depolarization → opening of plasma membrane calcium channels
2. Interstitial calcium entry → opening of internal calcium channels
3. Release calcium stored in sarcoplasmic reticulum → heart contraction



Electrocardiogram (ECG)

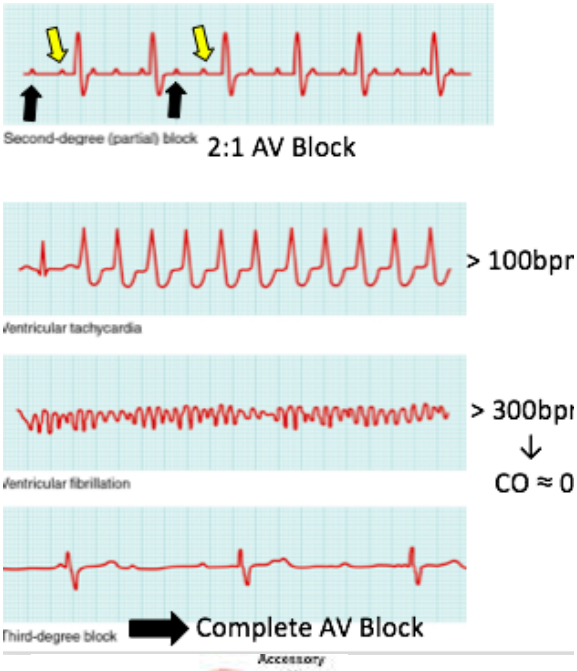
- Automaticity: diastolic (gradual) depolarization → calcium clock
- Rhythmicity: SA node = 60-100/min → AV node = 40-60/min → purkinje fibers = 30-40/min
    - Note: 3 types of cells with automatic properties: SA, AV nodes and purkinje fibers



Dysrhythmias

- Abnormal rhythm (SA node dysfunction) vs. abnormal conduction (circus re-entry)
- Range: single missed beat to fibrillation/cardiac arrest
- Bradycardia: <60 bpm (except athletes)
- Secondary arrhythmias
    - Increased vagal tone → decreased HR
    - Hyperkalemia/calcemia, hypoxia → increased HR

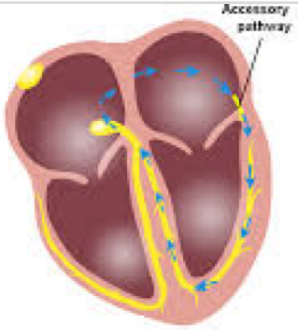
(Only review tables 32-12 & 32-13 for cases discussed in class)



- Yellow arrows = triggers full heart contraction vs. black arrows = atrial contraction only
- Complete AV block → QRS from AV or Purkinje

Circuit Re-entry Tachycardia

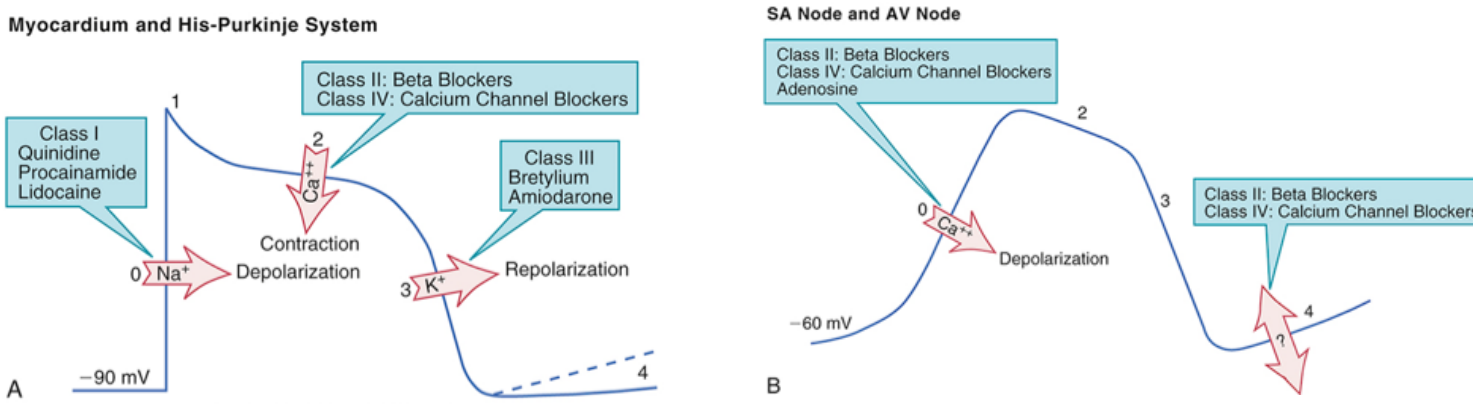
- Aberrant circular conduction
- Form of tachycardia → decreased CO
- Causes:
    - Around scar tissue
    - Accessory pathway



BACK TO PHARM

Antidysrhythmic (ADR) Drugs Classification

Class	Drug examples
Class I = sodium channel blockers	Quinidine (IA) / Lidocaine (IB) / Flecaine (IC)
Class II = beta blockers	Propranolol
Class III = potassium channel blockers (delay repolarization)	Sotalol / Amiodarone
Class IV = calcium channel blockers	Verapamil
Others	Digoxin & adenosine



- Adenosine is used as Dx tool
- Slows down the heart to determine the type of arrhythmia

<u>ADR Drugs: Prodysrhythmic Effects</u>

All ADR drugs can worsen existing dysrhythmias or generate new ones

- Monitor all patients
- Usage when benefits > risk
- Examples:
  - Non-sustained ventricular tachycardia → no major decrease in CO → benefits < risk
  - Serious ventricular fibrillation → risk of death → any Tx is worth it
- Class I & III agents → prolong QT interval → significant risk of Torsade de pointe

<u>Class IB: Lidocaine</u>

Differences vs. Class IA:

- Accelerate repolarization
- No ECG effects

Cardiac effects

- Decrease impulse conduction + ventricle's automaticity
- Accelerate repolarization
- No effect on vagal tone
- Ineffective against. supraventricular dysrhythmias

Other therapeutic use:

- Local anesthetic

Adverse Effects

- Usually well tolerated
- Risk of seizures & respiratory arrest

- IV admin → monitor BP & ECG for toxicity signs

Properties of Antidysrhythmic Drugs

Drug	Usual Route	Effects on the ECG	Major Antidysrhythmic Applications
CLASS IB			
Lidocaine	IV	No significant change	Ventricular dysrhythmias
Phenytoin	PO	No significant change	Digoxin-induced ventricular dysrhythmias
Mexiletine	PO	No significant change	Ventricular dysrhythmias

Class II: Propranolol

* Refresher: non-selective beta-blocker (both beta 1 & 2)

Cardiac & ECG Effects

- Beta1-block = decreased HR, conduction & contractility
- Prolongs PR interval

Other therapeutic use

- Hypertension
- Panic attacks/general anxiety

Adverse effects

- Well tolerated
- Risk of HF, AV block or sinus arrest
- Hypotension
- Bronchospasm - in asthma patients

Properties of Antidysrhythmic Drugs

Drug	Usual Route	Effects on the ECG	Major Antidysrhythmic Applications
CLASS II			
Propranolol	PO	Prolongs PR, bradycardia	Dysrhythmias caused by excessive sympathetic activity; control of ventricular rate in patients with supraventricular tachydysrhythmias
Acebutolol	PO	Prolongs PR, bradycardia	Premature ventricular beats
Esmolol	IV	Prolongs PR, bradycardia	Control of ventricular rate in patients with supraventricular tachydysrhythmias

Class III: Amiodarone

Oral therapy

- Best for atrial fibrillation / last resort
- K+ block = delay repolarization
- Also decreases SA node rate, conduction & contractility
- Metabolism by CYP3A4 → many interactions!

IV therapy

- Initial therapy of recurrent ventricular fibrillation
- Affect AV node: decrease conduction & increase refractoriness

Adverse effects
- Hypotension (15-20%)
- Bradydysrhythmia (5%)

PO adverse effects
- Long half life → prolonged toxicity
- Lung toxicity (ex. fibrosis) = greatest concern
- Pre-treatment chest x-ray is recommended
- Cardiotoxicity: HF, sinus bradycardia
- Thyroid toxicity: hypo or hyperthyroidism
- Hepatotoxicity: LFT recommended & look for signs
- Optic neuropathy or neuritis → rare
- Teratogen & enters breast milk
- Skin photosensitivity: wear sunblock & long clothing
- Some potential CNS impairment & GI distress

Properties of Antidysrhythmic Drugs

Drug	Usual Route	Effects on the ECG	Major Antidysrhythmic Applications
Amiodarone	PO, IV	Prolongs QT and PR, widens QRS	Life-threatening ventricular dysrhythmias, atrial fibrillation*
Dronedarone	PO	Prolongs QT and PR, widens QRS	Atrial flutter, atrial fibrillation
Sotalol	PO, IV	Prolongs QT and PR, bradycardia	Life-threatening ventricular dysrhythmias, atrial fibrillation/flutter

*Very effective but very toxic

<u>Class IV: Verapamil</u>
*Refresher: effects of CCBs = beta-blockers

Cardiac & ECG effects
- CC block = decrease HR, AV conduction & contractility
- Ineffective vs. ventricular dysrhythmias

Other therapeutic use
- Hypertension
- Angina

Adverse effects
- Well tolerated
- Risk of HF, AV block or bradycardia
- Increase vasodilation → hypotension
- Constipation

Drug interactions
- Digoxin: increased levels + additive action
- Beta blockers: additive action

Properties of Antidysrhythmic Drugs

Drug	Usual Route	Effects on the ECG	Major Antidysrhythmic Applications
CLASS IV			
Verapamil	PO	Prolongs PR, bradycardia	Control of ventricular rate in patients with supraventricular tachydysrhythmias
Diltiazem	IV	Prolongs PR, bradycardia	Same as verapamil

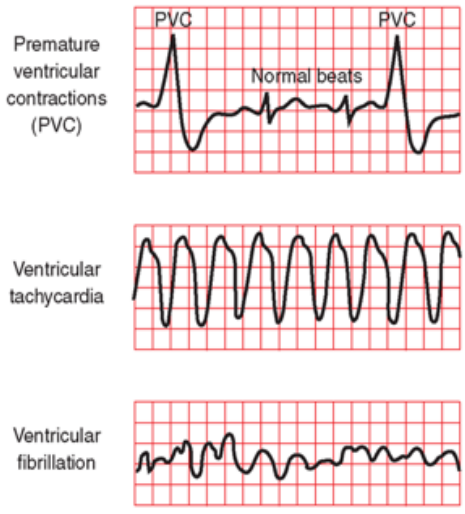
Supraventricular Dysrhythmias

- Anywhere above ventricles
- No major CO impairment
- Biggest concern = spread to ventricles → aim to slow down ventricular rate with cardioversion or class II & IV drugs

Atrial fibrillation	Most common Increased clot risk → stroke risk Anticoagulant prophylaxis Treatment: ● Slow rate via beta-blockers or CCBs = 1st choice ● Or restore rhythm with DC cardioversion
Atrial flutter	Increased stroke risk → anticoagulant prophylaxis Treatment: ● 1st line = DC cardioversion ● 2nd line = slow rate with CCBs or beta-blockers
Sustained supraventricular tachycardia SVT	Treatment: ● 1st line = carotid massage ● 2nd line = beta-blockers or CCBs

Ventricular Dysrhythmias

- Significant CO impairment
- Aim to abolish dysrhythmia
- 1st line = cardioversion
- Preferred ADR drugs = class I or III



Sustained ventricular tachycardia	150-250bpm → emergency intervention Treatment: ● 1st line = cardioversion ● 2nd line = IV lidocaine or amiodarone
Ventricular fibrillation (V.fib)	Multiple ectopic foci → CO drops to almost 0 Treatment: ● Defibrillation to restore rhythm ● Amiodarone for long-term prophylaxis
Premature ventricular complexes (PVCs)	Usually benign, treat only if MI present Treatment: ● 1st line = beta-blockers
Digoxin-induced ventricular dysrhythmia	Treatment: ● 1st line = phenytoin or Lidocaine (class 1B) ● Avoid DC cardioversion → can cause V.Fib
Torsade de pointe	Treatment = IV magnesium + cardioversion

<u>Nursing Capsule: ADR Therapy</u>

Risk-benefit analysis: usually treat only if ventricular pumping impairment

- Sustained or symptomatic dysrhythmias & ventricular dysrhythmias → benefits usually **>** risks
- Non-sustained or asymptomatic dysrhythmias & supraventricular dysrhythmias → risks usually **>** benefits

Phases of treatment

- Acute = terminate dysrhythmia → non drug measures (ex. DC cardioversion, carotid massage)
- Long-term = prevent dysrhythmia resurgence → risks usually **>** benefits
- Drug selection: **trial & error!!!** / use holter ECG monitoring to determine effectiveness & adjust

Minimizing risks

- Low initiation dose → gradual increase
- Holter monitoring of QT prolongation
- Monitor drug plasma concentrations

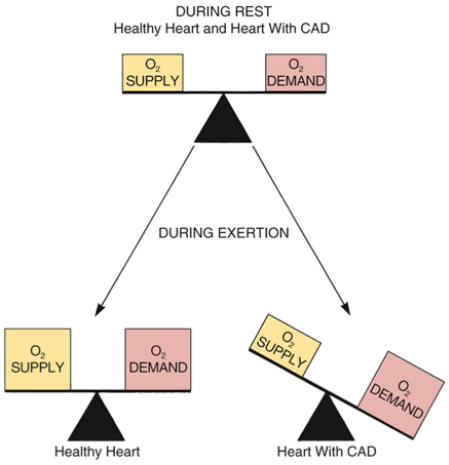
Angina Pectoris Therapy (Ch. 51)

Heart Disease Continuum

- Coronary artery disease (CAD) → myocardial ischemia (MI) → acute coronary syndrome (ACS)
- MI = intermittent imbalance between supply and demand
- Heart attack = acute, complete block of supply

Angina Pectoris

- Oxygen supply/demand imbalance → sudden chest pain
- Imbalance secondary to atherosclerosis development → symptoms vs. disease in itself
- Therapeutic goal = decrease attack intensity & frequency
- Options: increase supply or decrease demand



Types of Angina

Chronic Stable Angina treatment strategy:

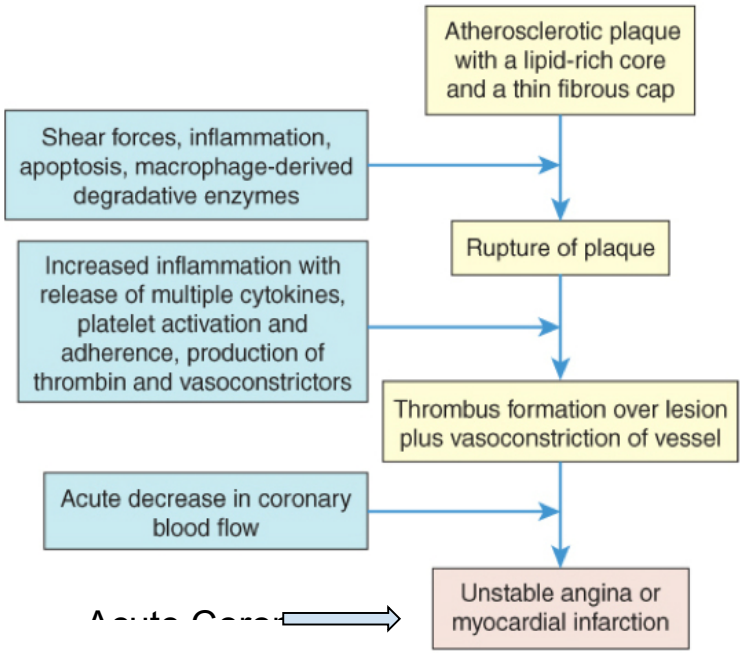
- Stable angina = coronary occlusion → decrease in demand = best option
- Best therapeutic agents:
  - Organic nitrates / beta-blockers / CCBs
  - Ranolazine = adjunct
  - Only Sx relief → no decrease in risk of MI
- Non-drug therapy:
  - Decrease in precipitating factors: stress, overexertion, cold exposure
  - Decrease in risk factors: smoking, HTN, HLD, sedentary lifestyle

Variant angina treatment strategy:

- Variant angina = coronary artery spasms → increase supply = best option
- Best therapeutic agents:
  - Organic nitrates / CCBs
  - Beta-blockers & ranolazine = inefficient
  - Only Sx relief → no decrease in risk of MI

Unstable Angina

**** Medical emergency, closer to MI ****



Antianginal Drugs

Mechanisms of Antianginal Action

Drug Class	Mechanism of Pain Relief	
	Stable Angina	Variant Angina
Nitrates	*Decrease oxygen demand* by dilating veins, which decreases preload	*Increase oxygen supply* by relaxing coronary vasospasm
Beta Blockers	*Decrease oxygen demand* by decreasing heart rate and contractility	Not used
Calcium Channel Blockers	*Decrease oxygen demand* by dilating arterioles, which decreases afterload (all calcium blockers), and by decreasing heart rate and contractility (verapamil and diltiazem)	*Increase oxygen supply* by relaxing coronary vasospasm
Ranolazine	*Appears to decrease oxygen demand,* possibly by helping the myocardium generate energy more efficiently	Not used

*Ranolazine is a new drug that has not been used much yet

Organic Nitrates: Nitroglycerin

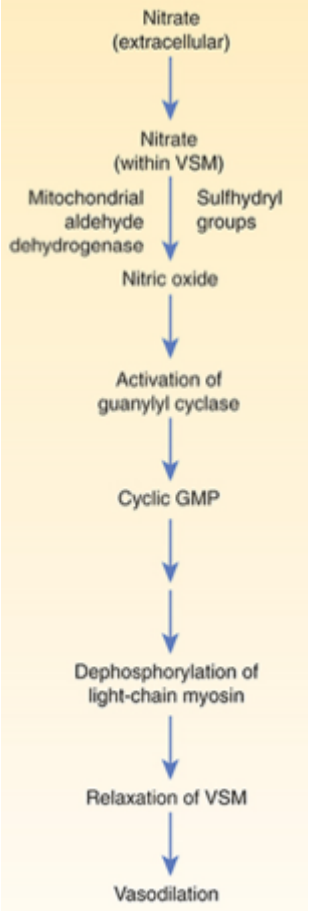
Antianginal effects:

- Stable: decrease venous return → decrease preload
- Variant: decrease risk of coronary vasospasms

November 14th, 2019
William Archambault

Kinetics:

- Very lipid soluble → many formulations
- Rapid hepatic metabolism → half life = 5-7 minutes



Adverse effects:

- Headache → intensity decreases over time
- Orthostatic hypotension
- Baroreceptor activation → reflex tachycardia

Drug Interactions:

- Beta-blockers or CCBs → decreases reflex tachycardia
- Hypotensive drugs/alcohol → potentiation
- PDE5 inhibitors (ex. viagra) → life-threatening hypotension - contraindicated

Tolerance issues:

- Very rapid (over 24h) - your body will quickly realize that the vasodilation is artificial and will build tolerance against it.
- Increase risk with high doses (sulfhydryl depletion)
- Intermittent schedule & smallest effective dose decreases risk

<u>Nursing Capsule: Nitroglycerin Management</u>

Preparation & administration:

- Equivalent efficacy → difference in onset & duration
- Acute therapy: rapid onset → termination of ongoing attack & acute prophylaxis
- Sustained therapy: long-acting preparations
- Intravenous therapy: surgery BP control or when other formulations fail

Discontinuation:

- Gradual for long-acting preparations
- Abrupt → reflex vasospasms

Organic Nitrates: Time Course of Action

Drug and Dosage Form	Onset[a]	Duration[b]
NITROGLYCERIN		
Sublingual tablets	Rapid (1–3 min)	Brief (30–60 min)
Sublingual powder	Rapid (1–3 min)	Brief (30–60 min)
Translingual spray	Rapid (2–3 min)	Brief (30–60 min)
Oral capsules, SR	Slow (20–45 min)	Long (3–8 hr)
Transdermal patches	Slow (30–60 min)	Long (24 hr)[c]
Topical ointment	Slow (20–60 min)	Long (2–12 hr)

Beta-blockers & CCBs

Beta-blockers (metoprolol, propranolol, etc.)

- 1st line for stable/effort angina
- Ineffective for variant angina

Antianginal effects:

- Decrease demand via decreased HR & contractility
- Decrease reflex tachycardia from nitroglycerin

Antianginal administration

- Lowest dose to achieve 50-60 bpm
- Discontinue gradually to avoid rebound MI

Adverse effects

- Classics:
    - Bradycardia
    - Hypotension
    - Bronchoconstriction

CCBs (verapamil, diltiazem, nifedipine)

- Effective for both stable & variant angina

Antianginal effects

- Arteriolar dilation → decrease afterload → decrease demand
- Decrease HR & contractility → decrease demand
- Coronary relaxation → decrease spasms → increase supply

Adverse effects

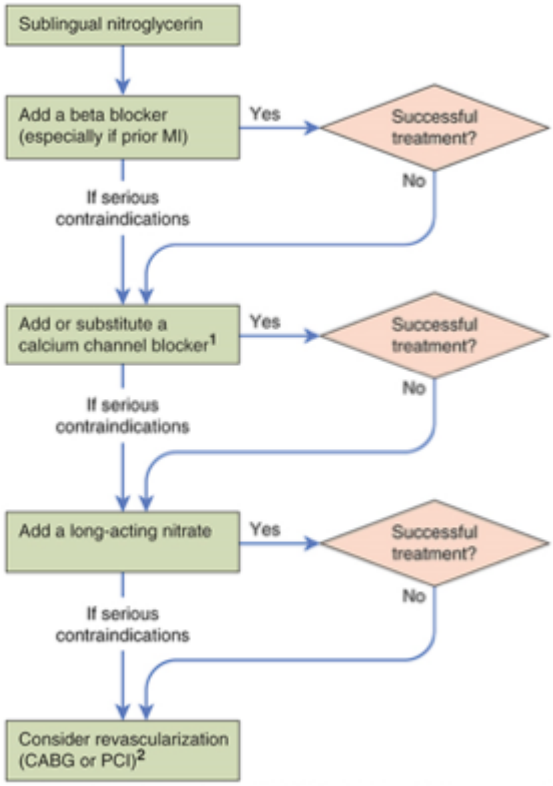
- Classics:
    - Bradycardia
    - Hypotension
    - Beta-blocker interaction

Nursing Capsule: Stable Angina Management

1. Decrease MI risk of death - PRIORITY
    a. Antiplatelet drugs (ex.. Aspirin or clopidogrel)
    b. Cholesterol-lowering drugs (ex. Statins, colesevalam)
    c. ACE-inhibitors (ex. captopril)

2. Decrease ischemic anginal pain
    a. Provide long-term prophylaxis via CCB, beta-blocker
    b. Sublingual nitrate in cases of attacks
    c. Risk factor decrease: exercise, lipid & glucose regulation, decrease stress/anxiety

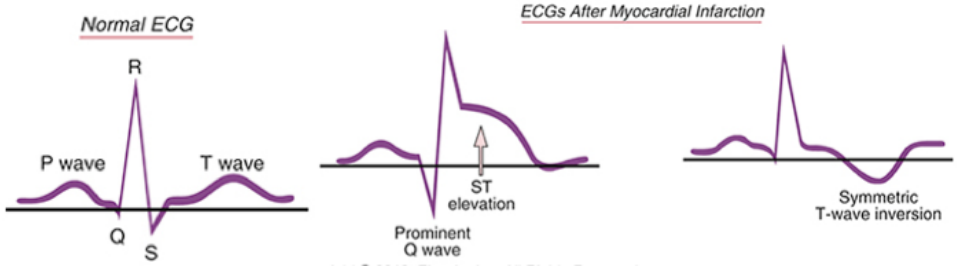
3. Follow algorithm for drug selection
    a. Use nifedipine if combine beta-blocker & CCB
    b. Synergistic actions of 3 class of agents
    c. Ex. contraindication situation: CCB > beta-blocker in asthmatic patients



ST-Elevation Myocardial Infarction (STEMI) (Ch.53)

STEMI

- Complete blockage of coronary blood flow → myocardial infarct → necrosis
- Hallmark signs/symptoms:
    - Chest pain > angina pectoris
    - Cardiac necrosis biomarkers
        - Cardiac troponin I & T = best markers
    - ECG changes



STEMI Management

- From onset to discharge = 6-10 days
- Key goals: reperfusion + decrease O2 demand
- Major threats:
    - Ventricular dysrhythmias
    - Heart failure
    - Cardiogenic shock

Routine Drug Therapy

*Initiate when STEMI suspected until clear diagnosis

- Oxygen supply → intuitive but no concrete evidence of benefits
- Aspirin → decrease in mortality + synergistic with reperfusion therapy
- Discontinue other NSAIDs! → increases mortality
- IV morphine → decrease chest pain + mild decrease in O2 demand
- Beta-blockers → decrease chest pain + infarct size + mortality
    - Oral administration preferred; make sure dosage is adequate
- Nitroglycerin → decrease O2 demand + infarct size + hypertension but not decrease in mortality
    - Sublingual administration followed by IV if necessary

Reperfusion Therapy

- Goal: restore blood flow of blocked coronary
- **PCI preferred to fibrinolytics**

Fibrinolytic therapy (ex. alteplase)

- Try to initiate within 30mins of hospitalization
- Increase ventricular functions + decrease mortality
- More contraindications than PCI
    - Ex. intracranial hemorrhage, severe HTN

PCI (balloon angioplasty + stent)

- Try to install within 90mins
- Adjunct: anticoagulant + antiplatelet drugs
- Success rate & duration > fibrinolytics Tx

Comparison of Fibrinolytic Therapy With Primary PCI

ADVANTAGES OF FIBRINOLYTIC THERAPY
• More universal access • Shorter time to treatment • Results less dependent on physician experience • Lower system cost
ADVANTAGES OF PRIMARY PCI
• Higher initial reperfusion rates • Less residual stenosis • Lower recurrence rates of ischemia/infarction • Does not promote intracranial bleeding • Defines coronary anatomy and LV function • Can be used when fibrinolytic therapy is contraindicated

LV, Left ventricular; *PCI,* percutaneous coronary intervention.

Reperfusion Therapy Adjuncts

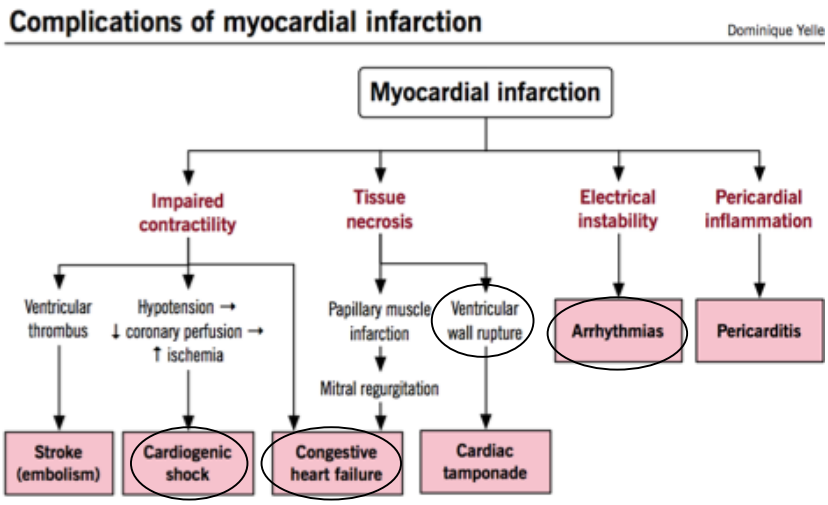
Used with both PCI or fibrinolytics therapy to increase success and decrease mortality

- Heparin → indicated for all STEMI reperfusion patients
    - With PCI: once before procedure
    - With fibrinolytics Tx: before until 72h post therapy
- Fondaparinux → factor Xa inhibitor
    - Alternative for fibrinolytic patients with contraindication for heparin
- Bivalirudin → direct thrombin inhibitor
    - Alternative for PCI patients with heparin-induced thrombosis
- Antiplatelet drugs → clopidogrel + aspirin = preferred combination for stent insertions
    - Watch out for severe bleeding signs & Sx
- ACE inhibitors → decrease in mortality

- Recommended for all STEMI patients unless contraindicated
- ARBs also seem equivalent

STEMI Complications

- Ventricular dysrhythmias
  - Major cause of death
  - Tx: defibrillation + IV Amiodarone for 24h-48h
  - Avoid prophylaxis anti-dysrhythmia Rx → increase mortality!
- Cardiogenic shock:
  - 7-10% of STEMI → large infarct = increase risk
  - Tx: inotropic drugs + vasodilator
  - Sx relief only, no mortality decrease
- Heart failure
  - Best Tx regimen: diuretic + beta-blocker + ACE-inhibitor
- Cardiac rupture
  - Rupture of ventricular wall → shock → rapidly fatal
  - Highest risk: first days of large anterior infarcts
  - Tx: vasodilator + beta-blocker = decrease risk



Secondary Prevention of STEMI

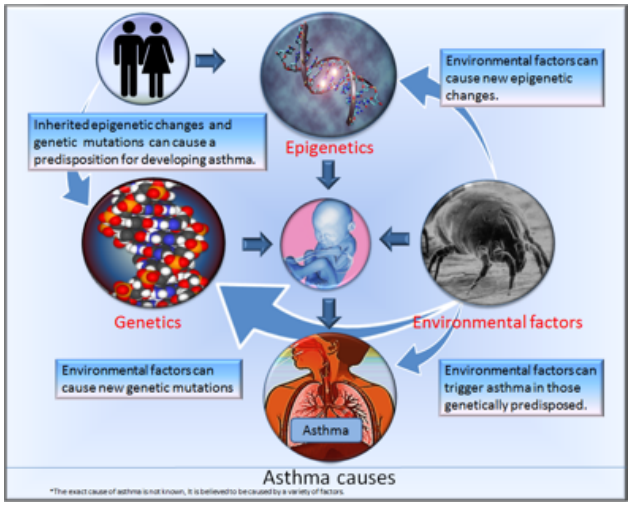
- Complication-free patients → discharge after 72h
  - High risk of reinfarctions (5-15%) & complications
  - Risk reduction Tx + long-term drug regimen decreases mortality
- Risk reduction Tx
  - Exercise, smoking cessation, metabolic syndrome management
- Long-term RX regimen: continue indefinitely
  - Beta-blockers
  - ACE-I or ARB
  - Antiplatelets or anticoagulant
  - Statins

Drugs for Asthma & COPD

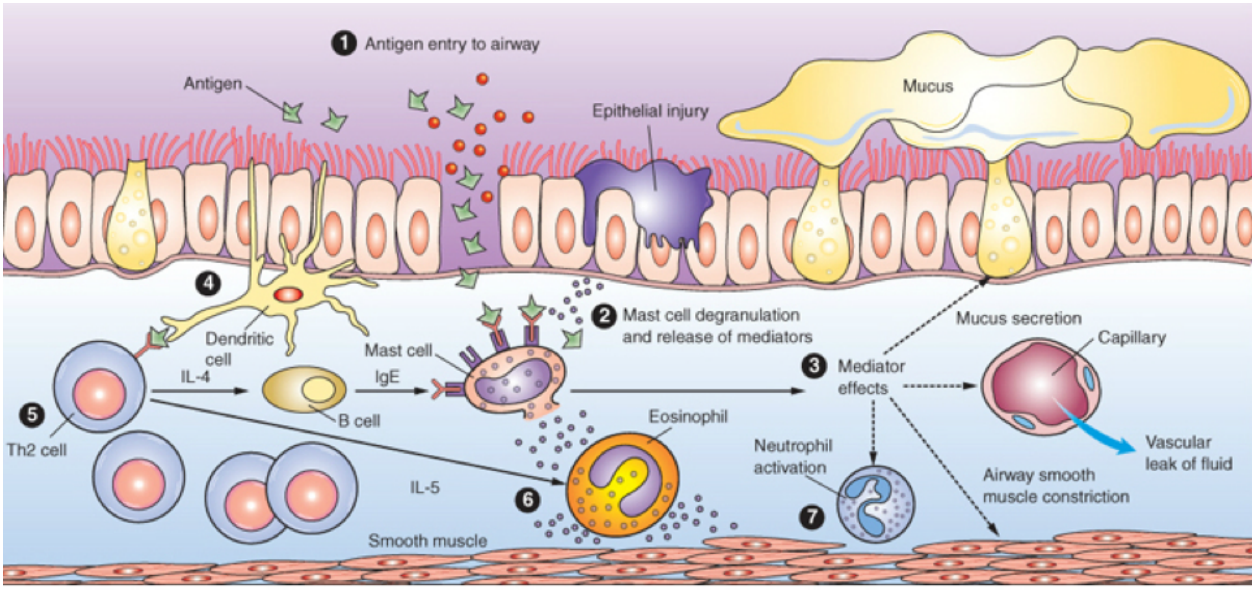
PATHO REVIEW

Asthma

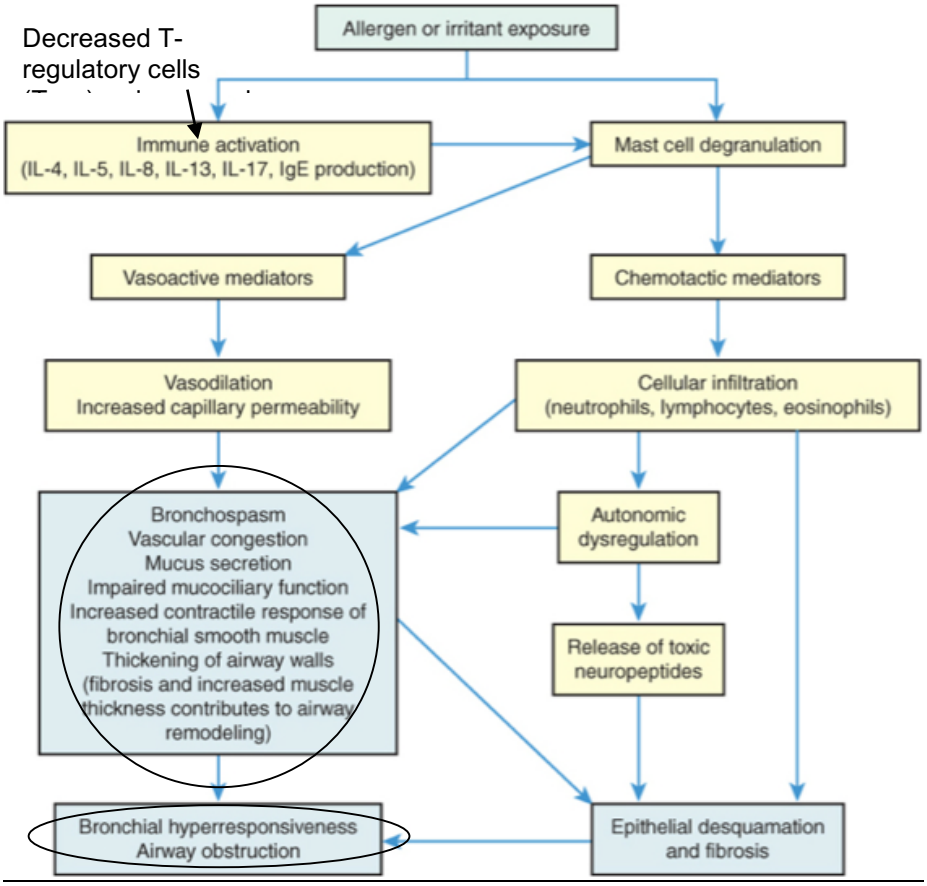
- Chronic inflammation of the bronchial mucosa → reversible airway obstruction
- Type-I IgE-mediated hypersensitivity reaction
  - Upon reexposure to allergen
- Complex mix of genetic susceptibility & environmental exposition
  - Nutrition → epigenetics & allergen exposure
  - Genes associated to T_H2 profile
  - Hygiene hypothesis: $T_H2 > T_H1$



Acute Asthma Pathophysiology

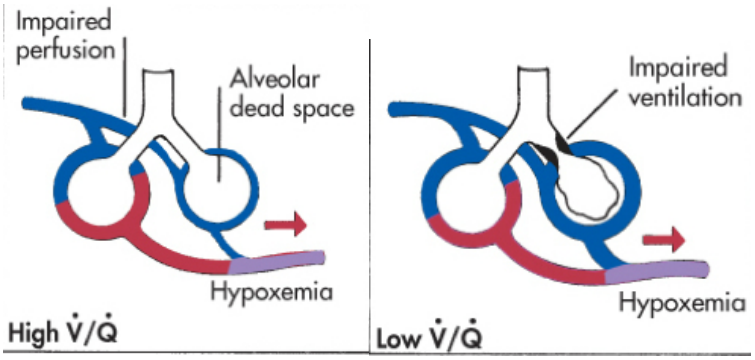


Chronic Asthma Pathophysiology



Asthma Pathophysiology

- Increased alveolar gas pressure → decreased perfusion
- Increased airway obstruction → decreased ventilation
- Variable V/Q mismatch across lungs



Asthma Manifestations

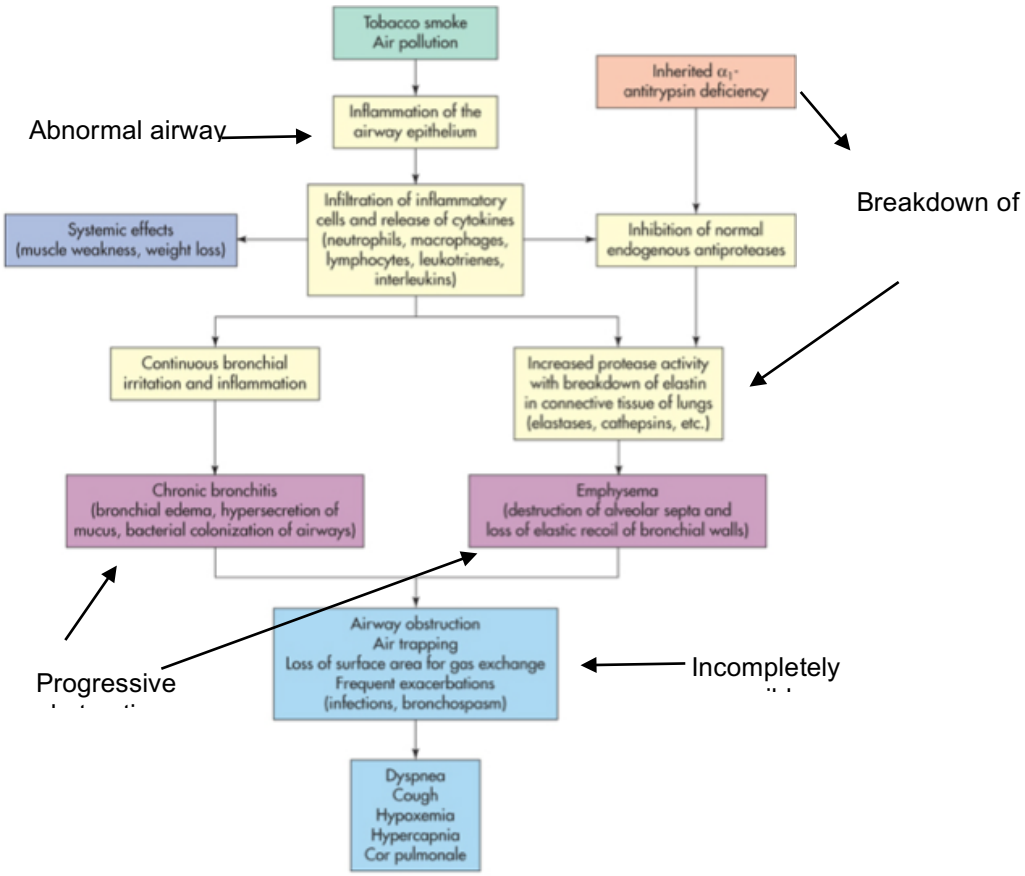
Acute obstruction:

- Hypoxemia → peripheral receptors → hyperventilation → decreased CO2 → increased pH → respiratory alkalosis

Untreated chronic obstruction + hyperventilation

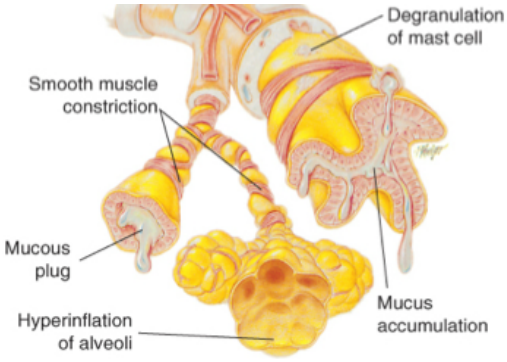
- Increased ++++ air trapped → decreased TdV → increased P_{CO2}
- Respiratory acidosis → respiratory failure

COPD



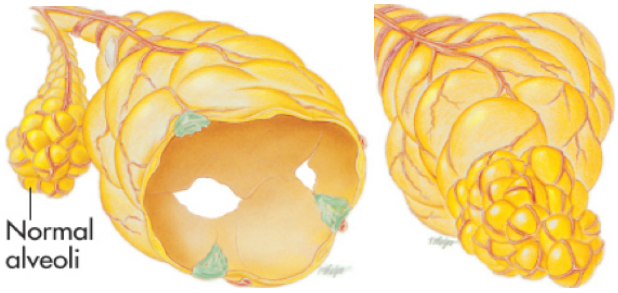
Chronic Bronchitis

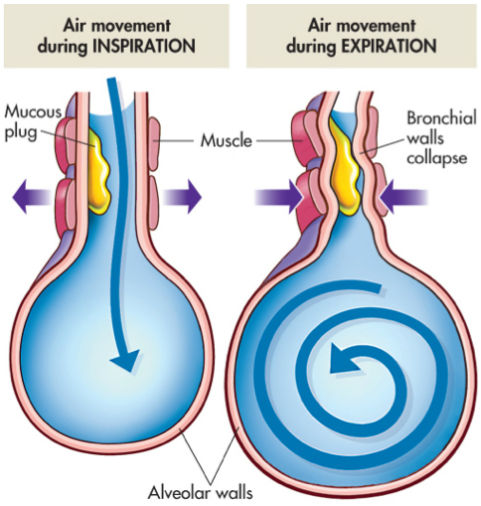
- Mucous + Mucous + Mucous + cough
- Club cells hyperplasia & hypertrophy + impaired ciliary clearance
- V/Q mismatch → hypoxemia



Emphysema

- Alveolar wall destruction w/o fibrosis → Acini or respiratory bronchiole enlargement
- Protease imbalance + oxidative stress → increased elastin breakdown
- Panacinar: adults + alpha1-antitrypsin deficient

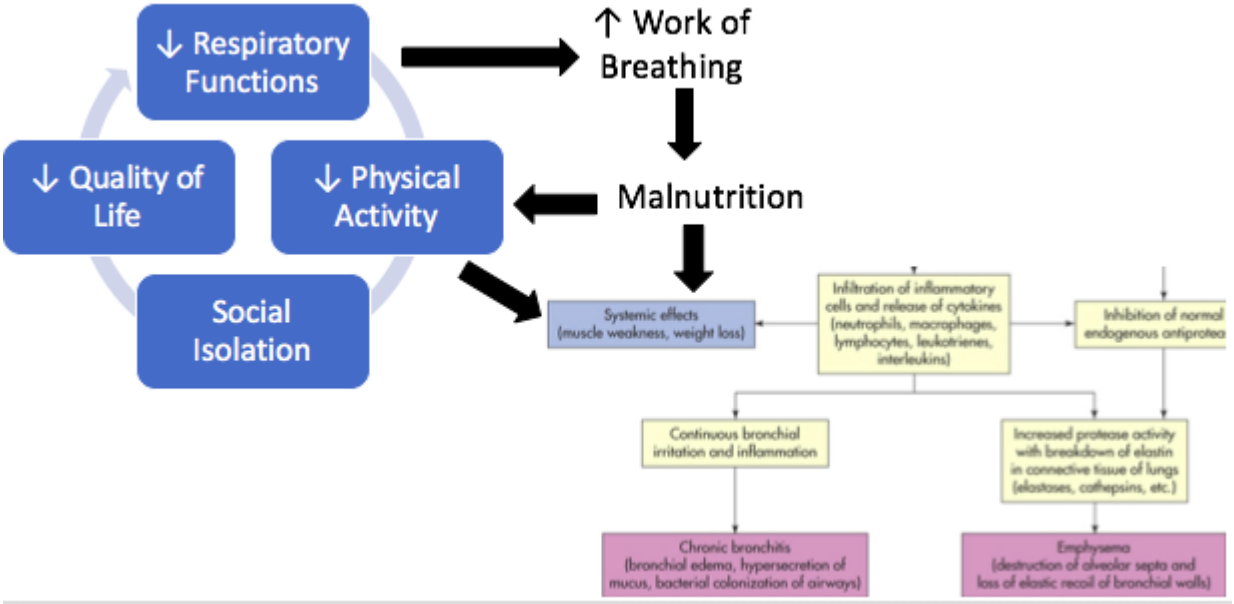




COPD Air Trapping

- Increased trapped air
  ↓
- Thoracic cage expands
  ↓
- Decreased TV + hypoventilation
  ↓
- Increased P_{CO2}
  ↓
- Respiratory acidosis

COPD Vicious Cycle



BACK TO PHARM

Drugs for Asthma & COPD: Overview

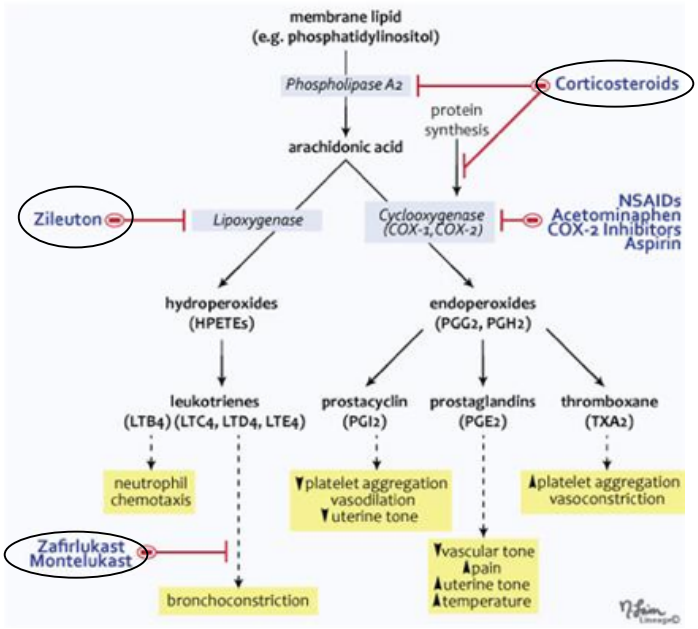
ANTI-INFLAMMATORY DRUGS
Glucocorticoids
Inhaled
Beclomethasone dipropionate [QVAR] Budesonide [Pulmicort Flexhaler, Pulmicort Respules, Pulmicort Turbuhaler ♣] Ciclesonide [Alvesco] Flunisolide [Aerospan] Fluticasone propionate [Flovent HFA, Flovent Diskus] Mometasone furoate [Asmanex Twisthaler]
Oral
Methylprednisolone [A-Methapred, Depo-Medrol, Medrol, Medrol Dose-Pak] Prednisolone [Flo-Pred, Orapred ODT, Millipred, Pediapred, Prelone] Prednisone [Deltasone, Winpred ♣]
Leukotriene Modifiers
Montelukast, oral [Singulair]* Zafirlukast, oral [Accolate]* Zileuton, oral [Zyflo, Zyflo CR]*
Cromolyn
Cromolyn, inhaled [Nalcrom ♣]*
IgE Antagonist
Omalizumab, subQ [Xolair]
Phosphodiesterase-4 Inhibitors
Roflumilast, oral [Daliresp, Daxas ♣]*

BRONCHODILATORS
Beta,-Adrenergic Agonists
Inhaled: Short Acting
Albuterol [ProAir HFA, ProAir RespiClick, Proventil HFA, Ventolin HFA, Airomir, Apo-Salvent MDI ♣] Levalbuterol [Xopenex, Xopenex HFA]
Inhaled: Long Acting‡
Arformoterol [Brovana]* Formoterol [Foradil Aerolizer, Perforomist, Oxeze Turbuhaler ♣]* Indacaterol [Arcapta Neohaler, Onbrez Breezhaler ♣]* Olodaterol [Striverdi Respimat]* Salmeterol [Serevent Diskus]*
Oral
Albuterol [VoSpire ER] Terbutaline (generic only)
Methylxanthines
Aminophylline, oral (generic only) Theophylline, oral [Theo-24, Elixophyllin, Theochron, Theolair ♣, Pulmophylline ♣, Theo ER ♣, Uniphyl ♣]
Anticholinergics
Aclidinium bromide, inhaled [Tudorza Pressair]* Glycopyrronium bromide, inhaled [Seebri Neohaler, Seebri Breezhaler ♣]* Ipratropium, inhaled [Atrovent HFA] Tiotropium, inhaled [Spiriva, Spiriva HandiHaler, Spiriva Respimat]* Umeclidinium, inhaled [Incruse Ellipta]

ANTI-INFLAMMATORY/BRONCHODILATOR COMBINATIONS
Budesonide/formoterol, inhaled [Symbicort]
Fluticasone/salmeterol, inhaled [Advair Diskus, Advair HFA]
Fluticasone/vilanterol, inhaled [Breo Ellipta]
Mometasone/formoterol, inhaled [Dulera, Zenhale ♣]

BETA AGONIST/CHOLINERGIC ANTAGONIST COMBINATIONS
Albuterol/ipratropium, inhaled [Combivent Respimat, Combivent UDV ♣]*
Indacaterol/glycopyrronium, inhaled [Utibron Neohaler, Ultibro Breezhaler ♣]*
Olodaterol/tiotropium, inhaled [Stiolto Respimat]*
Vilanterol/umeclidinium, inhaled [Anoro Ellipta]*

Arachidonic Acid Pathway



- In terms of management of respiratory disorders, we are more interested in the left branch of this pathway. Notice near the bottom, the molecules called leukotrienes.

During inflammatory responses, your body will produce all of the molecules (ie. prostaglandins & leukotrienes), but the bronchoconstriction effect is mostly mediated by the leukotrienes.

- Notice the corticosteroids block both branches.
- Question: why are NSAIDs not useful in using for COPD management, but can also make matters worse?
    - If you only inhibit the branch on the right and not the branch on the left, well all the arachidonic acid needs to go somewhere. So it's going to all go into leukotrienes, and you're going to have more bronchoconstriction.
    - You can use NSAIDs for other purposes in a patient with COPD, but it should not be used alone specifically for COPD management.

Nursing Capsule: Inhalation Administration

3 advantages:

1. Enhanced delivery
2. Decreases systemic effects
3. Rapid acute relief

Pumps:

- Metered dose inhaler (MDI)
    - Requires hand-breath coordination
    - Spacer increases lung delivery
- Respimat
    - Very fine mist = high delivery
- Dry powder inhalers (DPI)
    - Breath activated

Glucocorticoids (GC)

- Action: decrease inflammation → decrease mucous secretion + bronchial hyperreactivity
- Most effective Rx for long-term **asthma prophylaxis**
- Delayed effect (because it is a hormone) → useless in asthma crisis

Nursing safety alert:

- Adrenal insufficiency = possibly fatal
- Crucial compensation actions
    - Gradual discontinuation
    - IV GCC or increase dose in times of stress

Inhalation use:

- Preferred → best safety & efficacy profile
- Adverse effects:
    - Oropharyngeal candidiasis: decrease risk with water rinse or spacer
    - Adrenal suppression: low vs. oral administration
    - Slow growth but no long-term height reduction

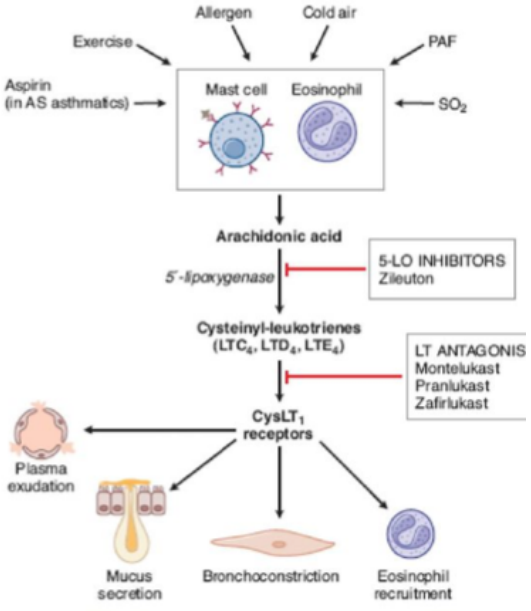
- Possible bone loss: low vs. oral administration

Oral use:

- Moderate to severe asthma only
- Adverse effects:
  - Toxicity depends on therapy duration more than dose
- Risk of:
  - Adrenal suppression
  - Osteoporosis
  - Hyperglycemia
  - Peptic ulcers

<u>Leukotriene Modifiers</u>

- All available PO
- Asthma uses:
  - 2nd line therapy after inhaled GC
  - Adjuncts to GC
- Major adverse effects:
  - Neuropsychiatric distress (ex. Depression, suicidal ideation)
  - Hepatotoxicity (zileuton & Zafirlukast) → monitor ALT levels
  - Inhibition of CYP450 enzymes (Zileuton & Zafirlukast)

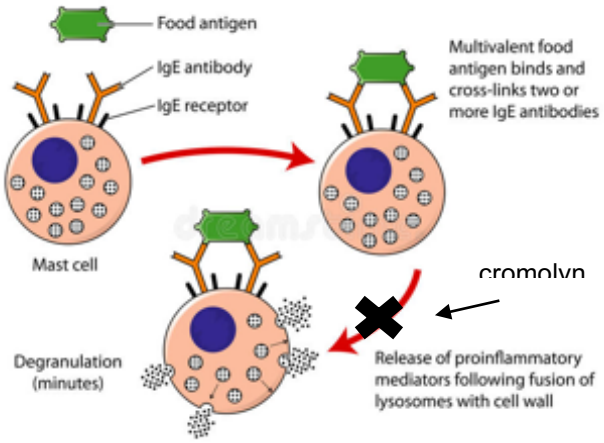


Leukotriene Modifiers: Preparations and Dosages

Drug	Preparation	Dosage
Montelukast [Singulair]	Granules: 4 mg/pkt Chewable tablets: 4, 5 mg Tablets: 10 mg	12–23 months: one pkt of 4 mg granules daily 2–5 years: one pkt of 4 mg granules or one 4-mg tablet every evening 6–14 years: one 5-mg chewable tablet every evening 15 years and older: one 10-mg tablet every evening *EIB prophylaxis*: one 10-mg tablet at least 2 hr before exercising*
Zafirlukast [Accolate]	Tablets 10, 20 mg	5–11 years: 10-mg tablet twice daily 12 years and older: 20-mg twice daily
Zileuton [Zyflo, Zyflo CR]	IR tablet: 600 mg ER tablet: 600 mg	12 years and older: • IR tablet: one 600-mg tablet 4 times daily • ER tablet: two 600-mg tablets twice daily

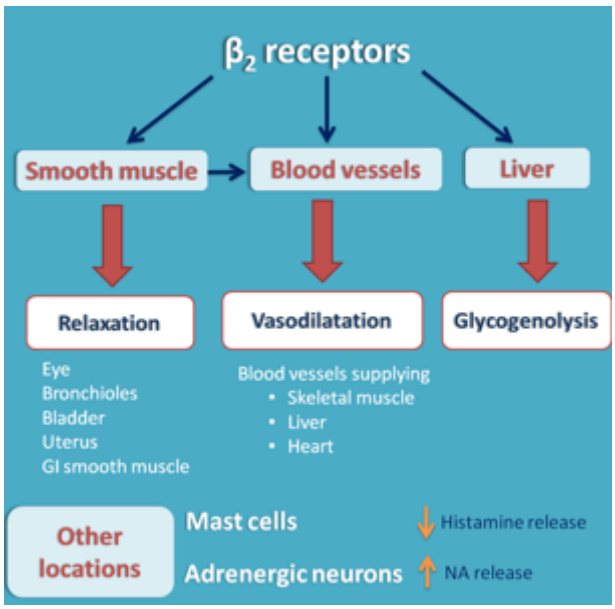
<u>Cromolyn</u>

- 2nd line agent for mild/moderate asthma prophylaxis
- Inhibition of mast cell degranulation → decreased inflammation
- No bronchodilation action (this is why it cannot be used for severe cases)
- Useful for exercise-induced bronchospasms prophylaxis
- Safest anti-asthma medication
- Administration: nebulizer
- Action: by reducing the vasodilation/edema effect from mast cells by inhibiting them, then you will get less mucus accumulation in the airways.



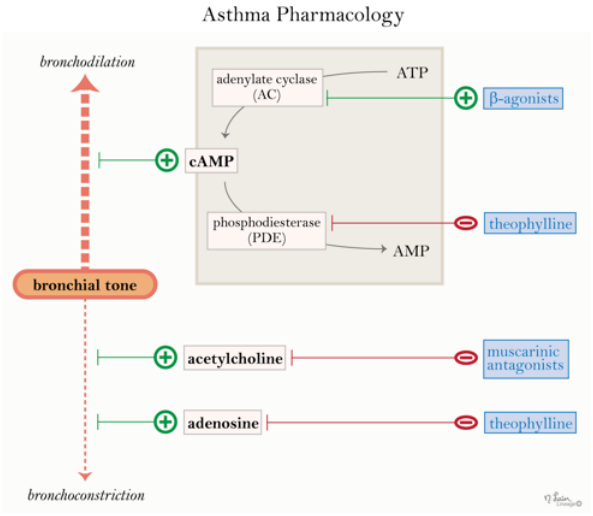
Beta2-Adrenergic Agonists

- Short-acting inhaled beta agonists (SABA)
  - Onset = immediate / duration = 3-5 hours
  - Abort acute attacks
  - Exercise-induced bronchoconstriction (EIB) prevention
  - Minimal adverse effects
- Safe alert:
  - Excessive SABA → beta1 activation → life-threatening angina & tachydysrhythmias
  - No more than 2x/week
- Long-acting inhaled or oral beta agonists (LABA)
  - Long-term control of asthma & stable COPD
  - Always combined with inhaled GC (monotherapy increased mortality)
  - Toxicity = beta1 activation → angina & tachydysrhythmias
- Therapeutic usage:
  - Asthma (selective beta2 agonists)
- Adverse effects:
  - Hyperglycemia (diabetic patients)
  - Transient muscle tremor



Long-Acting Muscarinic Antagonists

- Approved for COPD bronchospasms management
- Off-label use for asthma
- Administration: inhalers
- Adverse effects:
  - Systemic effects = minimal
  - Dry mouth & pharynx irritation



Combination Formulation

GCC + LABA:

- Advantage = convenience + adherence
- Disadvantage: fixed dosage
- 2nd line agents if GC-alone fails
- Age restrictions for children

Glucocorticoids and Long-Acting Beta$_2$ Agonists: Formulations and Dosages

Drug	Inhaler	Formulation	Dosage*
Budesonide/formoterol [Symbicort]	HFA	80 mcg/4.5 mcg	2 inhalations twice daily
		160 mcg/4.5 mcg	2 inhalations twice daily
Fluticasone/vilanterol [Breo Ellipta]	DPI	100 mcg/25 mcg	1 inhalation once daily
		200 mcg/25 mcg	1 inhalation once daily
Fluticasone/salmeterol [Advair Diskus]	DPI	100 mcg/50 mcg	1 inhalation twice daily
		250 mcg/50 mcg	1 inhalation twice daily
		500 mcg/50 mcg	1 inhalation twice daily
Fluticasone/salmeterol [Advair HFA]	HFA	45 mcg/21 mcg	2 inhalations twice daily
		115 mcg/21 mcg	2 inhalations twice daily
		230 mcg/21 mcg	2 inhalations twice daily
Mometasone/formoterol [Dulera]	HFA	100 mcg/5 mcg	2 inhalations twice daily
		200 mcg/5 mcg	2 inhalations twice daily

LABA/SABA + Anticholinergic:

- Synergistic action
- Approved for COPD only
- Off-label asthma use of Combivent

Beta$_2$ Agonists and Anticholinergics: Formulations and Dosages

Drug (Classification)	Brand Name	Preparation	Formulation per Inhalation	Dosage
Ipratropium/albuterol (anticholinergic + SABA)	DuoNeb	Solution	500 mcg ipratropium/2500 mcg of albuterol	3 mL 4 times daily using a nebulizer
	Combivent Respimat	Inhaler	20 mcg ipratropium/100 mcg albuterol	1 inhalation 4 times daily (maximum 6 inhalations in 24 hr)
Indacaterol/glycopyrronium (LABA + anticholinergic)	Utibron Neohaler	Inhaler	27.5 mcg indacaterol/15 mcg glycopyrronium (glycopyrrolate)	1 inhalation twice daily
Olodaterol/tiotropium (LABA + anticholinergic)	Stiolto Respimat	Inhaler	2.5 mcg of olodaterol/2.5 mcg tiotropium	2 inhalations once daily
Umeclidinium/vilanterol (Anticholinergic + LABA)	Anoro Ellipta	Inhaler	62.5 mcg umeclidinium/25 mcg vilanterol	1 inhalation once daily

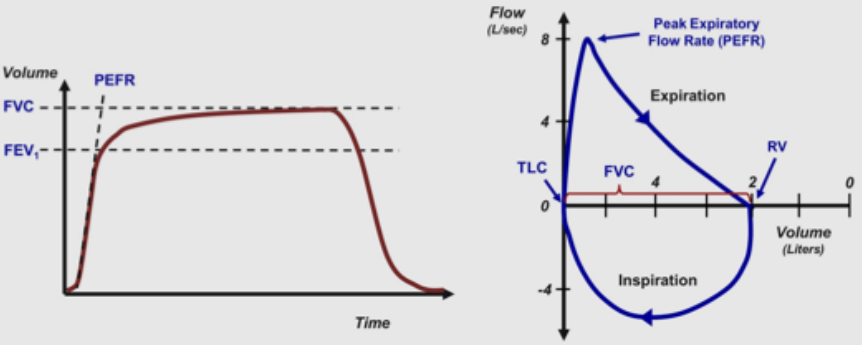
Asthma Management

Lung Function & Asthma Classification

- FEV1 = forced expiratory volume in 1 second
- FVC = forced vital capacity
  - Total expiration after full inspiration
- FEV1/FVC = % of expiration during 1st second
  - Healthy = 70%-85% (depends on age)
- PEFR = peak expiratory flow rate
  - Max airflow during expiration
  - Should be > 80% (depends on age)

Classification of Asthma Severity and Recommended Step for Initial Treatment

	Intermittent Asthma	Persistent Asthma		
		Mild	Moderate	Severe
Lung function tests	Normal FEV_1 between exacerbations FEV_1 > 80% of predicted FEV_1/FVC normal[a]	FEV_1 > 80% of predicted FEV_1/FVC normal[a]	FEV_1 >60% but <80% of predicted FEV_1/FVC reduced 5%[a]	FEV_1 <60% of predicted FEV_1/FVC reduced >5%[a]
Recommended step for initial treatment[b]	Step 1	Step 2	Step 3	Step 4 or 5



Stepwise Chronic Drug Therapy

Stepwise Approach to Managing Asthma

	Long-Term Control Drugs (Taken Daily)		Quick-Relief Drugs (Taken PRN)
	Preferred	**Alternative**	
ADULTS AND CHILDREN AGE 12 AND OLDER			
Step 1	No daily medication needed		SABA
Step 2	Low-dose IGC	Cromolyn, LTRA, or theophylline	SABA
Step 3	Low-dose IGC + LABA OR Medium-dose IGC	Low-dose IGC + either LTRA, theophylline, or zileuton	SABA
Step 4	Medium-dose IGC + LABA	Medium-dose IGC + either LTRA, theophylline, or zileuton	SABA
Step 5	High-dose IGC + LABA		SABA
Step 6	High-dose IGC + LABA + oral glucocorticoid		SABA
CHILDREN AGE 5–11 YEARS			
Step 1	No daily medication needed		SABA
Step 2	Low-dose IGC	Cromolyn, LTRA, nedocromil, or theophylline	SABA
Step 3	Low-dose IGC + either LABA, LTRA, or theophylline OR Medium-dose IGC		SABA
Step 4	Medium-dose IGC + LABA	Medium-dose IGC + either LTRA or theophylline	SABA
Step 5	High-dose IGC + LABA	High-dose IGC + either LTRA or theophylline	SABA
Step 6	High-dose IGC + LABA + oral glucocorticoid	High-dose IGC + either LTRA or theophylline + oral glucocorticoid	SABA
CHILDREN AGE 0–4 YEARS			
Step 1	No daily medication needed		SABA
Step 2	Low-dose IGC	Cromolyn or montelukast	SABA
Step 3	Medium-dose IGC		SABA
Step 4	Medium-dose IGC + either LABA or montelukast		SABA
Step 5	High-dose IGC + either LABA or montelukast		SABA
Step 6	High-dose IGC + either LABA or montelukast (Low-dose oral glucocorticoids, if needed.)		SABA

Goals & Special Cases

Chronic drug therapy goals:

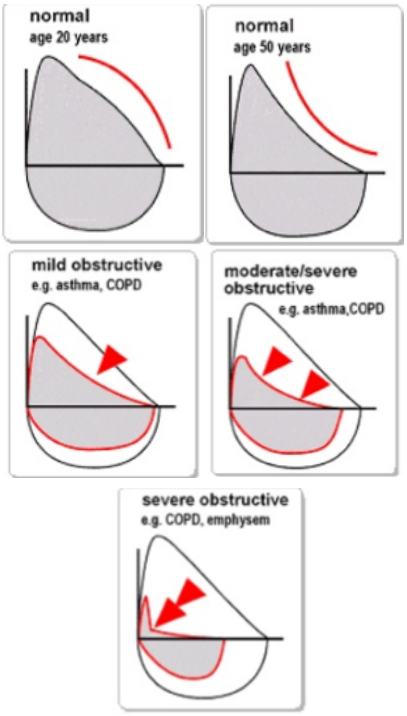
1. Reduce impairment
    a. Symptomatic relief
    b. Restoring normal lung functions
    c. Maintaining normal work, school, sport activities
2. Reduce risk
    a. Prevent recurrent exacerbation
    b. Minimize emergencies & hospitalization
    c. Prevent lung function deterioration
    d. Reducing exposure to allergens & triggers

Acute severe exacerbation Rx:

- Oxygen for hypoxia relief
- Systemic GC against inflammation
- Nebulized high-dose SABA & ipratropium
- Post-discharge: oral GC 5-10 days
- Gradually replace oral GC with inhaled GC

Drugs for EIB bronchospasms:

- Caused by heat & water loss from lungs
- Use SABA immediately before exercise
- Cromolyn 15 mins prior to exercise
- SABA > Cromolyn



COPD Management

Overview

Severity Scale (COPD diagnosis requires **FEV1/FVC test <70%**)

- Mild COPD: FEV1 > 80% predicted
- Moderate COPD: FEV1 = 50-79% predicted
- Severe COPD: FEV1 = 30-49% predicted
- Very Severe COPD: FEV1 < 30% predicted

Risk Categories

- Group A = low risk & symptoms
- Group B = low risk, high symptoms
- Group C = high risk, low symptoms
- Group D = high risk & symptoms

Stable COPD vs. Exacerbated COPD

Stable COPD:

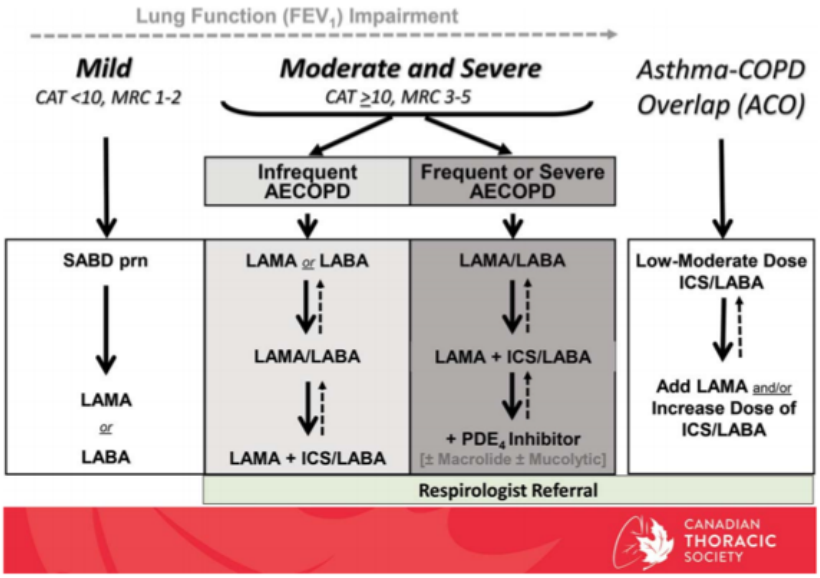
1. Bronchodilators
    a. Inhaled LABA or anticholinergic
    b. Theophylline = last resort
2. Glucocorticoids
    a. Inhaled long-acting GC = preferred
    b. Combination with LABA = preferred over monotherapy
3. Roflumilast: PDE4 inhibitors
    a. Decreased inflammation + cough & mucus production
    b. Combine with LABA or inhaled GC or Tiotropium
    c. Adverse effects:
        i. Decreased appetite & nausea
        ii. Depression
        iii. Insomnia

Exacerbated COPD:

- SABA preferred to LABA
- Systemic GC → outcomes improvement
- Antibiotics → if infection signs
- Oxygen supplement → 88-92% saturation

Canadian Pharmacological Guidelines

ICS = inhaled corticosteroids



Allergic Rhinitis, Cough & Cold (Ch. 77)

Drugs for Allergic Rhinitis

Overview of Drugs for Allergic Rhinitis

Drug or Class	Route	Actions	Adverse Effects
Glucocorticoids	Nasal	Prevent inflammatory response to allergens and thereby reduce all symptoms.	Nasal irritation; possible slowing of linear growth in children
Antihistamines	Oral/nasal	Block histamine$_1$ receptors and thereby decrease itching, sneezing, and rhinorrhea; do *not* reduce congestion.	*Oral:* Sedation and anticholinergic effects (mostly with first-generation agents) *Nasal:* Bitter taste
Cromolyn	Nasal	Prevents release of inflammatory mediators from mast cells and thereby can decrease all symptoms. However, benefits are modest.	Nasal irritation, unpleasant taste, headache
Sympathomimetics	Oral/nasal	Activate vascular alpha$_1$ receptors and thereby cause vasoconstriction, which reduces nasal congestion; do *not* decrease sneezing, itching, or rhinorrhea.	*Oral:* Restlessness, insomnia, increased blood pressure *Nasal:* Rebound nasal congestion
Anticholinergics	Nasal	Block nasal cholinergic receptors and thereby reduce secretions; do *not* decrease sneezing, nasal congestion, or postnasal drip.	Nasal drying and irritation
Antileukotrienes	Oral	Block leukotriene receptors and thereby reduce nasal congestion.	Rare neuropsychiatric effects

Intranasal Glucocorticoids

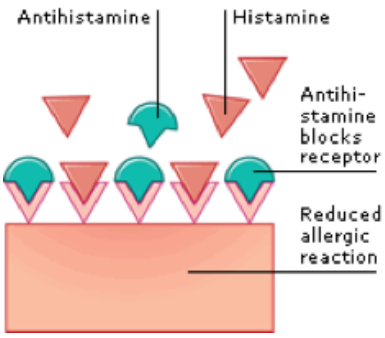
Allergic Rhinitis Considerations

- Most effective for treatment & prevention
- Delayed response = 1-2 weeks
- Daily dosage better than PRN
- Mild adverse effects (ex. Itching & sore throat)
- 2nd line generation: less systemic effects

Some Glucocorticoid Nasal Sprays for Allergic Rhinitis

Drug	Brand Name	Intranasal Bioavailability (%)	Dose/Spray	Patient Age
FIRST GENERATION: INCREASED SYSTEMIC ABSORPTION				
Beclomethasone	Beconase AQ	44	42 mcg	6–11 yr
				12 yr and older
	Qnasl	—	80 mcg	12 yr and older
Budesonide	Rhinocort Aqua	34	32 mcg	6–11 yr
				12 yr and older
Flunisolide	Generic only	49	25 mcg	6–13 yr
				14 yr and older
Triamcinolone	Nasacort AQ	46	55 mcg	6 yr and older
SECOND GENERATION: DECREASED SYSTEMIC ABSORPTION				
Ciclesonide	Omnaris	—	50 mcg	6 yr and older
Fluticasone propionate	Flonase	0.5–2	50 mcg	4–11 yr
				12 yr and older
Fluticasone furoate	Veramyst	—	27.5 mcg	2–11 yr
				12 yr and older
Mometasone	Nasonex	0.1	50 mcg	2–11 yr
				12 yr and older

Antihistamines



Actions (review from) OTC:

- Block histamine action (not release!)
- Some are also muscarinic blockers
- PNS: decrease pain, edema & mucus secretion
- CNS: 1st gen = sedation!! Vs. 2nd gen = non-sedative
- Sedation tolerance develops within days

Allergic rhinitis considerations

- Useless vs. common cold
- Prophylaxis > abortive use (because if mast cell degranulation has already happened, histamine is already released into your system and cannot be reversed)
- Nasal admin for severe rhinorrhea (runny nose)

Intranasal Cromolyn Sodium

Allergic rhinitis considerations

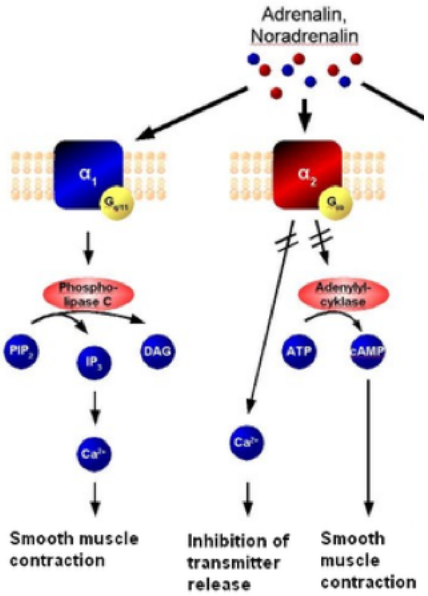
- Very safe
- Moderate efficacy (<intranasal GC)
- Prophylaxis > abortive use
- Delayed response = 1-2 weeks

Sympathomimetic Decongestants

- Nasal alpha-1 adrenergic agonists → decrease edema & mucus secretion
- Effective for both allergic rhinitis & common cold
- Topical administration: intense, rapid action
- Oral administration: delayed, moderate & prolonged action

Sympathomimetics Used for Nasal Decongestion

Decongestant	Mode of Use	Dosing Interval	Dosage Size*
Phenylephrine [Neo-Synephrine, others]	Drops	Every 4 or more hr	*6 yr and older:* 2–3 drops (0.25%–1%) *2–6 yr:* 2–3 drops (0.125%)
Low PO efficacy → extenssive 1st pass effect Good topical efficacy	Spray	Every 4 or more hr	*12 yr and older:* 2–3 sprays (0.25% –1%) *6–12 yr:* 2–3 sprays (0.25%) *2–6 yr:* Not recommended
	Oral	Every 4 hr	*12 yr and older:* 10 mg *6–11 yr:* 5 mg *4–5 yr:* 2.5 mg *Younger than 4 yr:* Not recommended
Pseudoephedrine [Sudafed, others]	Oral	Every 4–6 hr	*12 yr and older:* 60 mg *6–12 yr:* 30 mg *Younger than 6 yr:* 15 mg
Good PO efficacy	Oral SR	Every 12 hr	*12 yr and older:* 120 mg *Younger than 12 yr:* Not recommended
	Oral CR	Every 24 hr	*12 yr and older:* 240 mg *Younger than 12 yr:* Not recommended



Decongestants: Adverse Effects

- Rebound congestion
  - Cause: topical admin for 5+ days
  - Cycles of increased congestion & increased drug use
  - Abrupt withdrawal or intranasal GC 1 week prior to discontinuing
- CNS stimulation
  - Because of pseudoephedrine and other compounds found in it
  - Irritability, anxiety & insomnia = most common
- Abuse
  - Pseudoephedrine = amphetamine → crystal meth production
  - Limited purchase & behind the counter move
- Cardiovascular effects
  - Caused by systemic vasoconstriction → mostly patients with heart conditions
  - Oral administration = increased risk

Drugs for Cough: Antitussives

- Beneficial cough → removes mucus & foreign matter (ex. COPD)
    - Don't want to give antitussives for this
- Useless cough → discomfort + irritation + decreased sleep (ex. Common cold)

Opioid antitussives: Codeine

- Most effective: decreases intensity & frequency
- 10% dose of pain relief → very low abuse & ADR risk
- Not recommended for children

Other antitussives:

- Dextromethorphan
    - CNS action without euphoria & dependence
    - Most effective non-opioid antitussive
    - Mild & rare ADR
    - Analgesic properties
- Diphenhydramine
    - Antihistamine
    - Unknown antitussive mechanism

Nursing Capsule: Cold Remedy Preparations

Common cold considerations:

- Viral acute upper respiratory tract infection
- Main Sx: nasal congestion, coughing, myalgia, sore throat
- No cure, symptom-relief only

Combination preparations

- Combination mixture contain several active ingredients → select only required ingredients
- Fixed dosage → increase risk of toxicity or subtherapeutic effects

Use in young children:

- No proof of safety & efficacy + proof of serious ADR risks
- Current recommendations of American Academy of Pediatrics: restriction in children 6 and under
- Patient/parent education: consult HCP & follow administration guidelines carefully

CNS Stimulants & ADHD Drugs (Ch. 36)

CNS Stimulants: Overview

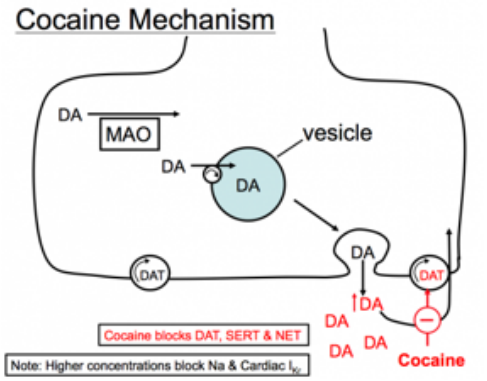
- Major action = increases neuronal excitation
- Minor action = decreases neuronal inhibition
- Toxicity: all can cause convulsions

- Psychomotor stimulants = increases euphoria + alertness + motor activity
  - Ex. methylphenidate, amphetamines, caffeine
  - Therapeutic applications: ADHD management & narcolepsy
- Hallucinogens = thought, mood and perception alteration
  - Ex. LSD, tetrahydrocannabinol (THC)
  - Mostly recreational

History Capsule (REVIEW) - Cocaine: the 1st Local Anesthetic

- Excellent local anesthetic but…
  - Substantial abuse potential
  - CNS stimulant → risk of seizures
  - Cardiovascular effects → increases HR & vasoconstriction

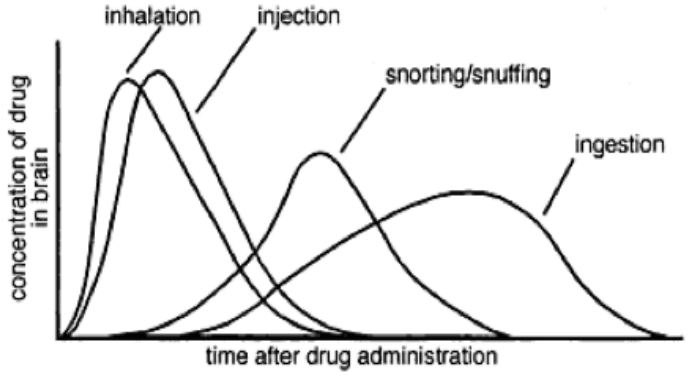
Cocaine: CNS Action (Ch. 40)



Cocaine blocks enzymes that are located on the presynaptic neurons. Neurons that release DA most of the time. DAT (=dopamine transporter) is a protein where its job is to reabsorb the DA in the synaptic cleft to: 1. terminate the signal 2. Recycle the DA to be later released. Cocaine will block DAT, causing DA to build up in the synaptic cleft. The more DA there is, the following neuron becomes overactivated.

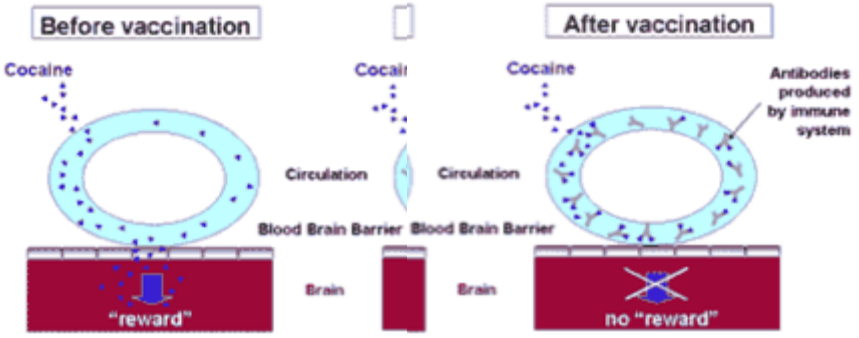
Cocaine has a higher affinity for DAT. Once these are all occupied, it will go bind to other transporters such as SERT (=serotonin transporter) and NET (=norepinephrine transporter). The main stimulant effect comes from the dopamine build up.

This diagram shows that when cocaine is ingested, the concentration in the brain is much less than if inhaled or injected, making it less addictive when ingested.



Cocaine: Toxicity

- Depends greatly on route of administration
  - Snorting: nasal mucosa atrophy → loss of smell sensation
  - Crack smoke: lung injuries
- Highly teratogenic → crack baby syndrome
  - Increase preterm birth risk + decrease birth weight
  - Attention, memory, & language deficits
- Mixed evidence for tolerance/withdrawal
  - Similar to amphetamine OR absence of withdrawal OR increase in sensitivity
- Cocaine use disorder treatment
  - Individual psychosocial therapy + group drug counseling decreases use by 70% within 1 year
  - Adjunct drug therapy under study:
    - Anti-cocaine vaccine: a vaccine that administers antibodies that will block the effects of cocaine is administered/ingested
    - Disulfiram: induces a toxic response if the pt were to take the drug



Amphetamine: Pharmacology

CNS effects

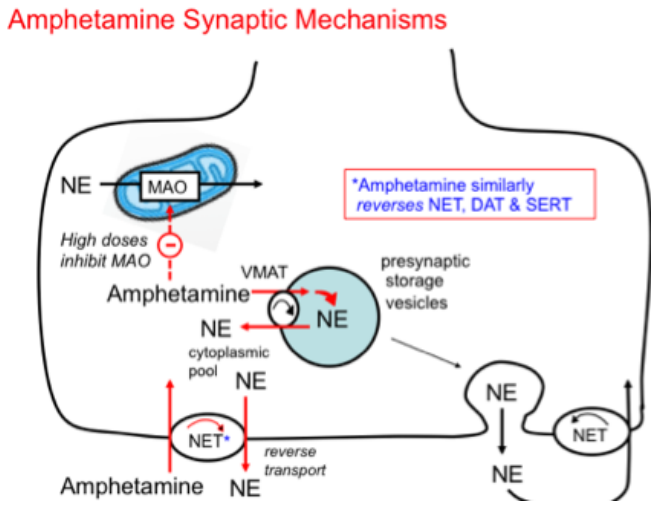
- Psychomotor effects
- Increased respiration & analgesia
- Decreased appetite

Vascular effects

- Increased NE release = vasoconstriction
- Toxicity = hypertension

Cardiac effects

- Increase NE release = increased HR & contractility
- Increased toxicity = dysrhythmias



Mechanism of Action:

- Increase in NE & DA release in the PNS and CNS via 2 mechanisms:

    - 1. inhibition of the NET & DAT, thus preventing the reuptake of NE & DA → increased NE& DA in the synaptic cleft
    - 2. Increase the amount of NE & DA that is released when the neuron is activated. It does so by increasing the amount of NE & DA that is stored into those vesicles.
- Because of this dual action, it has even more stimulant effects than cocaine.

**** Tolerance develops for most effects except euphoria ****

Amphetamine: Toxicity

Prominent withdrawal symptoms:

- Fatigue
- Prolonged sleep
- Excessive eating
- Depression

Abuse

- Euphoria effect + strong withdrawal = high abuse potential (because they fear the withdrawal symptoms)
- Effects & abuse = cocaine

Adverse effects

- CNS stimulation: insomnia + restlessness
- Decreased appetite → weight loss
- Cardiovascular effects: minimal in healthy patients / caution with heart patients
- Psychosis: increased DA release → schizophrenia-like state → hallucinations + paranoid delusions

Acute toxicity management:

- Alleviate psychosis via antipsychotic drugs
- Diazepam against convulsions + adrenergic blockers to decrease HTN

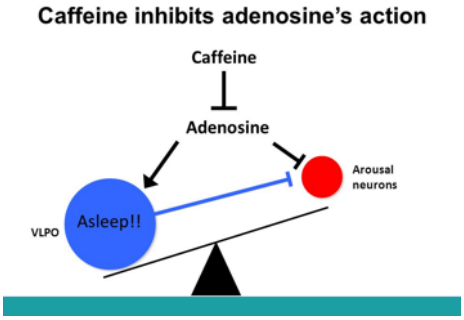
Methylphenidate

- Mech. of action: promotion of NE and DA release, and inhibition of NE and DA reuptake
- Pharmacology & toxicity = identical to amphetamines
- Difference in chemical structure only
- Ex: Ritalin, Concerta, etc.
- Available in IR, SR or once-daily formulations

Caffeine

Kinetics:

- Good GI absorption → peak = 1h
- Hepatic elimination → half-life = 3-7 hours



Mechanism of Action:

- Caffeine acts to block adenosine. Adenosine is believed to be a master switch of NTs. It regulates the activity of other NTs to regulate state between arousal & sleep.

Pharmacologic effects:

- CNS: increased stimulation
- Cardiac: increased HR → risk of dysrhythmia in heart patients
- Vasodilation of peripheral vessels
- Vasoconstriction of CNS vessels → headache alleviation
- Bronchi: bronchodilation
- Kidneys: decreased ADH release → increased diuresis
- Reproduction: associated with decreased birth weight (high dosage)

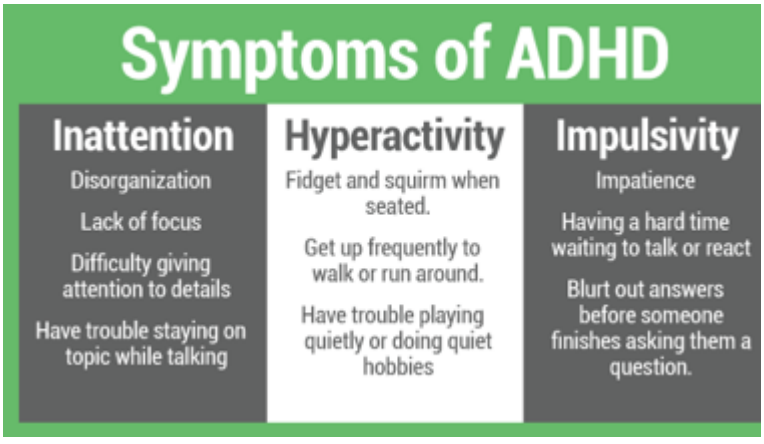
Therapeutic use:

- Neonatal apnea → decreased frequency + duration
- Promoting wakefulness
- Enhance analgesia action of opioids & aspirin

ADHD Management

Nursing Capsule: ADHD Basic Considerations

- Symptoms for 6+ months before 12 years old
- 30-60% of cases continue into adulthood
- Confounding Dx: anxiety & depression



3 causes for ADHD:

- Genetic factors
- Structural + functional CNS alterations
- NE, DA & 5HT dysregulation

Therapy:

- Cognitive + stimulant drug therapy → most effective long-term gains

Nursing Capsule: ADHD Drugs

- No abuse potential
- Convenient phone prescription refill

Major Drugs for Attention-Deficit/Hyperactivity Disorder

Drug	Brand Name	Duration (hr)	Dosing Schedule	Usual Pediatric Maintenance Dosage
STIMULANTS				
Methylphenidate				
Immediate Release	Ritalin, Methylin	3–5	2 or 3 times daily	10 mg at 8:00 AM and noon, and 5 mg at 4:00 PM
Sustained Release	Ritalin-SR, Metadate ER, Quillivant XR, Quillichew ER	6–8	Once or twice daily	20 or 40 mg in AM plus 20 mg in the early PM if needed
24-Hour	Concerta	10–12	Once daily	36 mg in the AM
	Aptensio XR	12	Once daily	10 mg in the AM
	Metadate CD	8–12	Once daily	30 mg in the AM
	Ritalin LA	8–12	Once daily	30 mg in the AM
	Daytrana	10–12	Once daily	One 15- or 20-mg patch, applied in the AM and removed 9 hr later
Dexmethylphenidate				
Immediate Release	Focalin	4–5	Twice daily	10 mg in the AM plus 10 mg in the early PM
Sustained Release	Focalin XR	12	Once daily	10 mg in the AM
Dextroamphetamine				
Immediate Release	Zenzedi, Procentra	4–6	Once or twice daily	5 mg in the AM
Sustained Release	Dexedrine	6–10	Once or twice daily	10 mg at 8:00 AM
Amphetamine Mixture				
Immediate Release	Adderall	4–6	Twice daily	5 mg in the AM and 4–6 hr later
Sustained Release	Adderall XR	10–12	Once daily	20 mg in the AM
Lisdexamfetamine				
Sustained Release	Vyvanse	13	Once daily	30 mg in the AM
NONSTIMULANTS				
Atomoxetine	Strattera	24	Once or twice daily	80 mg in the AM or 40 mg in the AM and early PM
Guanfacine	Intuniv	24	Once daily	1–4 mg in the AM
Clonidine	Kapvay	24	Twice daily	0.1–0.2 mg in the AM and PM

Use if:

Nonresponsive to stimulants

Nonstimulants mechanism of action: causes NE to accumulate at the synapses (selective inhibitor of NE reuptake)

Nursing Capsule: CNS Stimulants

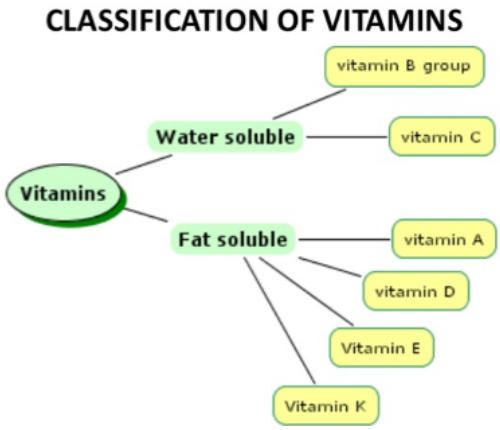
- 1st choice agents: superior to nonstimulants
- Similar efficacy between methylphenidate & amphetamines
  - Try others if 1st Rx ineffective
  - Dramatic improvements in focus & attention
  - Benefits diminish after few years
  - Tx buys time to teach behavioural strategies to kids
- 24h-formulation (once in the morning) = preferred
  - More convenient + decreases social stigma
- Main adverse effects = insomnia + growth suppression
  - Decreased insomnia via 24h formulation or 2nd dose before 4pm
  - Growth suppression from appetite suppression → reduce via post-meal administration

Nursing Key Takeaway

- ADHD management: rare in hospital setting
- Common issue with acute care patients: they stop taking their meds
    - Frequent problem with psychological Rx
- Strength-based nursing: follow-up and encourage patients to stay on their Rx!

Vitamins (Ch. 81)

Vitamins



- Organic compounds required in small amounts for energy transformation & metabolic processes
- Fat soluble vitamins can be stored for later.
- Water soluble vitamins get used up by the body, and whatever is leftover is immediately excreted
- Mixed evidence → 'don't stop - don't start'
    - Mixed evidence regarding taking multivitamins. There's no evidence saying that you should stop taking the vitamins if you already are - there's no evidence indicating that it's bad for you. At the same time, there's no evidence to support that you should start taking them either.
- Healthy diet = best behavior
- Watch out for excessive vitamin A & E, could be detrimental in very large amounts
- Evidence for 3 individual vitamins:
    - Vitamin B12 → everyone 50+ years old
    - Folic acid (B9) → childbearing age women
    - Vitamin D + calcium → postmenopausal women

Dietary Reference Values

- Adequate intake
    - Estimation of RDA when not enough evidence available
- Estimated average requirement
    - Level required for 50% of individuals (regardless of conditions)
    - Used to establish the RDA following extensive research
- Tolerable upper level intake
    - Maximum dose without significant ADR risk → safety index
- Recommended daily allowance
    - Average daily intake necessary for healthy individuals
    - Varies according to sex, age, pathologies

Vitamin A (Retinol)

Functions	Dim light adaptation Embryogenesis & spermatogenesis Skin & mucous membrane integrity Immunity & growth
Deficiency	Night blindness Corneal or conjunctiva lesions Skin/mucous membrane lesions
Toxicity	Liver injury

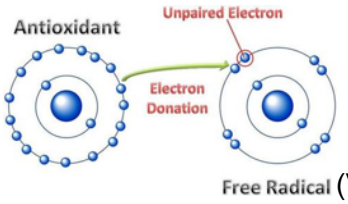
	Bone-related disorders Birth defects
Therapeutic use	Deficiency prevention Retinol derivatives → acne & skin disorders

Vitamin E

Functions	Antioxidant with unknown metabolic role
Deficiency	Neurologic deficits
Toxicity	Increased heart failure risk & cancer progression & all-cause mortality Inhibit exercise benefits on insulin sensitivity Inhibit platelet aggregation → increased hemorrhagic stroke risk
Potential benefits	Hemolysis & age-related macular degeneration prevention Man other false claims

The Case Against Antioxidants

- Theory & observational studies → promising results!!
- Actual robust scientific inquiries
    - Excessive beta-carotene (vitamin A) → increase lung cancer risk in smokers
    - Excessive vitamin E → increase prostate cancer risk & strokes
    - Other antioxidants → drug interactions



(Vitamin A, E, C)

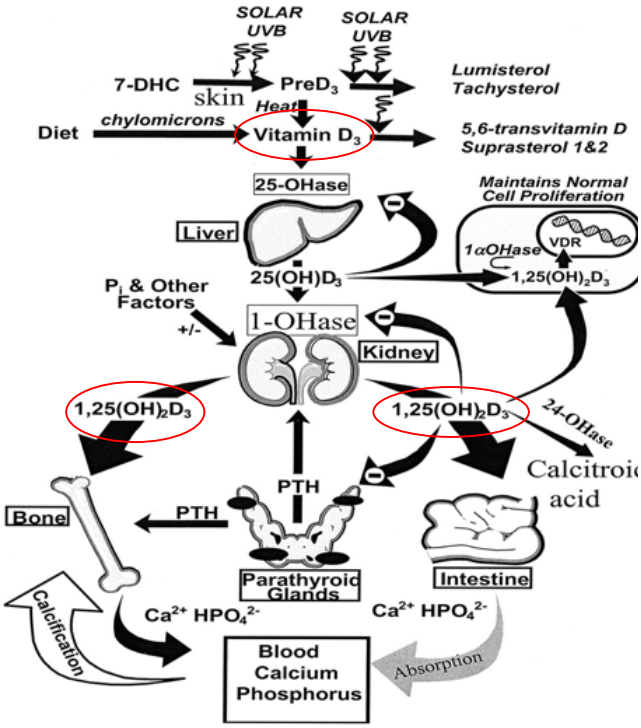
- Meta-Analysis conclusion:
    - “There is no evidence to support the use of vitamin and antioxidant supplements for prevention of cardiovascular diseases.”
    - “The meta-analysis of randomized controlled trials indicated that there is no clinical evidence to support an overall primary and secondary preventive effect of antioxidant supplements on cancer. The effects of antioxidant supplements on human health, particularly in relation to cancer, should be overemphasized because the use of those might be harmful for some cancer.”

Vitamin K

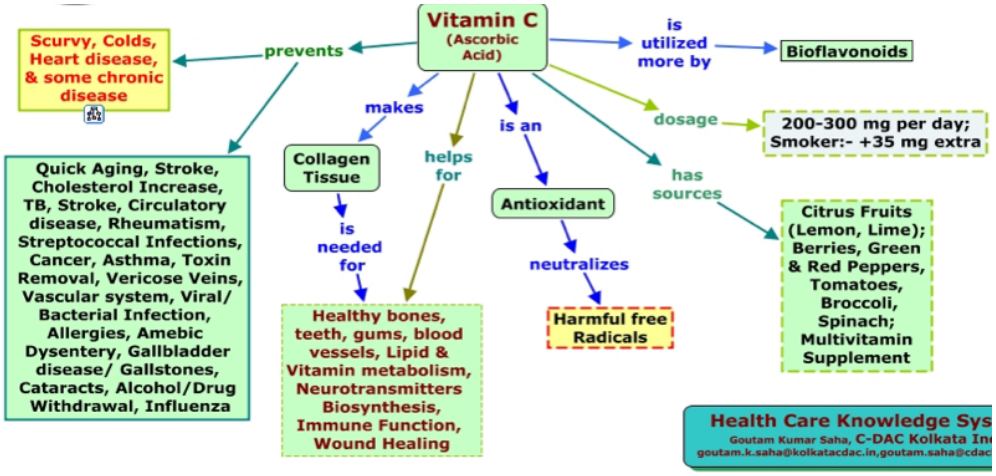
Functions	Prothrombin synthesis Activation of clotting factors VII, IX & X
Deficiency causes	Malabsorption syndrome or decrease (bile salts) Antibiotics → decrease GI flora vit K synthesis Warfarin toxicity
Deficiency symptoms	Prophylaxis injection in newborns Warfarin antidote
Adverse effects	IV administration → hypersensitivity/anaphylaxis risk Hyperbilirubinemia → kernicterus of newborn

Vitamin D

- Proven benefit = bon homeostasis
- Debated evidence → prevention of:
  - Arthritis & autoimmune disorders
  - Breast, prostate & colon cancer
  - Heart disease & T1DM
- Most important in children because, as adults, our growth period is over and we already have lots of calcium.



Vitamin C



Deficiency	Scurvy → lethal collagen tissue/matrix dysfunction
Therapeutic use	Scurvy prevention/treatment All other claims disproved (ex. Wound healing, common cold, etc)
Adverse effects	GI Sx: nausea, diarrhea, cramps

Vitamin B Group

Niacin (B3)

Functions	Precursor of NAD & NADP → major coenzymes
Deficiency	Pellagra: • Dermatitis, skin scaling • GI distress (cramps, diarrhea) • CNS: irritability + insomnia + memory loss
Therapeutic use	Pellagra prevention & treatment
Adverse effects	Low doses = none Very high dose = dizziness + nausea

Nicotinamide = preferred for Pellagra Tx

- Less toxicity
- No vasodilation

Pyridoxine (B6)

Functions	Amino acid synthesis coenzyme
Deficiency causes	**Isoniazid (tuberculosis) therapy** Poor diet Inborn metabolism error
Deficiency symptoms	Peripheral neuritis, Convulsions, Depression, anemia, seborrheic dermatitis
Therapeutic use	Deficiency prevention & treatment
Adverse effects	Low doses = none Very high dose = neurologic injuries **Drug interaction: decrease L-DOPA efficacy**

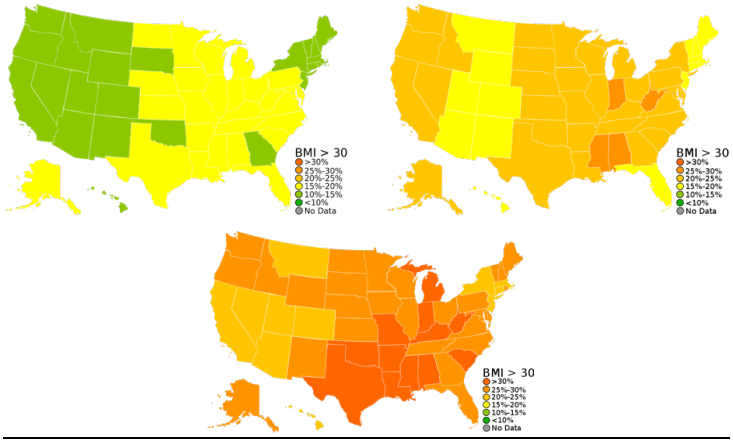
Folic Acid (B9) & Cyanocobalamin (B12)

- Discussed in the hemodynamic lecture
- Involved in RBC development
- Review those slides for information on actions & deficiencies

Drugs For Weight Loss (Ch. 82)

PATHO REVIEW

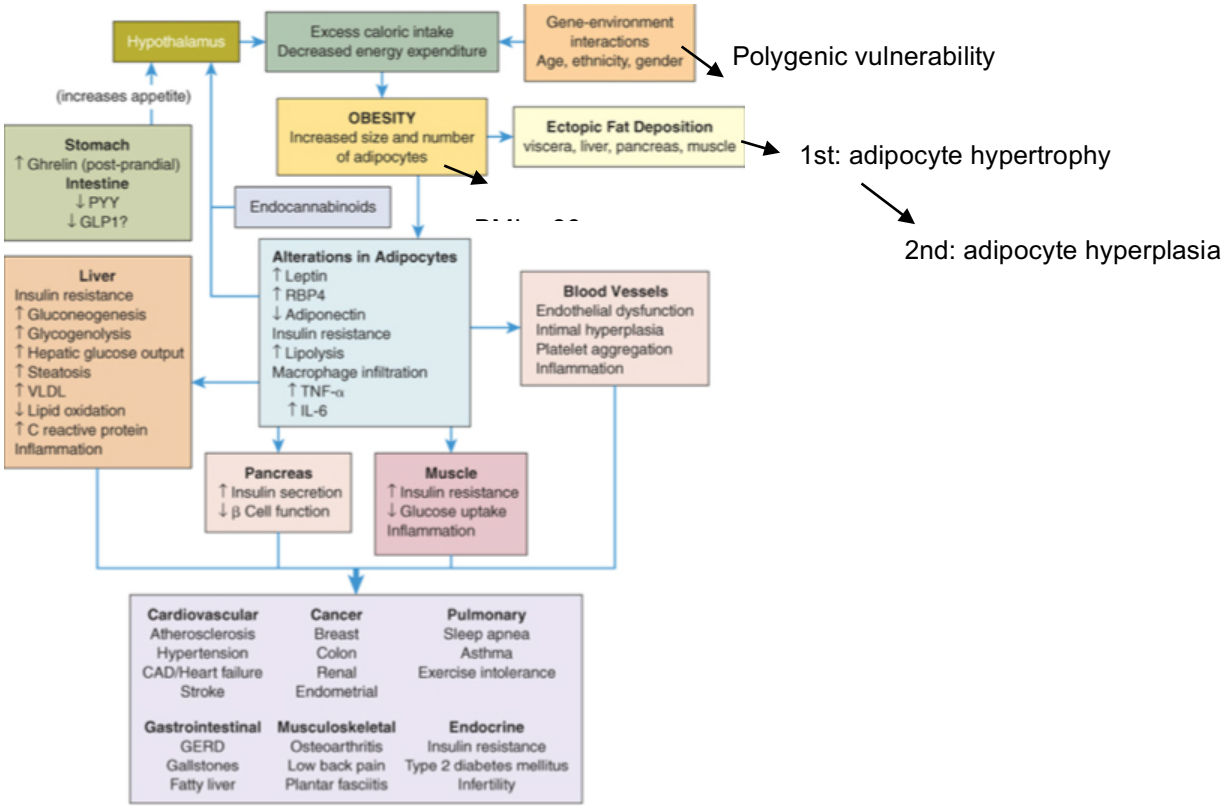
Obesity: growing epidemic



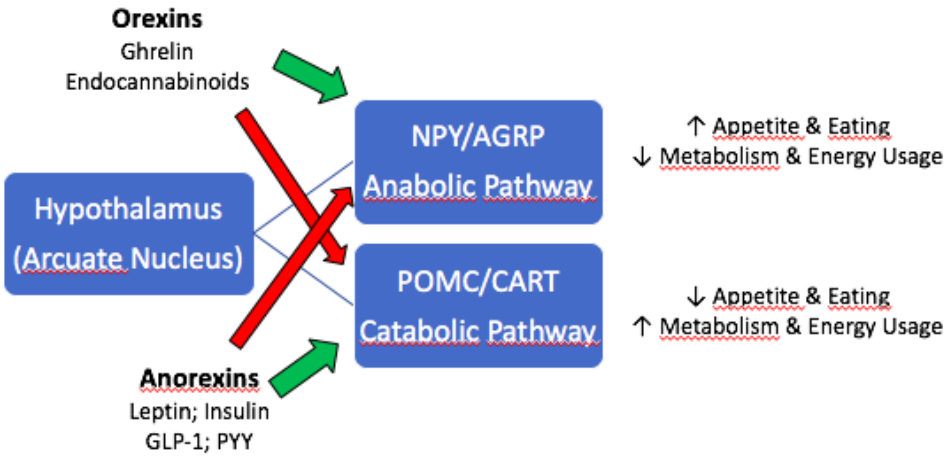
Obesity

- Caloric (appetite) input-output imbalance
- Increase body fat & metabolic disorder
- Association with:
    - Mental retardation (down syndrome)
    - Endocrine alterations (cushing's hypothyroidism)
    - Mutations: (increased appetite, obesity genes, leptin)

- Many adverse physical & psychosocial outcomes



Appetite Regulation



Adipocytes

- Fat (energy) storage cells + endocrine cells → release adipokines
  - Ex. Leptin & adiponectin
- Regulate multiple processes:
  - Appetite & satiety
  - Lipid storage & metabolism

    - Insulin sensitivity
    - Female reproduction
    - Inflammation & immune responses
    - General energy metabolism
- Obesity → low grade inflammation & adipokine pattern alterations → T2DM & cardiovascular diseases

<u>Leptin vs. Adiponectin</u>

Leptin

- Anorexin molecule acting on Hypothalamus
- Decreases appetite & increases energy expenditure
- Healthy:
    - Eat → adipocytes full of fat → increases leptin
    - Fast → adipocytes empty → decrease leptin
- Obesity
    - Increase adipocyte → increase ++ leptin resistance
    - Leptin resistance → overeating → weight gain
    - Hyperleptinemia → increase sympathetic activity → hypertension

Adiponectin

- Anti-inflammatory & anti-atherogenic
- Increases insulin sensitivity
- Obesity:
    - Decreases adiponectin release → increase in insulin resistance → T2DM + increased inflammation & atherosclerosis

<u>Apple vs. Pear</u>

Visceral (apple) obesity

- Men > women
- Metabolic lipid activity > peripheral obesity
- Increased risk:
    - Cardiovascular complications
    - T2DM
    - Cancer

Peripheral (pear) obesity:

- Women > men
- Metabolic lipid activity < visceral obesity
- Increased risk < visceral obesity

BACK TO PHARM

BMI

$$BMI = \frac{\text{Weight in pounds} \times 703}{(\text{Height in inches})^2}$$

OR

$$BMI = \frac{\text{Weight in kilograms}}{(\text{Height in meters})^2}$$

Weight-Related Health Risk

- Waist circumference
- Measure of abdominal fat
- Pear vs. apple shape
- Independent risk factor

	Men	Women
Normal	78–94cm	64–80cm
Overweight (Elevated Risk)	94–102cm	80–88cm
Obese (High Risk)	>102cm	>88cm

Overall Health Risks

- MOST individuals with BMI > 30
- MOST individuals with BMI > 25 + obese waist circumference
- Cardiovascular heart risks further increase health risk for all

Obesity Management

Obesity Therapy: Overview

- In theory: calories burned > calories intake
- In practice: complex struggle between internal homeostasis & behavioral habits

For whom?	**BMI > 30 or > 25 + 2 more risk factors**	
Benefits	Decreased risk for cardiovascular events, T2DM & mortality	
Goals	- Lower BMI as much as possible - Reach new BMI with significant risk improvement vs. starting BMI - 10% weight loss in 6 months → maintain loss for next 6 months	
Modalities	Caloric restrictions	1st line option, fat reduction = easiest
	Exercise	1st line option, minimum 150mins/week
	Behaviour modification	Reinforce eating & exercise habit changes
	Bariatric surgery	Very effective → 110-220 pounds lost in 6 months Very risky → 4.6% 1 year mortality
	Drug therapy	Introduce only after 6 months of diet + exercise

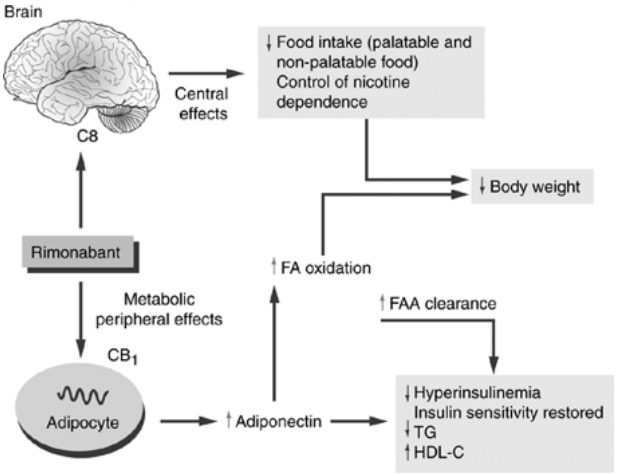
Weight-Loss Drugs

- Only modest benefits → huge $$ market → once on market, widespread use & abuse → many receive approval and then get withdrawn due to serious toxicity discovery
- Remember: losing weight is extremely hard. Everyone wants the simple/easy solution
- Smoking & stimulants (cocaine, amphetamines) are often abused for weight loss purposes.

Drug class	**Prototype**
Lipase inhibitor	Orlistat (least benefits)
5-HT_{2C} receptor agonist	Lorcaserin
Sympathomimetic	Diethylproprion & Phentermine
GLP-1 Agonist	Liraglutide
Combination products	Phentermine + topiramate (most benefits) Naltrexone + Buproprion

Cannabinoid Inhibitors: Rimonabant

- They figured that if stimulating the cannabinoid receptors stimulated appetite, then inhibiting it would suppress hunger.
- Marketed in 2005 → withdrawn in 2008
- Therapeutic window too narrow
- High risk of CNS depression & psychosis



Combination Products

Phentermine + Topiramate (Qsymia)

- Phentermine:
  - Sympathomemetic amine
  - Decreases appetite @ the hypothalamus

- Topiramate
    - Anticonvulsive drug
    - Increases satiety feeling
- Adverse effects:
    - Dry mouth, dizziness, insomnia
    - Serious ADRs: HTN tachycardia & birth defects
- Interactions
    - Antidiabetic agents → increases hyperglycemia
    - Oral contraceptives → increases estrogen levels
    - MAO inhibitors → contraindicated

Naltrexone + Buproprion (Contrave)

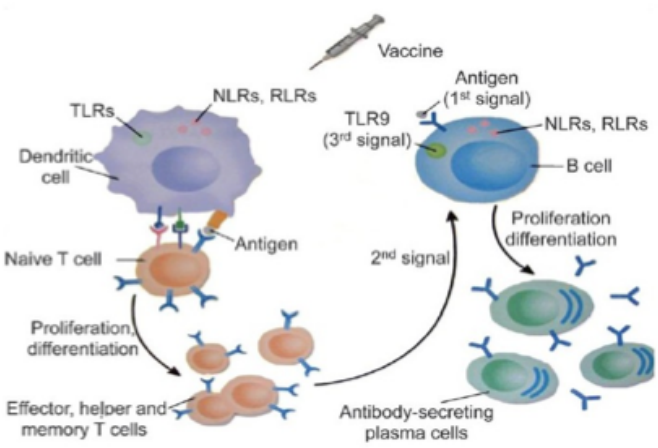
- Naltrexone
    - Opioid antagonist
    - Decreases appetite @ hypothalamus
- Buproprion
    - DA/NE reuptake inhibitor
    - Decreases reward feeling of food
- Adverse effects:
    - Nausea, vomiting, constipation, dizziness
    - Serious ADRs: depression, mania & suicidal ideation
- Interactions:
    - Other drugs with buproprion
    - Strong CYP2D6 inhibitor
    - Opioids & MAO inhibitors → contraindicated

Is obesity a problem intrinsically or is it a symptom associated to other issues?

Quick word on fat-shaming & weight-related myths

- Many studies show that weight gain is unrelated to:
    - Motivation / personality / bad health / nutrition quality
- Some individuals are predisposed to accumulate fat if the environment favors it → evolutionary advantage
- Obese indivudals are not lazy and could be in better health than many individuals within the 'healthy BMI range'
    - Cardiovascular fitness test is a better predictor of health outcomes than BMI
- Fat-shaming takes on many forms and only makes their health worse/scare them away from HCP
    - Intimidation / social isolation / many HCP spend less time with obese patients
    - Phrases such as: "Congrats for doing something about your weight" or "it's cool that he loves you so much despite your weight"

Childhood Immunization (Ch. 68)



Vaccine Types

- Immunization = process of increasing strength of immune system
  - Active immunity → endogenous antibody production (ex. vaccination)
  - Passive immunity → performed antibodies injection (ex. Specific immune globins)
- Live vs. killed vaccine
- Toxoid = harmless bacterial toxin
  - Ex. diphtheria or tetanus toxoid vaccines

History Capsule: Because Why Not Some Perspective?

- Variation in 15th century China
  - Used powdered scabs of infected smallpox patients
- Western Europeans notice that milkmaids are resistant to smallpox
- 1796: Edward Jenner vaccinates first patient
  - Vaccination refers to cowpox (vacca) vaccine against smallpox
- 1886: Louis Pasteur uses 1st laboratory designed vaccine (rabies)
- 1998: Dr. Wakefield publishes study linking vaccines with autism
- 2010: scientific journal The Lancet retracts his article
  - Dr. Wakefield loses license after discovery of falsified data

Vaccines: (Actual) Adverse Effects

Adverse Effects of Some Vaccines and Toxoids

Preparation	Mild Effects	Serious Effects
Measles, mumps, and rubella virus vaccine	Local reactions; rash; fever; swollen glands in cheeks and neck and under the jaw; pain, stiffness, and swelling in joints	Anaphylaxis, thrombocytopenia[a]
Diphtheria and tetanus toxoids and acellular pertussis vaccine	Local reactions, fever, fretfulness, drowsiness, anorexia, persistent crying	Acute encephalopathy, convulsions, shock-like state
Haemophilus influenzae type b conjugate vaccine	Local reactions, fever, crying, diarrhea, vomiting	None
Varicella virus vaccine	Local reactions, fever, mild varicella-like rash (local or generalized)	None
Hepatitis A vaccine	Local soreness, headache, anorexia, fatigue	Anaphylaxis
Hepatitis B vaccine	Local discomfort, fever	Anaphylaxis
Pneumococcal conjugate vaccine	Local reactions, fever, irritability	None
Influenza vaccine (inactivated)	Local reactions, fever	None
Influenza vaccine (live attenuated)	Runny nose, headache, cough, fever	None
Meningococcal conjugate vaccine	Local reactions, headache, fatigue	None
Rotavirus vaccine	Diarrhea, vomiting, ear infection, runny nose, sore throat	Intussusception (rare)
Human papillomavirus vaccine	Local reactions, fainting	None

[a]A study showing a connection with autism was disproved.

(need to know)

Vaccines: Contraindications

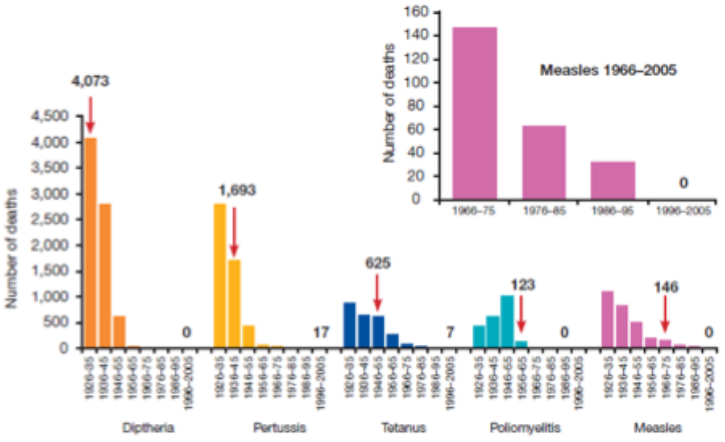
Contraindications That Apply to All Vaccines and Conditions Often Incorrectly Regarded as Contraindications

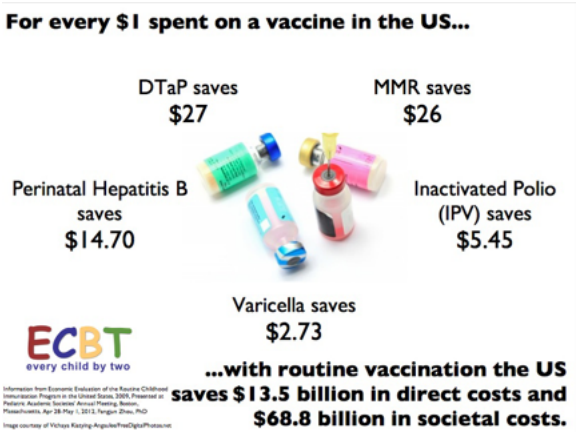
True Contraindications (Vaccine Should Not Be Administered)	Not Contraindications (Vaccine May Be Administered)
Anaphylactic reaction to a specific vaccine: Contraindicates further doses of that vaccine	Mild to moderate local reaction (soreness, erythema, swelling) following a dose of an injectable vaccine
Anaphylactic reaction to a vaccine component: Contraindicates use of all vaccines that contain that substance	Mild acute illness with or without low-grade fever
Moderate or severe illnesses with or without a fever	Diarrhea
	Current antimicrobial therapy
	Convalescent phase of illnesses
	Prematurity (same dosage and indications as for normal, full-term infants)
	Recent exposure to an infectious disease
	Personal or family history of either penicillin allergy or nonspecific allergies

- Vaccines have one of the best benefit:risk ratio of all Rx
- Minimize pain during administration → EMLA patch, quick IM injections
- Avoid prophylactic NSAIDs/Acetaminophen → decreases vaccine efficacy + hide early adverse effects
- Avoid live vaccines in immunocompromised children

Vaccines: Public Health Impacts

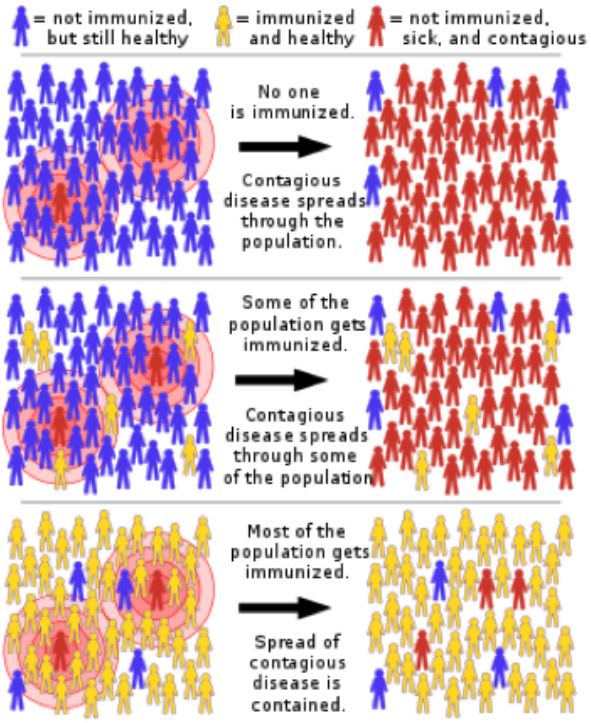
- Polio eradicated from all but 2 countries
- Smallpox eradicated from the planet!





Vaccines: Herd Immunity

- Arguably the most important action of immunization
- If everyone who can receive vaccines is immunized, this protects those who cannot receive vaccines
- Very newsworthy today with anti-vaxx campaigns



Childhood Vaccination Schedule

Vaccine protecting against:	At 2 months	At 4 months	At 12 months	At 18 months	Between 4 and 6	Elementary 4	Secondary 3
Diphtheria-tetanus-whooping cough-hepatitis B-polio-Hib	✓	✓	✓ (without hepatitis B)				
Pneumococcus	✓	✓	✓				
Rotavirus	✓	✓					
Meningococcus C				✓			✓
Measles-mumps-rubella-varicella			✓	✓			
Diphtheria-tetanus-whooping cough-polio					✓		
Diphtheria-tetanus							✓
Hepatitis A-hepatitis B				✓			
Human papillomavirus						✓	

IMPORTANT
For optimal protection for your child, do not forget any vaccines and have the child vaccinated at the recommended ages.

It's up to you to make an appointment with the CLSC or with your doctor to have your child vaccinated (except for vaccines given at school).

Some Target Diseases

Disease	Type	General Comments
Measles	Virus	Highly contagious, risk of death by encephalitis
Mumps	Virus	Attacks parotid glands
Rubella	Virus	Mild in adults, but extremely teratogenic
Diphteria	Bacteria	Potentially fatal, In US: 5 cases only between 2006-16
Tetanus	Bacteria	Painful muscle spasms caused by endotoxin
Pertussis	Bacteria	Whooping cough, affects mostly very young children
Poliomyelitis	Virus	Attacks CNS neurons leading to paralysis; 37 cases worldwide in 2016
Varicella	Virus	Highly contagious, most serious in adults
Hepatitis A & B	Viruses	Serious Liver infections
Type B Influenza	Virus	May cause permanent neurological deficits in children
Pneumococcal Infection	Bacteria	Affects airways & hearing, mortality = 10%
Meningococcal Infection	Bacteria	Leading cause of meningitis, mortality = 10-14% despite antibiotics
Rotavirus	Virus	Gastrointestinal infection which can lead to fatal dehydration
Human Papillovirus	Virus	Cause of almost all anogenital warts & cervical cancers

(don't need to memorize)

MMR Vaccine

Measles, Mumps & Rubella Live Virus

- Efficacy:
  - 97% success within 2-6 weeks
- Adverse effects
  - Mild: fever, local rash, pain, stiffness
  - Severe: anaphylaxis & thrombocytopenia (very rare), gelatin allergy → extreme caution
- Precautions & contraindications
  - Pregnancy
  - Severe immunocompromisation
  - Severe febrile illness
- Schedule
  - 1st dose = 12 months
  - 2nd dose = 18 months
  - Boosters for HCPs

DTaP Vaccine

Diphtheria + Tetanus toxoids + acellular Pertussis

- Efficacy
  - Protection success = 80-90% after 3rd dose
  - Lasts 6 years (pertussis) or 10 years (tetanus + diphtheria)
- Adverse effects
  - Mild: local rash, fever, anorexia, drowsiness
  - Severe: convulsions, shock-like state, acute encephalopathy
- Precautions & contraindications
  - Contraindicated if severe febrile illness
  - History of anaphylaxis reaction to previous DTap shot

- Schedule
    - Routine immunization: 2, 4, 12 months & 4-6 years
    - Booster DTaP → 10-12 years old
    - Booster every 10 years henceforth

Polio Vaccine: IPV

Inactivated polio vaccine (IPV) against polio types 1, 2 & 3

- Efficacy
    - Success is 97-100% after 2+ shots lasting several years
- Adverse effects
    - Mild local pain/reactions
    - Potential allergic reactions to antibiotics in vaccine
- Routine immunization = 2, 4, 12 months & 4-6 years old

Varicella Virus Vaccine

Live attenuated varicella vaccine

- Efficacy
    - 99% success with 2-dose series
- Adverse effects
    - Only mild ones: local varicella-like rash, fever, & soreness
- Precautions & contraindications
    - Contraindications: pregnancy, leukemias, neomycin or gelatin allergy
    - Avoid aspirin for 6 weeks after → reye's syndrome
- Schedule
    - 1st dose: 12 months; 2nd dose: 18 months; 3rd dose: 4-6 years
    - Administered with MMR

Rates of varicella vaccination are declining due to misconceptions:

- Anti-vaccine groups' scare tactics
- Low incidence of diseases providing false sense of eradication
- Majority of cases being mild in children

Hepatitis A & B Vaccine

Hep A vaccine = inactivated virus

Hep B vaccine = Hepatitis B surface antigen

- Efficacy
    - Hep A success = 100% 1 month after 2nd dose
    - Hep B success = 90% after 3rd dose
- Adverse effects
    - Among safest vaccines: mild soreness and headache
- Precautions & contraindications
    - Hep A booster for risk populations (ex. Homosexual men, travelling to outbreak countries, illicit drug use, chronic liver disease, etc)
    - Hep B contraindicated if previous anaphylactic reactions

- Schedule
    - Hep B given with DTap at 2 & 4 months
    - Combined Hep A & B: 18 months & 4th grade school year

HPV Vaccines: Gardasil-9

Virus sized empty capsid proteins - routine pap smear tests still recommended

- Efficacy
    - Protection against cervical, vaginal and anal cancer
- Adverse effects
    - Very safe, mild symptoms only
    - No causality with serious effects
- Who should get vaccinated?
    - Routine vaccination of males & females recommended
    - 11-12 years since it only protects, cannot treat
- Precautions & contraindications
    - Contraindicated in pregnant & breast-feeding women
- Schedule
    - 3 doses over 6 months whenever the patient decides
    - Now part of routine schedule during 4th grade school year

Seasonal Flu Vaccines

Developed twice per year due to rapid mutations of influenza
Inactivated or live-attenuated

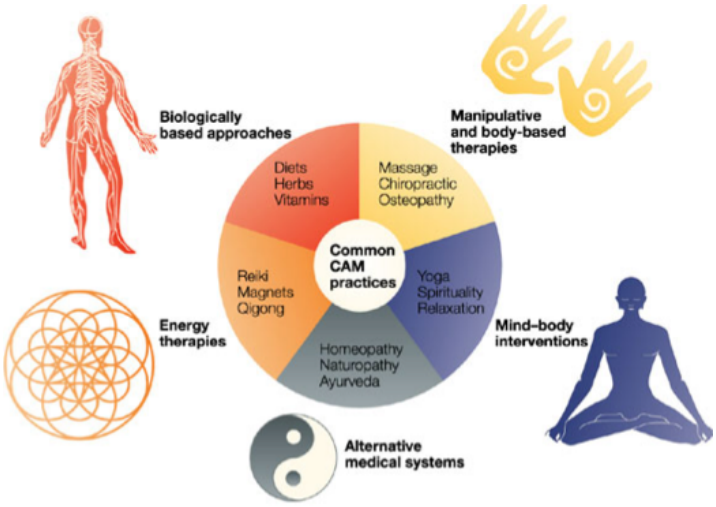
- Efficacy
    - Varies from year to year
    - Reduces risk of contracting infections & boosts recovery
- Adverse effects
    - Very safe
    - Transient fever
    - Muscle soreness in about 10% of cases
- Who should get vaccinated?
    - Healthcare professionals
    - Vulnerable populations: elderly (75+), respiratory diseases, children, pregnant women
- Precautions & contraindications
    - Individuals allergic to previous flu vaccines
- Schedule
    - Yearly around october

Complementary & Alternative Medicine (CAM) (Ch. 108)

CAM: Overview

- Benefit claims more or less evidence-based
- Complementary:
    - Non-mainstream approaches IN ADDITION to conventional medicine

- Alternative:
    - Non-mainstream approaches INSTEAD of conventional medicine
- 3 important aspects of CAM:
    - Marketing & money $$
    - Individual empowerment
    - Skepticism of medicine



Dietary supplements

= vitamins, minerals & herbal supplements

Why People Use Dietary Supplements

- Perception that supplements are safer and healthier than conventional drugs
- Sense of control over one's care
- Emotional comfort from taking action
- Cultural influence
- Limited access to professional care
- Lack of health insurance
- Convenience
- Media hype and aggressive marketing
- Recommendation from family and friends

Regulation of Dietary Supplements

- Dietary supplements health & education act (1994)
    - Reversed burden of proof → safe until proven hazardous
    - Investigate safety concerns or false efficacy claims ONLY after marketed
    - Manipulative labelling semantics (see next section)
    - No control on quality and actual content or products
- Dietary supplement & nonprescription drug consumer protection act (2006)
    - Serious adverse effects must be reported within 15 days
- Current good manufacturing practice (GMP) ruling (2007)
    - Addresses issues with quality control

    - Content of product must match labelling → most obtain "seal of approval" from a private laboratory
- Standardization
    - Differences in plant active ingredient depending on sunshine, rainfall, soil, etc.
    - Adjust concentration of extract to ensure consistency between batches produced
    - Allows for accurate dosing & safety/efficacy data interpretation

Dietary Supplements Labeling

- Shady labeling - super vague because you can't disprove it.
- Because it can't be proved wrong, it does not fall under false labelling.
- Not obliged to state adverse effects on the labels, because it is technically not a drug.

Adverse Interactions With 'Conventional Drugs'

- Many unknown interactions due to lack of safety/efficacy studies
- CYP3A4 induction
    - St John's Wort → decrease therapeutic efficacy of many drugs (ex. statins)
- Platelet aggregation inhibition
    - Interaction with warfarin, heparin, etc. → increase risk of bleeding
    - Ex. Ginko Biloba, feverfew, garlic
- Cardiovascular effects
    - Ma Huang = ephedrine → increased BP, HR & CNS
    - Interactions with beta-blockers, antidepressants, etc.
- 2 major issues:
    - Prescriber knowledge - some prescribers don't know all the effects of those agents, thus they can't properly educate patients about their effects.
    - Patient disclosure - they don't disclose they are taking those products because they don't think it matters.

Editorial Comment - NEJM

It is time for the scientific community to stop giving alternative medicine a free ride. There cannot be two kinds of medicine—conventional and alternative. There is only medicine that has been adequately tested and medicine that has not, medicine that works and medicine that may or may not work. Once a treatment has been tested rigorously, it no longer matters whether it was considered alternative at the outset. If it is found to be reasonably safe and effective, it will be accepted. But assertions, speculation, and testimonials do not substitute for evidence. Alternative treatments should be subjected to scientific testing no less rigorous than that required for conventional treatments.

Unfortunately, two decades later, little has changed.

- *New England Journal of Medicine Editorial*

NUR1 300 – Pharmacology for Nursing | November 28th, 2019
Lecture 12: Complementary & Alternative Therapies | William Archambault

Editorial Comments - W.A.

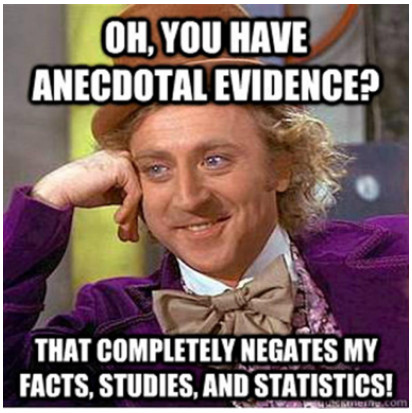
- The capitalization of health → age of skepticisms
- Internet: democratization of information → individual empowerment
    - Ex. anti-vaccine movement; big pharma & lobbying groups
- Looking for simple solutions to complex problems vs. using judgement & nuance (see youtube clip)
    - https://www.youtube.com/watch?v=j5U_6Vdm07w → Dallas Buyers Club – Judge Ruling(1 min)
- Rationalization: when you must adapt to your behaviour - when you start doing something, such as using natural products, well your attitude/beliefs towards it tends to change → "if i am using natural products, that must mean that I do not trust the use of medication, ergo i believe in it more."

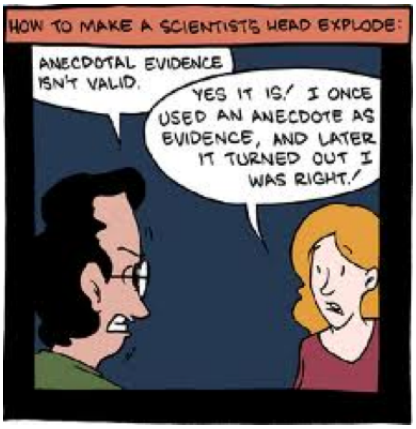
Logical Fallacies

- Pharmachien Tome 3 - Logical Fallacies Bible
    - Debunks a lot of myths
- "It's not that people are stupid. It's that life is hard." - prof. Richard Thaler (Nobel Prize of Economics)

Anecdotes - Scientist's Kryptonite

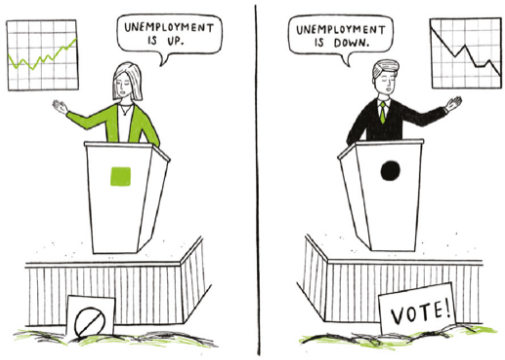
- Be careful when you are reading papers/articles when people are using arguments "i heard something..., i read something… "





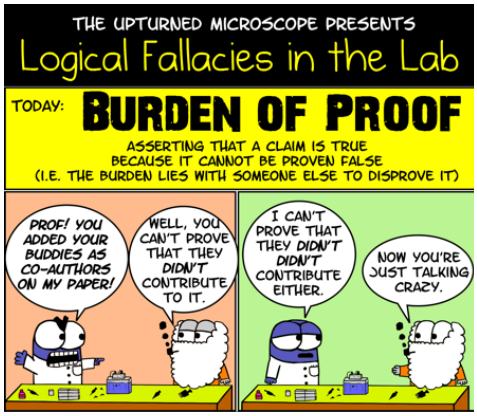
Cherry Picking

- https://www.youtube.com/watch?v=yJD1Iwy5lUY - If Google was a Guy (Part III) – Watch at 45 seconds
- Using an anecdote that fits your story rather than looking at the whole picture



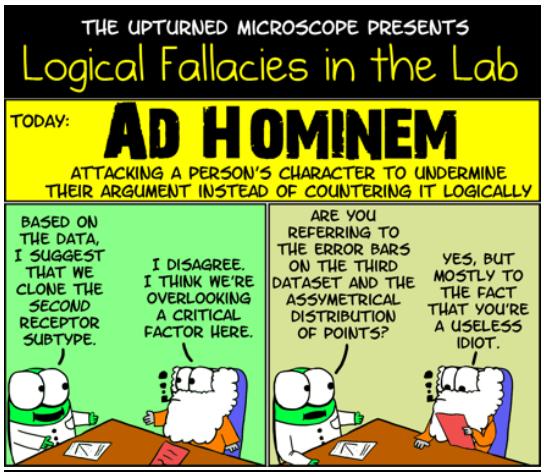
Burden of Proof

- Who needs to prove what and when - the person making the allegation should be the one to prove it and not the other person to disprove it.
- A hypothesis is said to be false, unless proven otherwise
- Extraordinary claims require extraordinary (robust) evidence
- Complex problems (most often than not) require complex solutions



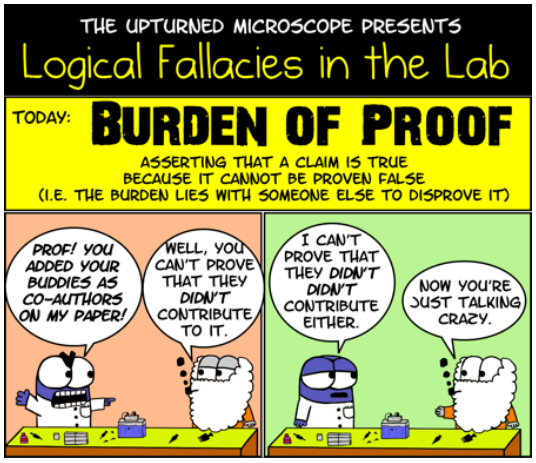
Ad Hominem

- Instead of attacking the claim, you attack the person making the claim



Strawman Fallacy

- Misrepresent an argument so that it is easier to destroy
- Anti-vaccine argument seen online: 'if you are for vaccines, then you should not mind me when i stab your children'



Appeal to Traditions

- 'Marriage should be between a man and a woman. It has been that way for hundreds of years.'
- It's much easier to stay with traditions than to have to change that. It gives us a sense of control.

Appeal to Authority

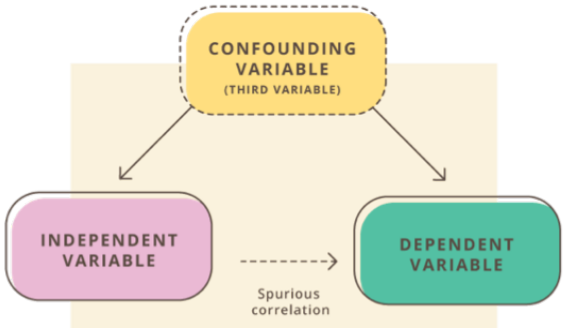
- Target authority figures to try and prove something. Such as cigarettes are healthy because even doctors smoke them.
- Becomes a cult of personality. I like this actress/blogger, so i like this too.

Appeal to Nature

- Your body doesn't care if it's natural or made in a lab, it can't tell the difference. It only cares about what it does to your body.

Correlation vs. Causation

- 2 big traps:
    - Reverse causation: when there is a correlation between two items, we don't know which one caused the other to change. We just know that when one changes, the other also changes.
    - 3rd confounding variable: 2 things have changed, it's not because one affected the other. There is another factor affecting them.



Many More Logical Fallacies

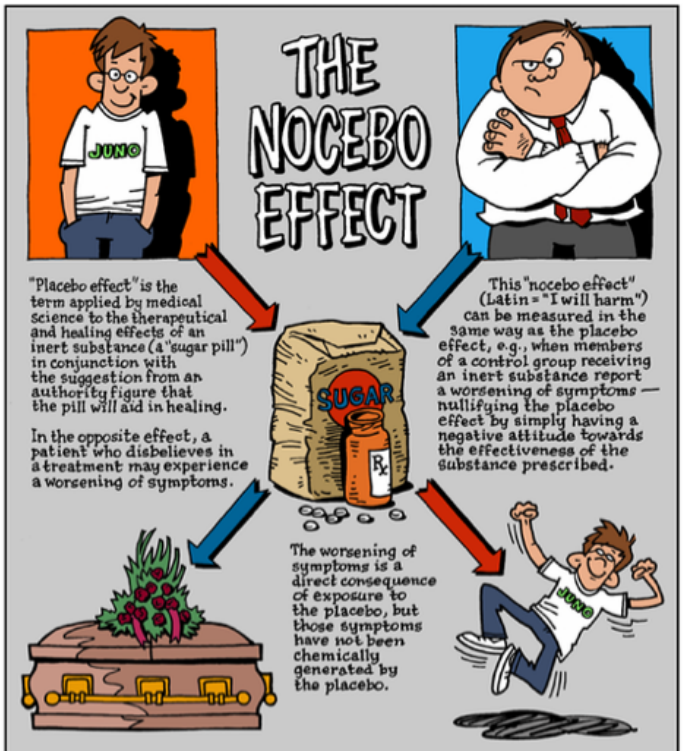
Please check out this website when you have an argument or just a moment to practice critical thinking.

https://yourlogicalfallacyis.com/

24 Cognitive Biases

Placebo Effect

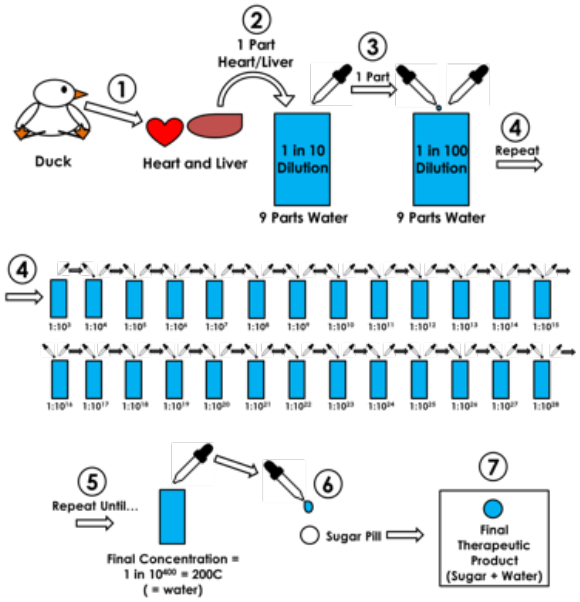
- Psychological fraction of drug response based on patients' attitude and expectations of the Rx.



Case Study: Homeopathy

Founding principles:

- Likes cures likes - if someone has a heart disease, you're going to give them a heart extract of something else.
- Water potentization power - belief that water has a memory. That the more diluted it is, the better it is. They believe that the dilution is stronger because the water remembers. If the water was exposed to the molecule of that product, it will remember it and keep this property. They think that if you take that water, and place some in a different jar of water, it will give that property to the other jar.



Homeopathy: When it is Good

- For mild conditions like common cold, minor fatigue, headache or winter blues, the placebo effect of homeopathy can be sometimes more beneficial rather than taking medication for it.
- Placebo effect + sense of self-efficacy + social support of authority figure = very strong placebo
- 'Homeopathy users who saw a practitioner were significantly more likely to feel that homeopathy was 'very important in maintaining health and well-being' and that it helped their health condition "a great deal" than were homeopathy users who did not see a practitioner. Homeopathy users who did not see a practitioner were significantly more likely than were supplement users to find the modality they used helpful.'

Homeopathy: When it Goes Too Far

- Homeopathy only becomes a problem when it goes too far, such as trying to cure hepatitis C with homeopathy.
- It also becomes a problem when patients refuse proper treatment because they truly believe that homeopathy is helping them.

Some Commonly Used Dietary Supplements

Garlic

Active Ingredients	Allicin & Ajoenes
Claims	Decrease cholesterol synthesis Antiplatelet effect Increase nitric oxide vasodilation
Effectiveness	Recent robust NCCIH review included: - No effect on LDL cholesterol - Modes decrease in BP & atherosclerosis development
Adverse effects	Bad breath & odor Potential GI irritation
Interactions	Warfarin, aspirin, heparin, etc → antiplatelet effects Increase metabolism of cyclosporine & Saquinavir

Ginkgo Bilboa

Active ingredients	Flavonoids (24%) & Terpenoids (6%)
Claims	Increase memory / decrease dementia & erectile dysfunction
Effectiveness	Early findings = promising More robust & recent research = conflicting results No evidence for dementia prevention in alzheimer's study
Adverse effects	Well tolerated - mild vertigo or dizziness Eating raw or roasted seeds = extremely toxic
Interactions	Warfarin, aspirin, heparin, etc → anticoagulation effects Increase seizure risk drugs & patients (ex. antipsychotics)

Probiotics

Active ingredients	Normal GI gut flora bacteria: lactobacilli & bifidobacteria
Claims	Tx of irritable bowel syndrome, ulcerative colitis & diarrhea
Effectiveness	Some evidence of decrease in diarrhea duration & increased UC recovery Larger more robust studies required
Adverse effects	Flatulence & bloating = most common Infections only in severely immunocompromised patients
Interactions	Abx & antifungal drugs → administer probiotic 2h post-Tx

Ginger Roots

Claims	Suppress vertigo & nausea/vomiting
Effectiveness	Monitoring sickness prevention: good evidence! Other types of nausea/vomiting: conflicting results Rheumatoid arthritis Sx alleviation: potential but weak evidence
Adverse effects	Very well tolerated Very excessive doses: CNS depression, GI disturbances, dysrhythmias Theoretical risk of effects on fetus but no evidence
Interactions	Warfarin, aspirin, heparin, etc. → anticoagulation effects insulin/antidiabetic agents → decrease blood sugar

Resveratrol

Sources	Skin of grapes, red wine, blueberries, cranberries, peanuts
Claims	Antioxidant with anti-aging properties
Effectiveness	Clear benefits in animal studies: decreased mortality of obese mice Increased bone density, CVS or motor functions in healthy mice Decreased tumor growth in mice & blood glucose in diabetic rats Early human studies show promising results
Adverse effects	Antiplatelets action + estrogen analog + increased insulin sensitivity
Interactions	

St-John's Wort

Active Ingredients	Hyperforin & hypericin extracts
Claims	Antidepressant Mild anti-inflammatory & analgesics
Effectiveness	Mild to moderate depression: better than placebo Severe depression: inferior to antidepressants
Adverse effects	Skin allergic reactions, CNS effects & GI disturbances High dose therapy: risk of phototoxicity
Interactions	CYP3A4 induction → decreases therapeutic effects Increases P-glycoprotein synthesis → decrease therapeutic effects Increase serotonin transmission → risk of serotonin syndrome

Harmful Supplements

Comfrey

- Carcinogenic
- Veno-occlusive hepatic disease → 2001 FDA advisory of removal
- Still available online

Kava

- Promoted as alternative of benzodiazepines
- Risk of severe hepatotoxicity → 2002 FDA public warning
- Sales restricted in Canada

Ma Huang (Ephdra)

- High-dose Ephdra associated with stroke, myocardial infarction & death
- 17 000+ ADR reported → 2004 FDA ban

Nursing Capsule: Patient Education

- When asked for advice, use evidence-based approaches
- SBN time: respect patient's beliefs → don't ruin their placebo effect
- Explain to them the importance of disclosing all the dietary supplements they use
    - Adverse effects undocumented
    - Potential interactions with other drugs

About the final exam

- FINAL exam is on Dec 12th at 9h00 in the gym most likely…
- Don't forget the bonus question :) refer to the link on the first slide:
    - http://revisionisthistory.com/episodes/09-generous-orthodoxy
- Final exam breakdown
    - About 9 MCQs on the pre-midterm courses (none on the 1st short lecture)
    - 10 or 11 MCQs / post-midterm lectures
        - 1 passage with 4-5 questions associated / post-midterm lecture
    - 1 bonus question based on the podcast
- Pre midterm material to review:
    - 4 main class of drug receptors
    - Kinetic vs. dynamic interactions
    - Ideal general anesthetic
    - Dose-dependent selectivity or neurological agents
- Material to review:
    - Endocrine pharmacology:
        - Mechanisms of action of antidiabetic drugs
        - Insulin administration
    - OTC pharmacology
        - Best migraine management practices
        - Differences between types of laxatives
    - Cardiovascular pharmacology
        - Monitoring of anemia deficiencies
        - Advantages vs. drawbacks of drugs with similar action/within the same class
        - Combination of cardiovascular drugs to manage toxicity
        - Digoxin
        - Angina & STEMI complications
    - Respiratory/ADHD pharmacology
        - Asthma vs. COPD management similarities/differences
        - Cocaine vs. amphetamine
    - Complementary & alternative medicines
        - Main application of each vitamins
        - Examples of cognitive biases → play at spotting them in newspaper ads and pseudoscientific websites!