5 Phases of Drugs

1. **Preclinical studies**: when drug found effective, go on to animal exp's for ~2-5 yrs, to see if it's **safe & useful.** Know that all new molecules are 1st tested in lab (*in vitro*) & then in animals (*preclinical studies*). If found to be both EFFECTIVE & SAFE, they're tested in humans (clinical trials)

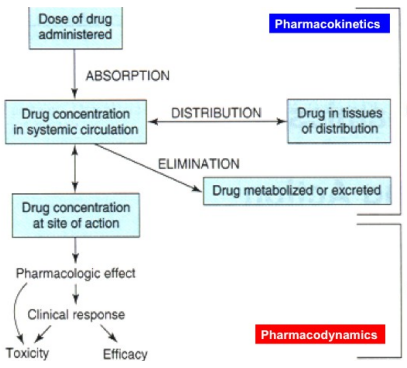
- Why clinical trials? Diff steps involved in trials (refer slides). In Each phase you should know:
    1. Why is it done? Is it to test safety or efficacy or both or rare side efx?
    2. What is the sample size? ... is it only few pt's? Or 100s or 1000s of pt's
    3. In Whom is it conducted? ..pt's or normal volunteers

2. **Filing IND (investigation new drug) to FDA ⊔ Clinical Trials**: study of new drug in HUMANS; 4 phases:
3. **Phase 1**: test **safety (ANSWER) &** side efx but **not efficacy**/effectiveness; conducted in **normal volunteers** **(ANSWER; not pt's) but** exception if drug expected to cause sig toxicity (ie. tx of AIDS & cancer) where its tested on pt's; conducted in **small** # of volunteers 20-30 **/sample size" as "open labelled study"**
4. **Phase 2**: **in specific pt's (not in volunteers)** to study both **efficacy & safety;** in **Small # of pt's** (100-200); "single-blind, Placebo controlled study"
5. **Phase 3**: in large sample of specific pt's (>1000) as **multicenter study** (in many hospital centers) to further establish safety & efficacy w/great care; randomized double-blind placebo controlled, comparative study
6. NDA: New Drug Application ⊔ FDA Reviews ⊔ FDA grants approval for marketing of drugs ⊔ Drug released into market
7. **Phase 4**: Post marketing study/ Surveillance done only **after drug releases into market;** monitoring safety of new drug under actual conditions of use in very large # of pt's only after drug released in market. Specifically monitors rare, severe side efx/toxicity of drug; physicians/pt's/media'll rep't any rare toxicity or DI's (<1/10,000 pt's)

- **Placebo controlled study**: 1 group of study subjects get placebo & other gets new drug which is in study
- **Comparative study**: 1 group of study subjects get established drug & another gets new drug in study
- **Open labeled study**: Both physician & study subject know which drug is being given
- **Single blind study**: Either Physician or study subject, any one knows which drug is being given to whom
- **Double blind study**: Neither Physician nor study subject knows which drug is being given to whom

⊔*Drug Nomenclature*: 3 categories – chem'al name (chem'al nature, ie. N-acetyl-p-aminophenol), non proprietary name (know this one! Name given by scientific body/council, ie. Acetaminophen (paracetamol in UK)), & proprietary (brand, trade) name (given by manufacturer, Tylenol, Anacin);

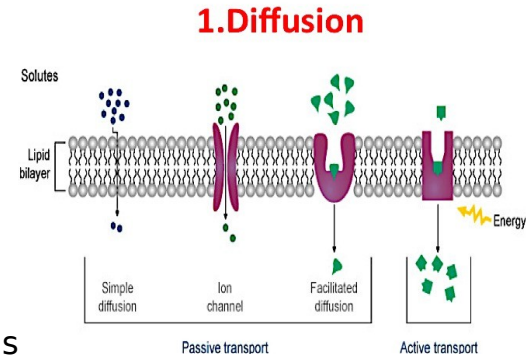
- **Essential drugs**: those that satisfy health care needs of majority of pop; must be available at all times in adequate quantity; 1977 WHO released "National essential drug list" maintained by each nation
- **Orphan drugs**: some dis'ss very rare so drugs used for them have least market; thus drug companies not very keen in making these drugs; eg. Desmopressin used in DI; their production encouraged by federal gov't by provision of incentives & subsidies
- **Pharmacodynamics**: drug interacts w/body & produces efx, good &/or bad; drug does something to body
- **Pharmacokinetics**: similarly body also does something to DRUG; ***quantitative*** **study of drug's** Absorption, Distribution, Metabolism & Excretion; studied in 2 sections: Basic & Advanced Pharmacokinetics



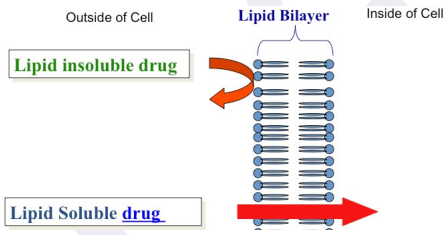
L1 PK-1 Drug transport mechanisms

Dr. Chanz

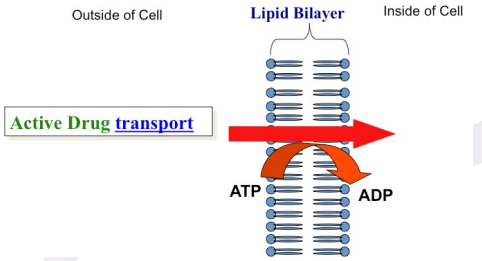
- In order to get <u>absorb</u>, <u>distribute</u> & <u>excrete</u> **(**pharmacokinetic processes**)**, drug needs to be transported, by passing thru several cell memb's; involves mainly *<u>2 types of permeation processes</u>*:



1. **Diffusion** thru cell memb's
   a. **<u>Simple/Lipid diffusion:</u>** most frequent process of drug permeation across lipid bilayer of cell memb's; directly proportional to [ ] gradient of drug & to area of diffusion, but inversely proportional to memb thickness of memb (Fick's law of diffusion); passive process, NOT selective process (doesn't depend on structure) but depends on lipid solubility & molecular size



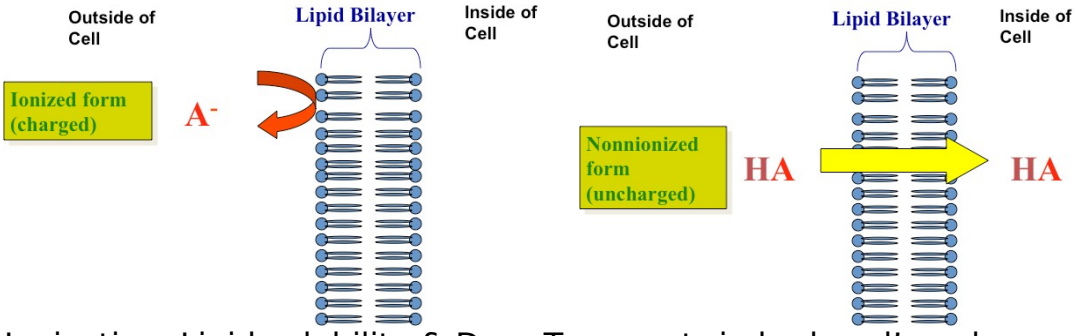
   b. **<u>Aqueous diffusion</u>** – drug passes thru* thru *<u>narrow</u>* protein channels of cell memb* (Aquaporins) that traverse lipid bilayer. These channels restrict passage of any molecule larger >100 MW; ie. *lipid insoluble* drugs w/lesser MW <100; just know SMALL size is beautiful, SIZE MATTERS.
   c. **Facilitated diffusion**: transport facilitated by protein-carrier molecules; passive, selective & saturable
2. **<u>Active drug transport</u>**: moves drug <u>against [ ] gradient</u>; requires metabolic energy (ATP); facilitated by Protein-carrier molecules; Active, Selective & Saturable



3. **<u>Endocytosis</u>**: many cells (intestinal epithelium, capillary endothelium) engulf solid particles or water droplets; very large drug molecules (MW 2000-100000) can enter cells by endocytosis & exit by **<u>exocytosis</u>** (both are active transport mechanisms); best ex's – bacterial toxins (botulin toxin for wrinkles), Ab's (IgG, IgM, IgE,) & protein hormones; rmr drugs w/higher MW, ie. peptides of hormones, are ex's are endocytosis
4. **<u>Filtration/bulk flow transfer/convective transport</u>:** move across cell barriers thru intercellular pores, like maculae/fenestrae of capillaries; directly proportional to pressure gradient across capillary wall; **<u>non selective, passive*</u>** process but <u>depends on molecular size</u>

<u>L2 PK-2 Absorption; Factors that affect drug absorption:</u>

- **<u>Absorption</u>**: transport of drug from its site of admin to blood stream & its site of axn; **<u>depends on 5:</u>** route of admin, size (Smaller is better), [ ] gradient, surface area & vascularity of that area & lipid solubility of drug



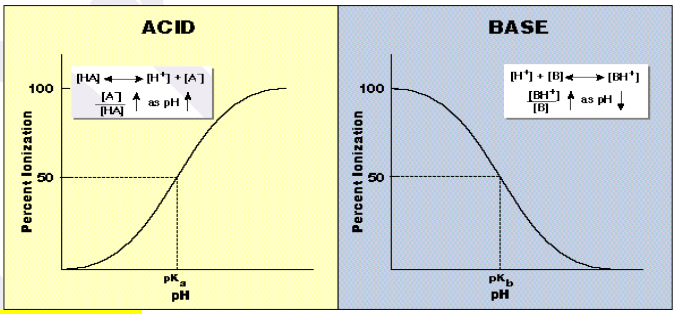
Ionization, Lipid solubility & Drug Transport**:** in body sol'ns, drug exists as mixture of 2 interchangeable forms –

1. Ionized/elec'ally ***charged:*** non lipid soluble (Water-soluble) – **can't easily cross memb; fit for excretion**
2. Non-Ionized/***uncharged***: Lipid-soluble; **easily cross memb. Fit for absorption**; proportion (%) of ionized or unionized drug in body compartment determines lipid solubility. Which in turn influences transportation of drug across memb & its absorption; ***more nonionized state = better lipid solubility & absorption

3 factors affecting ionization: & determines ratio of ionized to non-ionized portion of drug in body compartment; Only pH of medium is a variable factor. Other 2 factors are characters of a given drug

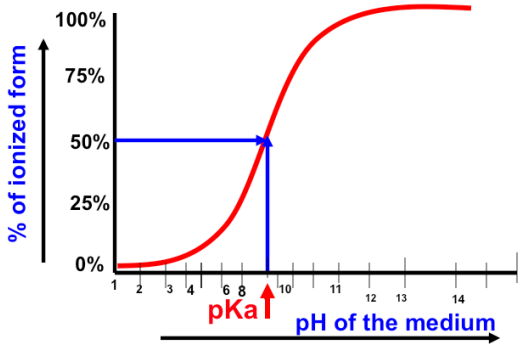
1. ***Nature of drug: acid or a base***
2. ***pH of medium (Body compartment)***

1. **Weak acids become highly ionized as pH ⬇**
2. **Weak bases become highly ionized as pH ⬆⬆**
3. **As pH ⬆**, weak BASE will become ⬇& more unionized, **lipid soluble** & better absorbed. More efx in body
4. **As pH ⬆⬆**, weak BASE will become more & more ionized, **lipid insoluble** & won't be absorbed. Also becomes more water soluble & better excreted. Less efx in body
5. **As pH ⬆**, weak ACID will become ⬇& ⬇IONIZED, lipid insoluble & WON'T be absorbed. Also becomes more water soluble & better excreted
6. **As pH ⬆⬆**, weak ACID will become ⬇& ⬇UNIONIZED, lipid soluble & better absorbed
7. ***Acidic** drugs are **A**bsorbed best in **Acidic** medium. Acidic drugs excreted best, if **urine (in tubules)** is Basic
8. Basic drugs are Best absorbed in Basic medium. Basic drugs excreted best, if **urine (in tubules)** is Acidic
9. Note: above statements true only if pKa values not taken into consideration. **What is this pKa?**



3. ***pKa of drug:*** equivalent to that pH, at which 50% drug is ionized & 50% is unionized; If we know pKa of given acidic or basic drug, we can calculate proportion (%) of ionized or unionized drug in body compartment of a known pH. This calculation based on Henderson-Hasselbalch eq'n that expresses ratio of unionized to ionized for weak acid or weak base; relates ratio of protonated to unprotonated weak acid or weak base to molecule's pKa & pH of medium

pKa: One other factor which determines the ionization



pH = pKa + Log of (UPF/PF)

- pH - **pKa** = log (Unprotonated / Protonated)
- For Acids: pH – **pKa** = log (ionized / Nonionized)
- For Base: pH – **pKa** = log (Nonionized / Ionized)
- pH = pKa + log of Unprotonated form/log of Protonated form OR pH –pKa = log of Unprotonated form/log of Protonated form

Qn 1. pKa of basic drug Meperidine is 8.00. What %age of the drug is in an absorbable form at pH of 6.00?

- A.0.1%
- B.1%
- C.10%
- D.90%
- E.99%

Sol'n: pKa = 8.00 basic drug Meperidine; pH = 6.00

- pH - **pKa** = log (Unprotonated / Protonated) ▭ -2 = log (Nonionized / Ionized)
- 10^{-2} = Nonionized / ionized ▭ 1/100 = Non-ionized / ionized
- Therefore, ratio is 1: 100 & in terms of %, nonionized is 1% & ionized is 99%.
- Non ionized (absorbable lipid soluble) form is around 1%

pH-pKa	-2	-1	0	+1	+2
Weak acid: %nonionized	99 (best absorbed)	90	50	10	01
Weak base: %nonionized	01 (worst absorbed)	10	50	90	99

- For a weak acidic drug:
  - If pH-Pka is ┐, drug will be more nonionized & good for absorption
  - If pH-Pka is ⏝, drug will be more ionized & good for excretion
- For a weak basic drug:
  - If pH-Pka is ┐, drug will be more ionized & fit for excretion
  - If pH-Pka is ⏝, drug will be more nonionized & fit for absorption
- Qn. 2. A pharmacologist is determining PK parameters of novel antibiotic in order to determine proper dosage. Drug is weak acid w/pKa of 5.0. Assuming pH of 8.0 in urine, ~ what % of drug will be in a form that can be rapidly excreted?
  A. 0.1
  B. 1
  C. 90
  D. 99
  E. 99.9

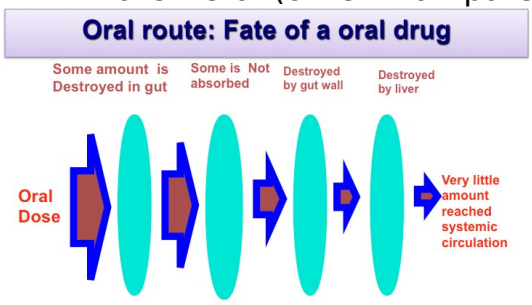
Qn. 3 Which of following combos of pH & pKa results in greatest urinary excretion of the unchanged drug ?

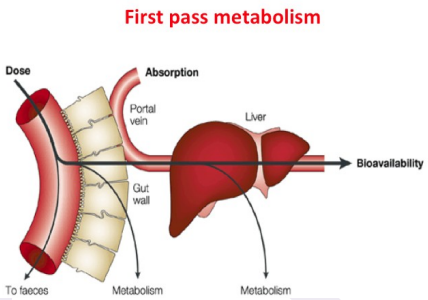
Drug	Drug pKa	Urine pH
A. Weak acid	4	7: Ph-pka= 3
B. Weak acid	4	8 Ph-pka= 4
C. Weak acid	8	8 Ph-pka= 0
D. Weak base	5	9 Ph-pka= 4
E. Weak base	8	7 Ph-pka= -1

Drug B is answer

L4 PK-3 Diff routes of drug admin (Oral (worst), Sublingual (Placed under tongue), Intravenously (best), Intramuscularly, Transdermal, Inhalation, Subcutaneously, Intrathecal (Into space around spinal cord), Per rectal, Per vaginally)

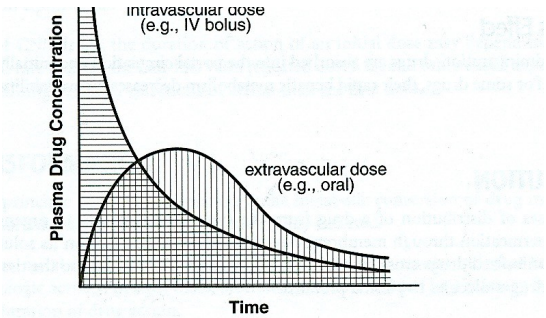
- Drugs are introduced into body by several routes; routes may be broadly divided into 2 types:
  1. Enteral (eg: oral & rectal route)
  2. Parenteral (other than parenteral routes)





http://www.icp.org.nz/html/oral_availablity.html

- **1st pass metabolism (ANSWER)**: drugs given by oral & other routes, must pass across memb's of GI tract & then thru liver b4 reaching general circulation; if drug is metabolized in gut wall or in liver, fraction of active drug will be eliminated during this so-called **1st pass** b4 reaching general circulation; metabolism of drug b4 it reaches systemic circulation
- **Bioavailability**: fraction of admin'd dose reaching systemic circulation in its chem'ally *unchanged* form; pharmacokinetic parameter that gives quantitative measure of drug **absorption**; 100% if given IV & ranges from 0-100% if it is by any other route; Why less Bioavaililbity for drugs given other than IV route? B/c, drugs given by other than IV route generally undergoes ***1st Pass Metabolism***
  - designated as **" F "**; if BA is 100%..... **" F"** =1; if BA is less than 100%..... **" F "≤1**
  - Steps in measuring Oral bioavailability of drug X –
    1. Following IV admin of drug X, draw Time-Concentration curve
    2. Measure Area Under Curve (AUC), aka **AUC_{IV}**
    3. Same steps repeated following oral admin of same drug. AUC (Area under curve) measured as **AUCoral**
    4. Compare both **AUC_{IV} & AUC_{oral}** assuming equal doses, F = / AUC IV



Measure of the fraction of a dose that reaches the systemic circulation. By definition, intravascular doses have 100% bioavailability, f = 1.

Rel'n btwn BA & [plasma]:

a. If Bioavailability ↓[plasma] ↓& BA ↓[plasma] also ↓. Direct rel'n.

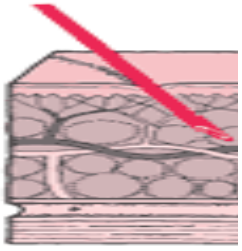
b. If F doubles, [plasma] doubles. If BA ↓by half, [plasma] ↓to half

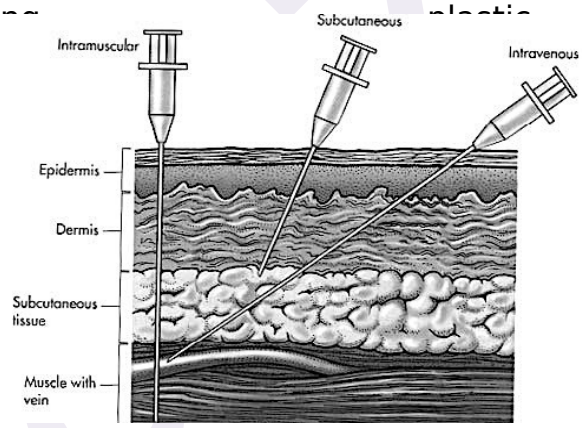
c. If F doubles, ↓dose of drug to be given to half of it.

d. If F is ¬¬by half, dose admin'd should become double

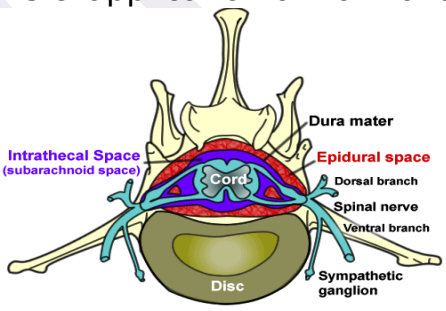
- **Oral Route**: most convenient, safest, least expensive & most used w/self medication possible; 3 limitations: delayed efx, thus not good for emergency, gastric irritation, & less *Bioavailability*
- **IV route**:
  - *Adv's*: Immediate effect & good for emergency, & 100% bioavailability
  - *Disadv's*: Adverse efx will be more severe & immediate

- **Subcutaneous Route**: needle inserted into fatty tissue just beneath skin; for many protein drugs b/c such drugs would be digested in digestive tract if taken orally; certain drugs (progestin, used for birth control) may be given by inse[illegible] capsules under skin (subcutaneously); commonly vacci[illegible]



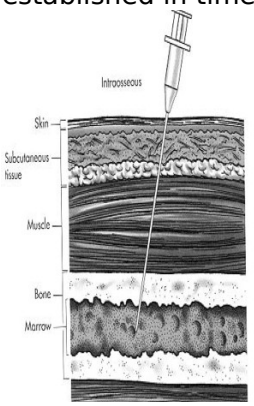


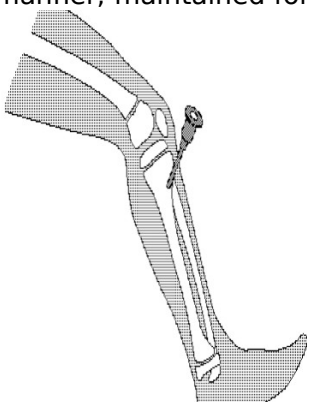
- **Intramuscular Route**: subcutaneous route when **larger volumes** of drug product needed; injected into in upper arm, thigh, or buttock
- **Inhalational Route**: used to administer drugs that act on lungs, such as aerosolized antiasthamatic drugs in metered-dose containers
- **Sublingual Route**: rapid absorption & drug immediately enters bloodstream w/out 1st passing thru intestinal wall & liver; esp good for **Nitroglycerin**—used to relieve angina
  - Adv's: immediate drug efx, by passing of 1st pass metabolism, axn terminated voluntarily by spitting
  - Disadv's: erratic drug absorption which leads to unpredictable drug efx w/respect to drug [ ]'s
- **Rectal route**: for drug admin to paediatric & geriatric group, tho not well accepted; useful for pt's who cannot swallow, including those near end of life; MC'ly by suppository or enema; adv's: by-pass liver (Some of v's draining rectum lead directly to general circulation) & consciousness not required
- **Vaginal route**: some drugs may be admin'd vaginally to women as sol'n, tablet, cream, gel or suppository; drug slowly absorbed thru vaginal wall; called as vaginal pessaries; used to treat vaginal infections & application of hormonal meds; E.g. Clotrimazole (antifungal)



- **Intrathecal route**:
- **Intra-arterial route**: used to localize efx of drug in particular tissue/organ by delaying their systemic distribution (dx'ic agents, anticancer drugs)
- **Intraosseous infusion** (IO): process of injection directly into marrow of bone; in emergency situations to provide fluids & med when IV line can't be used. Needle injected thru bone's hard cortex & into soft marrow interior which allows immediate access to vascular system; used on adult or pediatric pt's when traditional methods of vascular access difficult or impossible. Often antero-medial aspect of tibia used as it lies just under skin & easily palpated & located. Ant aspect of femur, sup iliac crest & head of humerus are other sites that can

be used; route of fluid & medication admin is alternate 1 to preferred intravascular route when latter can't be established in timely manner; maintained for 24–48 hrs, after which another route of access should be obtained





L4 PK-4 Drug Distribution & plasma protein binding

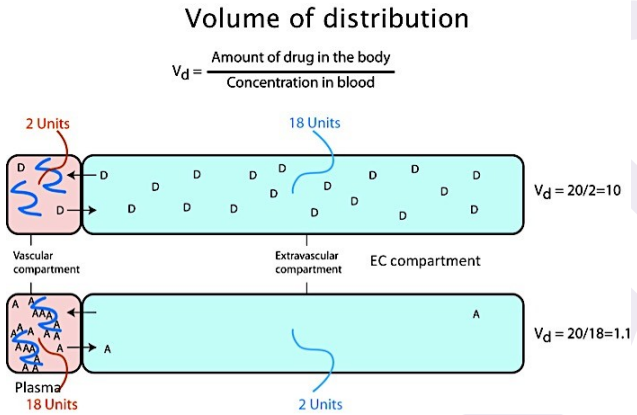
- After absorption, drug distributes into various body fluid compartments –
  - EC fluid – 14 L ▭ Plasma volume – 4 L + Interstitial fluid – 10 L
  - IC fluid – 28 L
- **Total body water is 42 L.** **Distribution** = delivery of drug from systemic circulation into tissue; dynamic phenomenon & thus, initial distribution of drug may not be same as its final distribution (redistribution)

Factors affecting drug distribution:

1. **Size of organ**
2. **Rate of BF**: well perfused tissues like kidneys, liver & brain achieve high [tissue]'s sooner than poorly perfused tissues like fat or bone
3. **Solubility**: regional differences in pH
4. **Plasma protein binding**: drugs that are highly protein upon entering circulation, bind mainly to albumin (if acidic) or to α1-acid-glycoprotein (if basic); extent to which drugs are bound to protein is highly variable (ex. 0% for Lithium in bipolar disorder pt's, 99% for warfarin)
   a. **Ex: **Warfarin**: anticoagulant – has ability w/very good affinity to bind to plasma proteins, drugs that are bound to plasma proteins cannot pass memb, once disassociated from it, only its broken off particles can distribute thru out body. But if ***sulphonamide displaces Warfarin in drug DI's ▭ warfarin will be free to exert its efx lot more than usual, further producing side efx – bleeding!!!
   b. If drug has more affinity to bind to proteins in plasma, drug restricts its distribution to vascular compartment eg: 99% of Warfarin will strongly bind to plasma albumin. Thus Warfarin seen >in plasma than in any other compartments of body.
   c. If drug has least affinity for plasma proteins, it's likely to distribute into some other tissue compartments of body. Eg: ***Chloroquine w/least affinity for ***plasma proteins;*** thus less [plasma] but very high [Chloroquine **tissue]** seen
   d. Plasma [ ] of drug, is not true representation of total [drug] in body
   e. If drug A & B both known to have high plasma protein binding. Competition from drug B, for binding to same protein may displace drug A from protein & ▭[plasma] of free form of drug A▭ leads to ▭adverse efx of drug A; Eg: Sulfonamide displaces warfarin & produces bleeding, adverse effect of warfarin
   f. If drug highly tissue bound (least plasma protein bound), not easily accessible for removal by dialysis; Eg: TCAs
   g. Age, dis & pregnancy can have effect on %age of plasma protein binding & final efx of drug
   h. **Protein bound drugs**: can't cross cell memb, can't be distributed, not available for their axn (free form of drug in plasma only available for all axns), can't be filtered in kidney (excreted mainly by secretion), not available for metabolism, known for drug-drug protein binding displacement interax'ns, these drugs will have least Vd

i. **Volume distribution (Vd)**: pharmacokinetic parameter, gives quantitative %age measure of drug distribution in serum expressed as L/70Kg body weight; Value of Vd for any given drug is fixed; always constant/fixed value (given)! if drug needs to be distributed in whole body, it needs larger amt of space to be uniformly distributed; ***volume apparently necessary*** to contain amt of drug *homogeneously* at [ ] found in blood (ANSWER); Vd relates amt of drug in body to [ ] of drug (C) in plasma. **$Vd=D/C_0$ (amt of drug in body / initial [ ] in blood) on QUIZ, BLOCK & FINAL**; since Vd never changes, it's dosage we give that allows amt of drug & [ ] in blood fluctuate

i. **D** = total amt of drug in body (aka dose given IV). (or to Dose x F, when dose given by other routes)
ii. **C_0** = drug [ ] in plasma (mg/liter) at zero time
iii. V_d
iv. **Ex**. Warfarin, 99% of drug is protein bound, ie. 99 mg of 100 mg; 1 mg remains in extravascular compartment, whereas the remaining is in vascular compartment/plasma
v. **If Vd is 10 L, drug is ⁊⁊ in tissue than in plasma, b/c plasma volume 4L is highly exceeded**
vi. **If Vd is 1.1 L, drug is ⁊⁊ in plasma than in tissue, b/c plasma volume 4L is not exceeded much**
vii. Vd & Protein binding have inverse rel'n. Drug w/higher protein binding affinity such as warfarin will have least Vd and vice versa for chloroquine. **Highly protein bound drug, ie. Warfarin, will remain in plasma, so drug must have least Vd ie. 1.1 A lower protein bound drug, more in tissue, so drug must have more Vd**



- Blood Brain Barrier & Placental Barrier
  - BBB limits transfer of lipid-insoluble or highly ionized drugs into CNS
  - When axn on CNS needed, drugs that don't cross BBB admin'd by intrathecal injection directly into CSF
  - BBB permeability is ⁻ in newborn baby & many CNS path'al conditions (inflammation, trauma, hypertensive crisis, hyperglycemic crisis, tumors etc.)
  - Placental barrier generally quite permeable to most drugs.

L5 PK-5 Drug Metabolism (biotransformation)

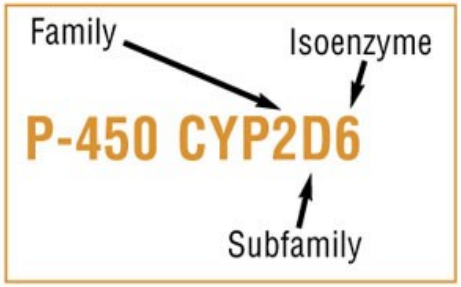
- Drug metabolism = chem'al alterating drug in body which converts *non polar* ***Lipid soluble*** compounds to *more Polar & water soluble*. Thus makes drug more suitable for excretion
- Liver most imp organ where most drug metabolism occurs. Other organs could be Kidney, Intestine & lungs
- Factors that affect drug metabolism are: co-admin'd drugs, genetic variation, age & diseases

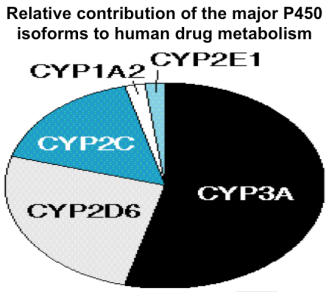
Fate of Drug

1. Metabolites that result from drug metabolism are generally inactive, nontoxic & fit for excretion (95% cases)
2. In some cases metabolites may be similar to parent drug
3. In few cases, metabolite could be active form of original drug. Such drugs called as **Prodrugs**. eg: Enalapril, Prednisone, Spiranolactone, Cyclophosphamide; S.C.E.P.

Biotransformation Rxns: rxns involved in drug metabolism are broadly categorized into 2 groups –

1. **Phase- I (Non Synthetic) rxns: take place in ER; convert parent drug to **more polar metabolite** by introducing func'al group ie. –OH, -SH; include oxidation (MC, w/CYP enzymes), reduction, hydrolysis, cyclization & decyclization
   a) **Oxidation (MC) rxns**: imp phase-1 drug metabolizing rxns; most drugs metabolism catalyzed by microsomal enzymes (mixed func oxidases or monooxygenases or CYP450) & also by non microsomal enzymes (alcohol DH, xanthine oxidase, etc.)
      1. CYP450 Fam's: **12 CYP gene fam's** in humans based upon protein sequence homology; most drug metabolizing enzymes are in **CYP 1, 2 & 3 fam's**. **CYP3A4** very common to metabolism of many drugs; its presence in GI tract is responsible for poor oral availability of many drugs





      2. **CYP 450 enzyme induction**: drugs on repeated admin that "induce" more CYP P450 enzymes in liver ⇩causing (1) acceleration of substrate metabolism & (2) ⇩ in pharmacologic axn of co-admin'd drugs & inducer itself; ex: ***Drugs causing CYP 450 induction***: Rifampicin, Barbiturates, Phenytoin, Carbamazepine, GC's & Alcohol chronic admin 'RBCGAP'. Interferes w/drug efx of other drugs ⇩ enhanced liver metabolism (*ANSWER quiz & FINAL); CYP3A4 induced by *anticonvulsants & rifampin*. Majority of drugs (60%) are substrates of 3A4; CYP2C9 induced by *phenobarbitone, phenytoin & rifampin*. Warfarin & phenytoin – common substrates
      3. **CYP 450 enzyme inhibition**: some drug on repeated admin, inhibit CYP P450 in liver causing (1) inhibited substrate metabolism & (2) ⇧pharmacologic axn/adverse efx of co-admin'd drugs; ***CYP 450 inhibitors***: **Cimetidine, SSRIs, KTZ, Macrolides, Fluoroquinolones, HIV PI's & **Grape fruit juice; ex: Some drugs ***inhibit*** CYP450 enzymes that breakdown Warfarin ⇩means Warfarin gets less metabolized & exerting more efx (ie. Pt on Warfarin for DVT, gets drug to treat his new peptic ulcers, this drug inhibits those enzymes, Warfarin more effective ⇩ more side efx ⇩ pt comes back w/petechial hemorrhages all over body)
      4. Non-microsomal metabolism: by non-microsomal enzymes –can be inhibited but not induced by drugs
         1. Alcohol & aldehyde DH for alcohol
         2. Xanthine oxidase for allopurinol (for gout)
         3. Monoamine oxidase (MAO) for DA, 5-HT & NE
         4. Esterases for procaine; Certain drugs hydrolyzed by plasma esterases that rapidly cleave ester linkages after drug enters circulation; rapid inactivation allows for short duration axn of these meds like those in anesthesia – SCh, tetracaine, remifentanil metabolized by plasma hydrolysis
      5. **Hydroxylation**: phase I oxidation transformation catalyzed by CYP450 monooxygenase system; adding hydroxyl group reduces lipid solubility & facilitates excretion
   b) **Hydrolysis**: phase I rxn in which compound is cleaved by adding water (ex. esterase or amidase enzymes); usually precedes phase II conjugation metabolism
2. **Phase-II rxns (Synthetic/Conjugation): takes place in cytosol; Phase I metabolites couple w/ endogenous substance to yield drug conjugates (polar molecules that readily excreted &

often inactive); includes Glucuronidation (most drugs), acetylation***, sulfation, glutathione conjugation & methylation

a) **Glucuronidation:** most drugs
b) ***Acetylation: INH (for TB), Hydralazine (for severe HTN), Procanamide (for arrhythmias esp WPW);**
   1. **Fast** & **slow** acetylators: genetic variation in ind's ability to metabolize drugs which are acetylated. As a result of this, Fast acetylators may need more dose of drugs
   2. Slow acetylators (ANSWER on final for idiosyncratic rxn); may develop adverse efx of above drugs; Eg: **Drug-induced lupus (SLE like syndrome) caused by Hydralazine**
c) **Sulfation/Sulfate conjugation: Steroids;** biotransforms drug into more polar compounds – more water soluble & easily excreted
d) **Glutathione conjugation: Acetaminophen**
e) **Methylation – adrenaline, histamine**

Drug ▭ Phase I ▭ Phase II ▭ Excreted
Drug ▭ Phase II ▭ Excreted
Drug ▭ Phase II ▭ Phase I ▭ Excreted
Drug --------▭ Excreted

In any one of these manners, drugs can be metabolized & eliminated

Drug metabolism afx [plasma drug] & net efx of drugs; Other factors that'll affect [drug] & net efx of drugs are:

1. **P-glycoproteins (P-gp):** expressed in some bacteria & cancers as a MOR, expels drugs/foreign substances from intestinal mucosa into lumen & thus enhance their excretion; some drugs can inhibit P-gp ▭prevent other drug excretion, leading to their ▭[plasma] ▭ effect &/or toxic efx of drug; eliminates digoxin & cyclysporin; Ex's of P-gp inhibitors: ****Verapamil, Grapefruit juice**
   1. ****Verapamil** used to prevent dev't of resistance in tx of malaria; by inhibiting P-gp, prevents expulsion of chloroquine from protozoa
2. **Enterohepatic recirculation/cycling**: recycling of drug btwn liver & gut; drugs inactivated by *glucoronidation* in liver & these glucoronides delivered via bile into intestine where they're hydrolyzed releasing active drug. Active drug can be reabsorbed in this process – this cycle prolongs residence of active drug in body; Ex's: amphetamine, morphine, estradiol, OCP's; ▭results in Long plasma half life & prolonged drug effect
   1. Drugs like **antibiotics can interfere w/enterohepatic circulation & ↓activity of above mentioned drug. Eg: Lady on contraceptives, if she takes antibiotic, may become pregnant!!!!!!

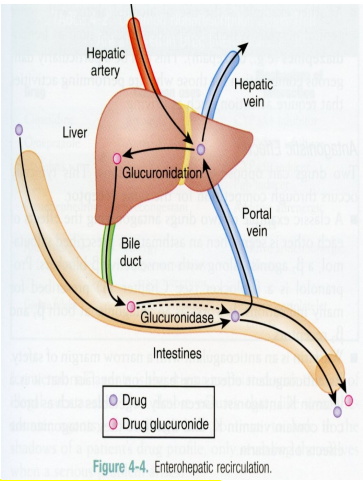
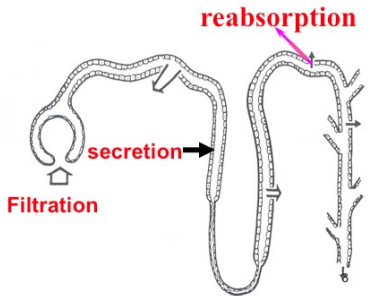


Figure 4-4. Enterohepatic recirculation.

L6 PK-6 Drug Excretion: filtration, secretion & reabsorption

- Drugs are excreted thru urine***, feces, exhaled air, saliva, sweat & breast milk
- Renal excretion; depends on 3 factors – glomerular filtration, tubular reabsorption, tubular secretion

1. **Glomerular filtration**: not affected by lipid solubility of drug but affected by its size (MW<65000), protein binding & renal BF; only protein unbound drug is filtered
2. **Tubular reabsorption**: depends on ionization & lipid solubility; thus pH of urine afx reabsorption; Lipid soluble, non ionized drugs are reabsorbed back; Lipid insoluble, ionized drugs can't be reabsorbed & excreted

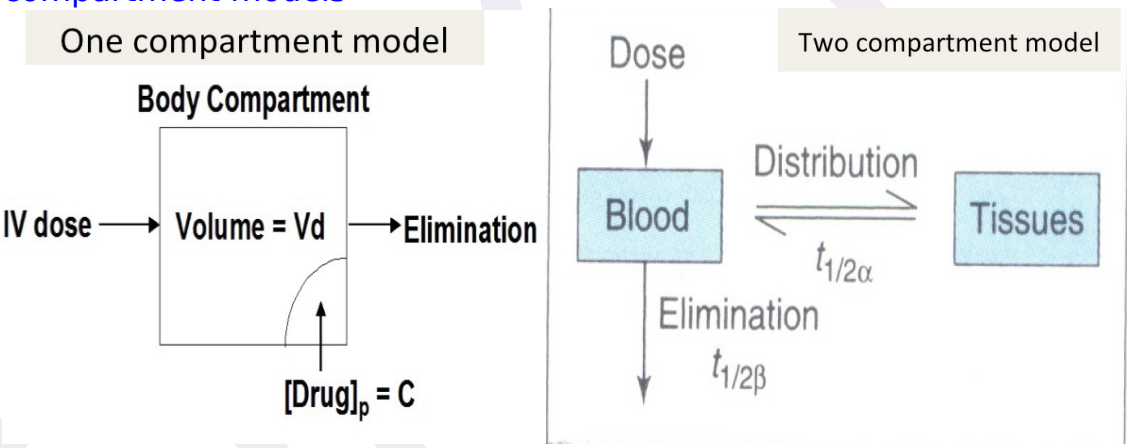


1. Manipulation of tubular reabsorption: know Absorption is better, if drug non-ionized (*Uncharged, lipid soluble, unpolarised)* ↓also know Excretion better, if drug more ionized (*Charged, Lipid insoluble, Polarised, Water soluble*)
2. In case of any drug poisoning, goal of tx is to enhance excretion of drug. This can be achieved only if more drug is **ionized.** How do you ionize the drug?
3. **Acidic** drugs are more ionized & not reabsorbed if urine is more basic. Thus, urine is alkalinized in case of poisoning of acidic drugs like Barbiturate & Aspirin
   ↓***Alkalinization of urine: by giving Sodium bicarbonate or Acetazolamide
4. Basic drugs more ionized & not reabsorbed if urine is more acidic. Thus, urine is acidified in case of poisoning of basic drugs like Morphine & Amphetamine, Propranolol
   ↓***Acidification of urine: by giving Ammonium chloride or Vit C or Cranberry juice

3. **Tubular secretion**: *mainly in PCT by carrier mediated transport; t*hese transport systems are bidirectional; it's independent of plasma protein binding & lipid solubility of drug
   1. **Penicillin, Probenecid**, Mtx, Furosemide/Frusemide & Diuretics imp drugs secreted in tubule
   2. **Probenecid:** competes w/penicillin in PCT ↑↑Penicillin secretion from tubules & thus penicillin plasma life prolonged ↓ prolonged axn ↑so use probenecid w/penicillin to ↓penicillin's duration of axn (b/c interfere w/penicillin metabolism) useful for GP bacteria; also competes w/**Uric acid** for its reabsorption in PCT – thus ↓reabsorption of uric acid & gets it excreted in urine ↓ useful in tx of Gout

L7 PK-7 Advanced Pharmacokinetics

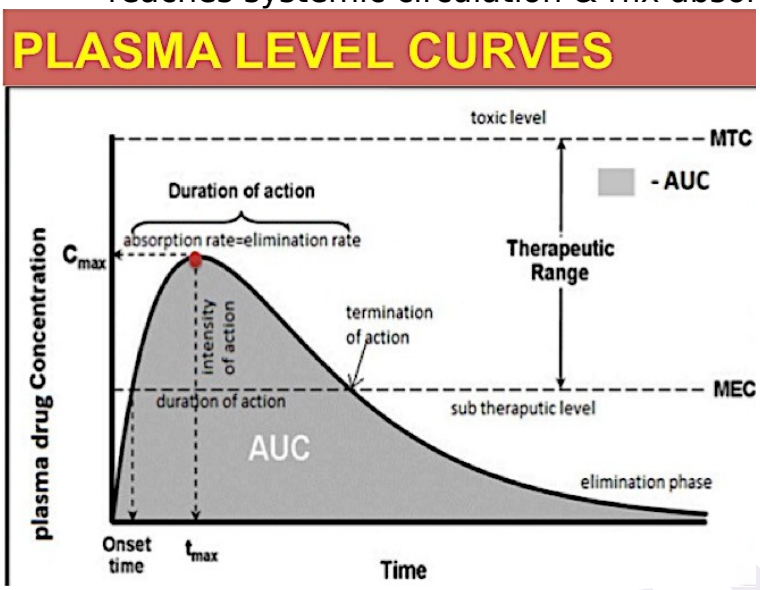
- Advanced pharmacokinetics: involve concepts & calculations rel'd to: plasma [ ] curve, concept 1 compartment & 2 compartment models, Bioavailability, Bioequivalence, AUC, volume of distribution (Vd), Plasma protein binding, 1st & 0 order kinetics of elimination, plasma ½ life, clearance, steady state [ ], loading & maintenance dose
- Brief review of compartment models - Pharmacokinetic models: body can be viewed as a space formed by 1 or more compartments; 2 most imp are single compartment & two compartment models

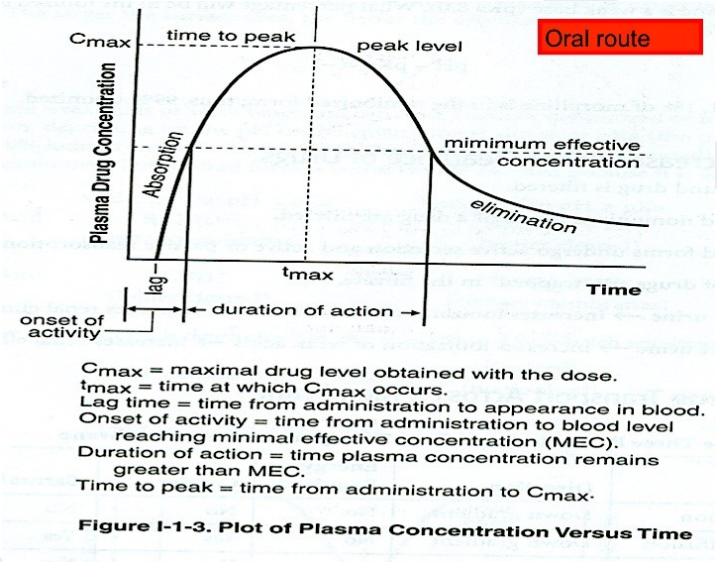


  - In simplest case body considered as **single compartment** where drug is uniformly distributed
  - In **2 compartmental model**, body considered to have 2 compartments – (1) Central (blood) & (2) peripheral compartment (tissues); drug distributes from central to peripheral & back
- **Plasma concentration vs time curve**: hypothesis in pharmacokinetics that rel'nship exists btwn pharmacologic (or toxic) effect of drug & [drug] in blood; in pharmacokinetics, most **parameters** can be calculated from [**plasma] vs time curve** of drug, determined by admin'ing dose of drug & then measuring drug [plasma] at diff times (fig below); suppose given dose of drug admin'd by oral route. Since in beginning absorption processes greater than distribution & elimination processes, [drug plasma] will ↓in time. Peak lvl reached when

absorption is = to elimination. Then elimination processes prevail & [drug plasma] will ¬¬; *Plasma lvl curves*:

- **Peak [ ] (Cmax):** max [drug] reached in plasma after admin of given dose; rel'd to dose & to extent of absorption, distribution & elimination of drug; when absorption rate = elimination rate
- **Time to [peak] (Tmax):** time of max [drug] in plasma; ~inversely proportional to drug absorption rate
- **AUC (Area under curve):** total area subtended to curve; rel'd to total amt of drug that reaches systemic circulation & rflx absorption, distribution & elimination factors of drug





- **TDM (Therapeutic Drug Monitoring):** measuring & monitoring [drug] in plasma at diff time intervals; special drugs w/special features: most work best over small range; below this range, not effective & pt begins having sx again; above it, drug has bad/toxic side efx you want to avoid; ex's of drugs that need TDM
  - Eg: **Phenytoin (antiseizure)** [plasma] should be 10-20 mg/L. [Plasma] >20: Toxicity (Nystagmus, diplopia) but [Plasma] <10: Failure of therapy
  - **Antiepileptics-** Phenobarbital, phenytoin, valproic acid, carbamazepine, ethosuximide,
  - **Cardiac drugs-** Digoxin, quinidine, procainamide
  - **Antibiotics-** Aminoglycosides
  - **Psychiatric drugs**- Lithium
- 2 types kinetics in elimination – 1st order & 0 order kinetics: *time course of drug movements* in body follows certain rules described by mathematical eq'ns; kinetic processes are '**order kinetics**' & 2 most imp are –
  - **1st order kinetics**: absorption, distribution & elimination of most drugs when constant fraction/%age of drug absorbed, distributed or **eliminated** per unit time; rate of elimination varies & directly proportional to [plasma] of drug & dose admin'd; most drugs following 1st-order kinetics will follow 0-order kinetics when given in toxic doses; drugs that follow 1st order kinetics, will have constant fixed Half life, VD & Clearance values.
  - **0 order kinetics** (saturation kinetics): kinetics of drug absorption, distribution & elimination when constant *amt* of drug absorbed, distributed or **eliminated** per unit time; **constant** rate of elimination **independent** of [plasma] of drug & dose admin'd; occurs when biological system is rate-limiting or saturable process. For ex, enzyme which metabolizes alcohol, alcohol DH, is saturable, max amt of alcohol that can be metabolized is ~9 g/hr; Alcohol only drug that follows always 0 order kinetics (on FINAL!); few other follow 0 order kinetics if given at high therapeutic doses. Eg: Aspirin & Phenytoin; drug which follows 0 order kinetics, will've variable & unpredictable Half life, VD & Clearance values

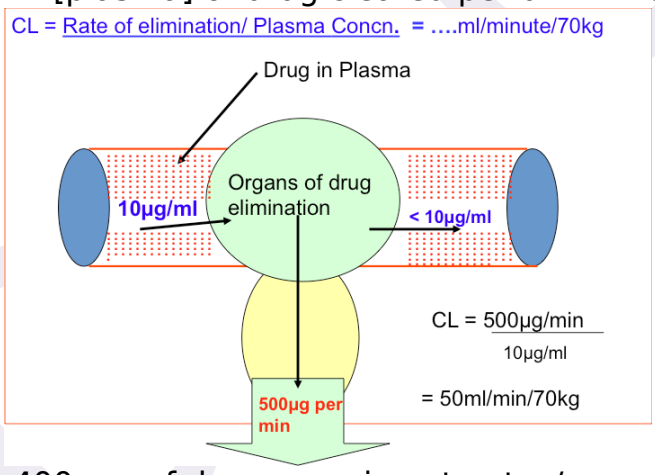
- Q: Pt who abused alcohol, has a dosage of 400 mg. After 2 hrs, his plasma [ ] was 250 mg. After another 2 hrs, it was 200 mg. What would his plasma [ ] after 8 hrs from ingestion? I put 100 mg. Because it's a constant amt you are losing, as alcohol follows 0 order kinetics – you subtract 50 mg again twice from the 4 hour period (because you can tell the half life was 50 mg per 2 hrs).

Drug follows 0 Zero order kinetics			
Time	**Plasma [ ]**	**Amt of drug eliminated in each hr**	**Fraction of drug eliminated in each hr**
O hour	200 mg	---	----
1 hour	175 mg	25 mg	12.5%
2 hour	150 mg	25 mg	14. 28%
3 hour	125 mg	25 mg	16.66 %
4 hour	100 mg	25 mg	20 %
5 hour	75 mg	25 mg	25 %

Drug follows 1st order kinetics			
Time	**Plasma [ ]**	Amount of drug eliminated in each hr	**Fraction of drug eliminated in each hr**
O hour	200 mg	---	------
1 hour	175 mg	25 mg	12.5 %
2 hour	153.13 mg	21. 87 mg	12.5 %
3 hour	134 mg	19.13 mg	12.5 %
4 hour	117.25 mg	16. 75	12.5 %
5 hour	103.45	14.65	12.5 %

Pharmacokinetic parameters:

- **Bioavailability:** gives quantitative measure of drug absorption
- **Volume of distribution**: gives quantitative measure of drug distribution
- **Clearance**: measure of drug elimination (Metabolism plus Excretion); rate of elimination in rel'n to [plasma] of drug; **volume of plasma (blood) cleared of drug, in unit time;** determines Maintenance Dose & Duration Of axn of drug
  - CL = Rate of elimination/ [Plasma]. = **……**ml/min/70kg
  - For drugs eliminated w/1st order kinetics, clearance is constant (i.e. same fraction of [plasma] of drug cleared per unit time).



INVERSE REL'N

If clearance , [plasma] & If clearance , [plasma]

If clearance doubles, [plasma] to its half, so double dose of drug to be given.

If clearance by half, [plasma] doubles, so reduce by half dose to be given

Qn. 400 mg of drug was given to pt w/normal liver & kidney twice a day. This drug is eliminated 50% thru liver & 50% thru kidney. Same drug, if it requires to be admin'd to a pt w/1 non func'ing kidney what dose of drug has to be admin'd to maintain same amt to kidney? This pt's other kidney & liver are normal.

A. 200mg twice a day
B. 400mg ~~once~~ a day
C. 600mg ~~once~~ a day
D. 800mg ~~once~~ a day
E. 300 mg twice a day

Dr. Chanz

- Drug that's excreted in urine w/no active renal secretion or reabsorption, will have clearance equal to GFR. **CL=GFR= 120ml/min/70kg**
- If drug is reabsorbed by tubule that drug will have clearance LESS than GFR
- If drug is secreted by tubule that drug will have clearance MORE than GFR
- If drug is protein bound: **CL = GFR x free fraction (ff)**
- Total clearance = to summation of $CL_R + CL_L + CL_{blood}$

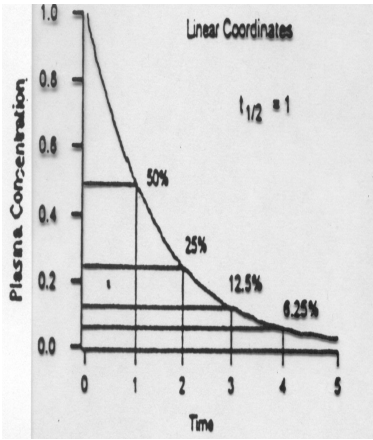
Q: A subject in whom renal clearance of inulin is 120 mL/min is given drug, clearance of which is found to be 18mL/min. If drug 40% plasma protein bound, what %age of filtered drug must be reabsorbed in renal tubules?

A. None
B.12.5
C. 25
D. 50
E. 75

We know CL=ff x GFR. Data says
- GFR=120ml/min
- ff=60/100=0.6 (unbound to protein)

- As per calculation CL= 0.6 x120= 72ml/min. But ques states CL= 18ml/min. So, some amt must've been reabsorbed in renal tubule. That amt is 72-18ml= 54ml. So 54 ml out of 72 ml is reabsorbed, i.e. nothing but **75%** out of 72ml is reabsorbed

➢ **Plasma Half-life (t1/2) (Elimination half life):** time required to ↓↓[plasma] of drug to its half of its original value. Denoted as "t1/2"; useful in estimating Dosing interval; half life constant for drugs which follow 1st order kinetics but varies for drugs that follow 0 order kinetics; 3 fundamental parameters of pharmacokinetics, F, Vd & CL independent 1 from another; half-life instead not independent parameter which is indicated by eq'n **$t_{1/2}$= 0.693 x Vd/CL**



- **5 half lives required for almost complete drug elimination**
  - **In 1 $t_{1/2}$ =50% drug eliminated**
  - **In 2 $t_{1/2}$ =75% drug eliminated**
  - **In 3 $t_{1/2}$ =87.5%Drug eliminated**
  - **In 4$t_{1/2}$ =93.75% drug eliminated**
  - **In 5 $t_{1/2}$ =~97% drug eliminated**
  - **5 half-life rule: drug is considered to be essentially eliminated from body after 5 half-lives**

Q: In pt weighing 70 kg, acetaminophen has Vd= 70 L & Cl= 0.7L/min. Elimination half-life of drug is

A. 35 min
B. 70 min
C. 140 min
D. 210 min
E. 280 min

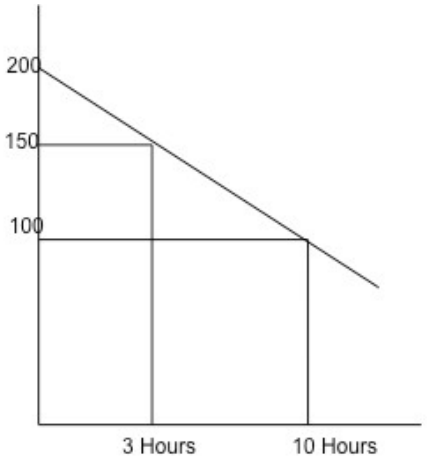
Data: Vd= 70L,Cl= 0.7L
t1/2= 0.7 x Vd/cl
t1/2=0.7 x 70L/ 0.7L=70
t1/2= 70minute

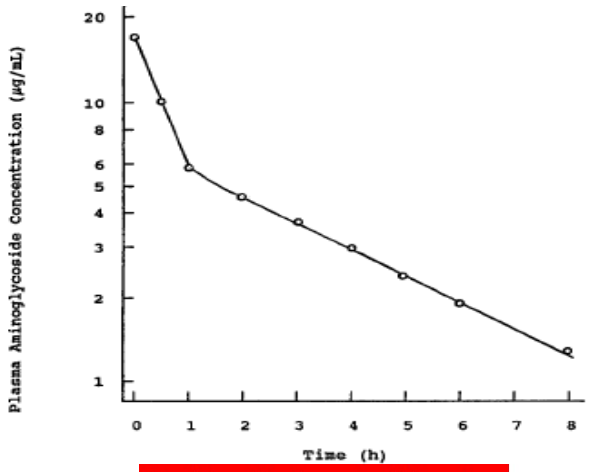
Qn: At 12 h after IV admin of a bolus dose, plasma level of a drug is 3 mg/L. If the Vd= 10 L & elimination half-life= 6 h, what was the dose admin'd?

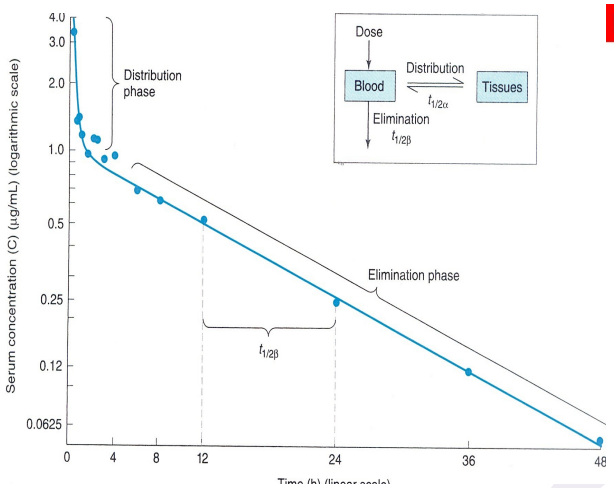
A. 120 mg
B. 180 mg
C. 240 mg
D. 480 mg
E. 600 mg

$Vd=D/C_0$, so Dose = Vd x C
Vd is 10L . C_0=?
3mg is not C_0. [ ] at 0 time has to be calculated
Data says that after 2 half life Plasma [ ] is 3mg.
Concentration at zero time is 12 mg/L
Dose=12x10=120mg

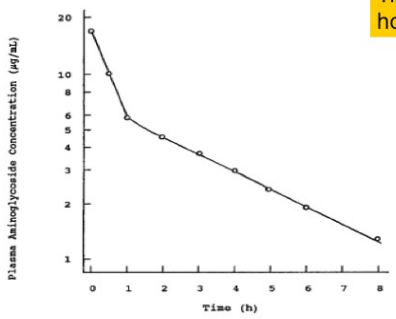
Concentration at zero time







Eg: Drug X given by IV route

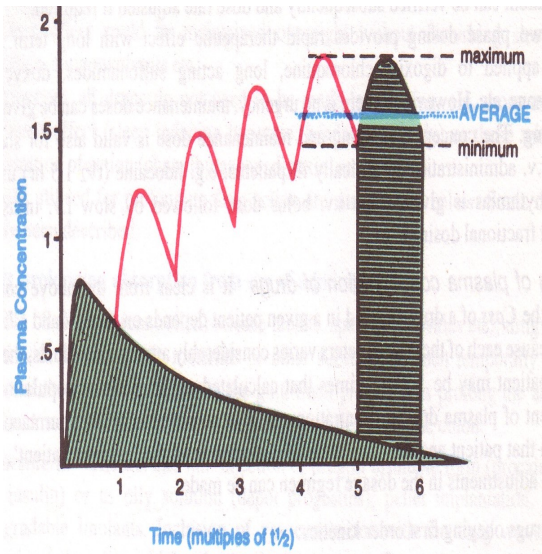


Time in hours	Plasma concn in micrograms
0.0	18.0
0.5	10.0
1.0	5.8
2.0	4.6
3.0	3.7
4.0	3.0
5.0	2.4
6.0	1.9
8.0	1.3

Note : Concentration at zero time in this example is 7 microgram not 18 microgram

half life of the drug is 3 hours

- **[Target]**: desired/optimal [plasma] required to have clinical efx of drug; achieved only by admin'ing appropriate dose of drug in regular intervals; usually achieve & maintain this [ ] by admin'ing Maintenance Dose at interval equal to half life of drug; eg: Phenytoin (antiepileptic) [plasma] should be 10–20 mg/L of plasma; If [plasma] >20, leads to toxicity (nystagmus, diplopia). If [plasma] is <10, leads to failure of therapy
- **C^{ss} (Steady state plasma [ ])**, Maintenance & loading dose – drugs admin'd in regular intervals of time, in way to maintain **steady state** of drug in body, ie, just enough drug given in each dose to replace drug eliminated since preceding dose
  - **Steady state** = state when ***Rate in = Rate out;*** when drugs admin'd repeatedly at regular intervals, observe oscillations w/large peaks & troughs of [drug's plasma]; takes while to get stable ("Steady") [plasma]. When [plasma] becomes almost stable = [steady state] = **Css of drug achieved when** avg [drug's plasma] is maintained w/out much fluctuation; when rate of drug admin becomes equal to rate of drug elimination.



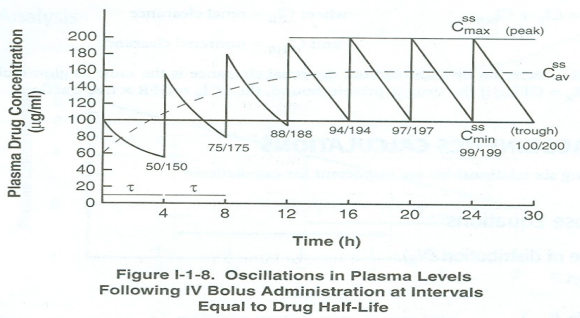
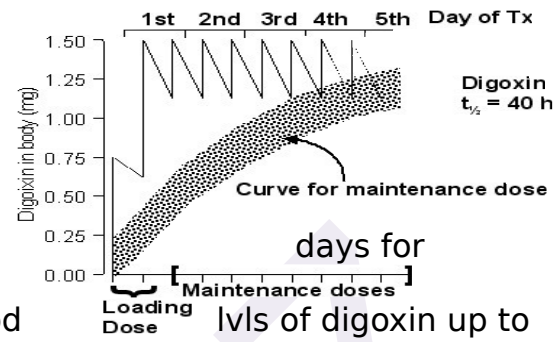


Figure I-1-8. Oscillations in Plasma Levels Following IV Bolus Administration at Intervals Equal to Drug Half-Life

- Generally 5 or + plasma half lives of a drug required to achieve nearly 100% of $C^{ss.}$
- One t1/2 is required to achieve 50% of C^{ss}
- Two t1/2 are required to achieve 75% of C^{ss}
- Three t1/2 are required to achieve 87% of C^{ss}
- Four t1/2 are required to achieve 93% of C^{ss}
- Five t1/2 are required to achieve 97 to 100% of $C^{ss;}$ Usually Target concentration is Css
- Digoxin treats CHF (life threatening condition) w/half-life of 40 hrs. According to five half-life rule, would take ~8 days for digoxin to achieve steady state lvls. Pt could deteriorate markedly in 8 days. So, how can we rapidly get pt's blood lvls of digoxin up to target [ ] (that is, [ ] at steady state)??? GIVE LOADING DOSE



- **Loading dose** = large dose given initially to get lvls up to [target] rapidly; ex: 2 large doses digoxin admin'd on 1st day; this process called ***digitalization***; large doses get blood digoxin up to target [ ] on 1st day. Thereafter, pt takes maintenance dose once each day that maintains digoxin lvl at steady state

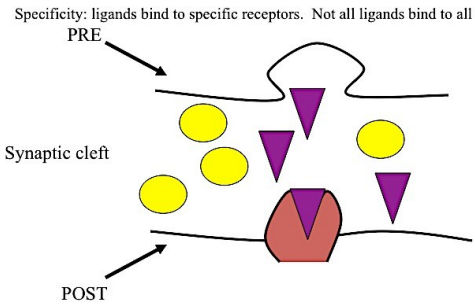
- Calculations using 5 IMP formulas ***
  - **t1/2 $= 0.693 \times V_d/CL$**
  - $V_d = D/C$
  - Loading Dose (LD) = D $= V_d \times C$
  - ~~Maintenance dose (MD) = CL x Css /F~~
  - ~~Rate of infusion K_o = Cl x C^{ss}~~
  - "C" should be considered as plasma [ ] of drug at zero time, unless specified
  - If various [plasma]'s of a drug at diff intervals given, ideal to consider **[ ] of drug at zero time**
  - Weight of adult is 70kg. Unless specified, Vd is 70kg. Unless specified, drug follows 1st order kinetics

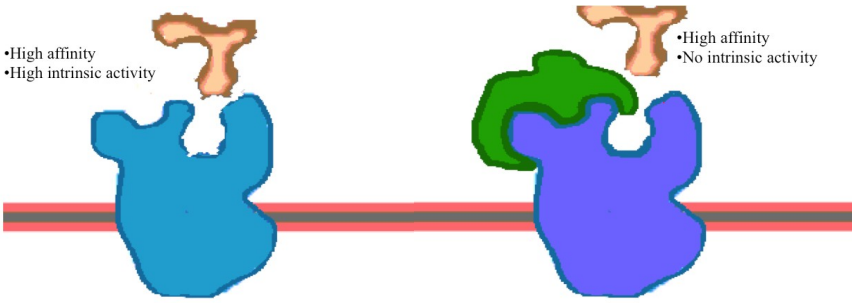
L9 Pharmacodynamics: mechanism of drug, diff receptors, 2nd msngrs & their rel'n w/observed drug efx, dose-resp rel'nship, combined efx of drugs, adverse efx, factors affecting drug efx (age, dis, genetics)

Types of drug axn: stimulate or inhibit physio'al process, replacement physio'al substance, or cytotoxic efx

Mechanisms of drug axn: thru receptors (most drugs), enzymes, physical axn (very few), chem'al axn (v. few)

- ***2.*** *Thru Enzymes*: either by *stimulating* or *inhibiting*, Drugs ↓ or ↑ rate of rxns; eg: Aspirin inhibits PG's synthesis by inhibiting COX
- ***3.*** *Physical axn*: radioactivity: ^{131}**I;** Osmotic activity: Mannitol
- ***4.*** *Chem'al axn*: like antacids (neutralize gastric acid), or chelating agents (inactivate toxic metals)
- ***1.*** *Receptor*: binding site for drug or chem'al agent; macromolecular component of cell situated on cell surface or inside cell; majority of drugs act by binding to receptors; have specificity: ligands (drugs) bind to specific receptors. Not all ligands bind to all receptors; drugs binding to receptors will have either both *Affinity* & *Intrinsic Activity* or just *Affinity* alone w/no *Intrinsic Activity*

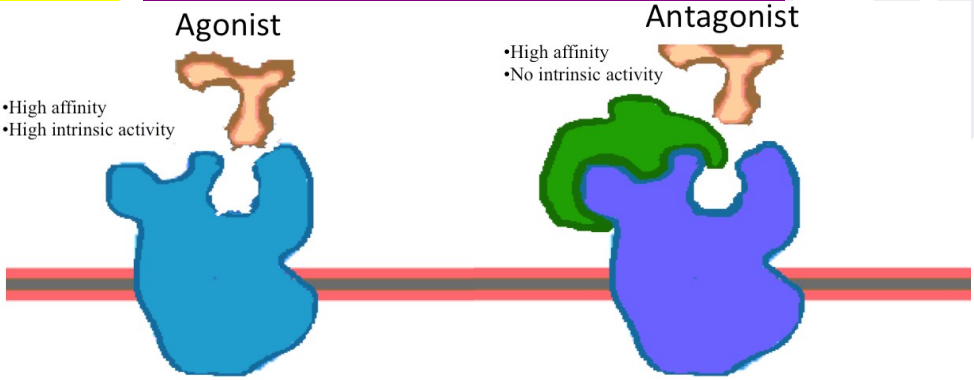


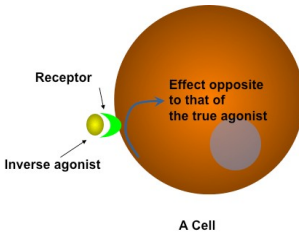


- **Affinity:** ability of drug to combine w/receptors
- **Intrinsic activity:** drug's ability to activate & induce conformational change in receptor after occupying receptor

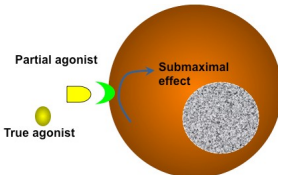
Based on Affinity & Intrinsic activity, 4 drug types: *Agonists*, *Antagonists*, *Partial agonists* & *Inverse agonists*

1. **Agonist**: Both *Affinity* & maximal *Intrinsic activity;* drugs that bind & interact w/receptor, so initiate chemical rxn inside cell & produces effect; ie. **ACh is agonist at Nicotinic receptors in skeletal m**
2. **Antagonist**: Only *Affinity* but no *Intrinsic activity;* drug that binds to receptor but can not activate it; blocks effect of agonist for that receptor; ie. ***d-Tubocurarine: Ach antagonist, at** Nicotinic receptors**; prevents Ach mediated m contraction skeletal m relaxation; toxicity of it tx'd by neostigmine*** (Nm)**

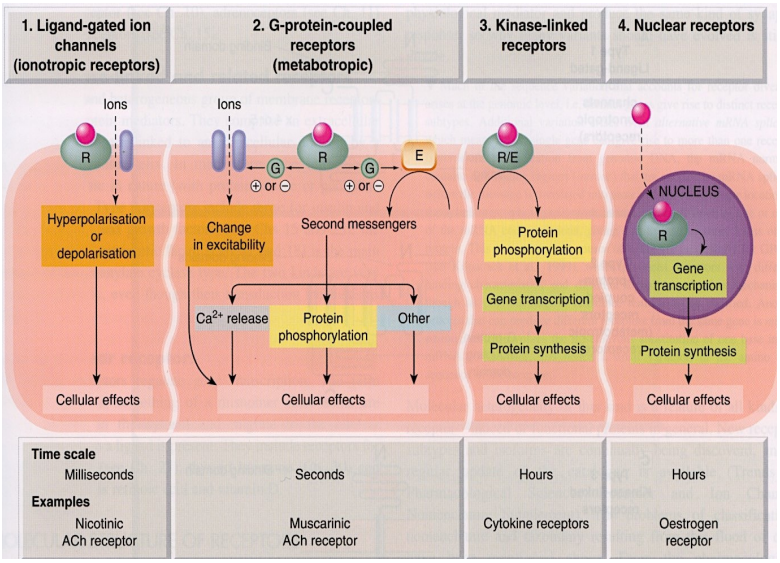




3. **Inverse agonist**: drug that binds to receptor & produces OPP efx of agonist; have ***Affinity*** & -ve ***Intrinsic activity;*** ie. Bicuculline at GABA receptors inhibits/GABA!!!
4. **Partial agonist**: have *Affinity* but sub maximal *Intrinsic activity;* when given alone partial agonist activates receptor to produce efx but w/less resp than full agonist; when given along prior to w/agonist, partial agonist blocks agonist axn; ie. Buprenorphine given b4 morphine makes morphine less effective due to its less efficacy at mu receptors (partial activity)



- **Axn effect sequence**: Drug axn & efx not synonymous; series of intermediate steps btwn drug axn & drug effect; known as Signal transduction or Trans memb Signaling
- **Drug axn**: initial combo of drug w/receptor resulting in conformational changes in cell
- **Drug effect:** ultimate change in biological func as consequence of drug axn
- **Trans memb signalling:** transduce many diff signals, most accomplished by small # of diff molecular mechanisms that include **receptors** on cell surface & w/in cell, & **enzymes** & other components that generate, amplify, coordinate & terminate post receptor signalling by chem'al **2nd msngrs** in cytoplasm; depending upon diff transducer mechanisms, drug receptors can be categorised into 4 types –

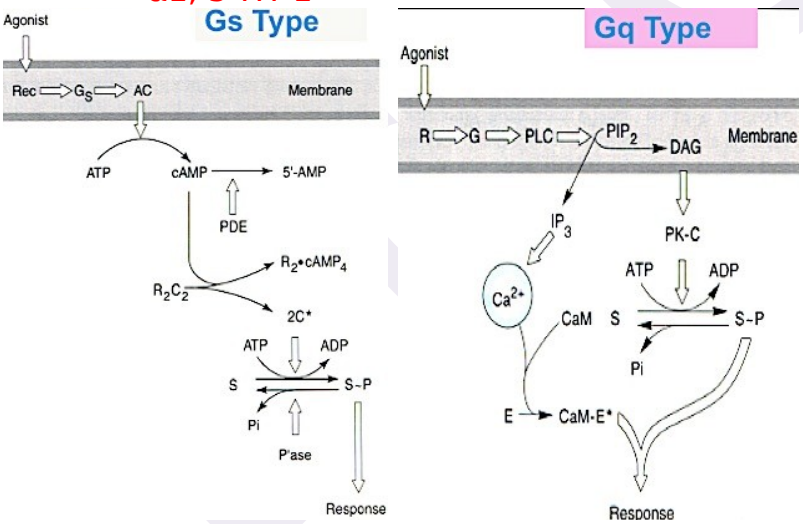


TYPE A = IONOTROPIC receptors
TYPE B = METABOTROPIC receptors

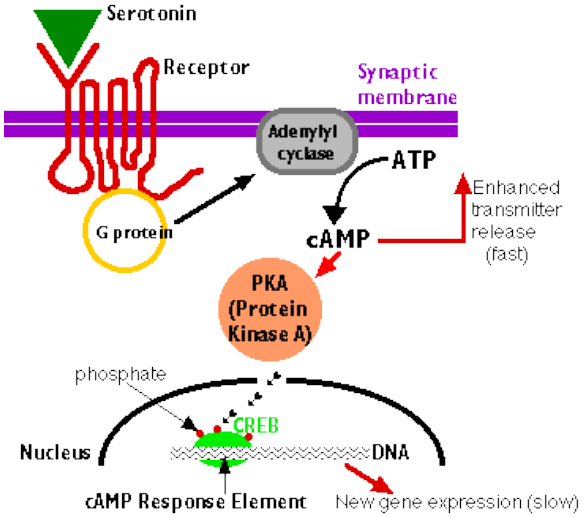
- **G-Protein coupled Receptors (METABOTROPIC):** cell memb receptors linked to effector mechanisms thru G-proteins; includes adenylyl cyclase, phospholipase C, Effector mechanisms of resp in secs; eg: channel reg; onset receptors, histamine adrenergic receptors; *diff types of G proteins:* **Gi, Gq, & Go**

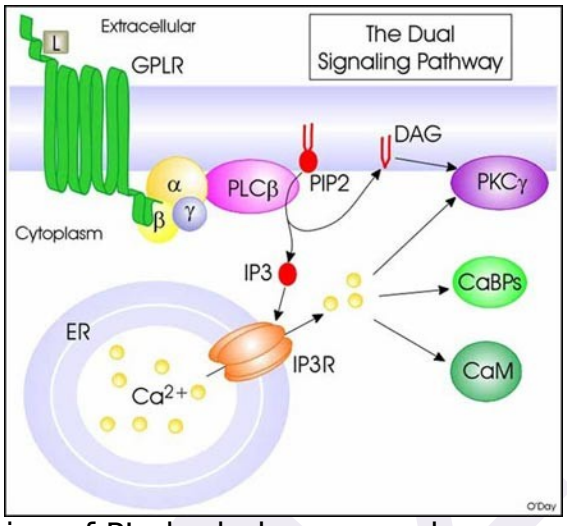
Name	Type	Effector enzyme	2nd msngr
M_1 M_3 α_1 5-HT1	Gq	↑PLC	↑IP3 & DAG
M_2 α_2	Gi	1. Inhibits adenylyl cyclase 2. ↑K^+ conductance	↓cAMP
β_1 β_2 β_3 D_1 H2 5-HT4	Gs	↑adenylyl cyclase	↑cAMP
N_M N_M	Ion Channel		

  - **↑Gs** ↑adenylyl cyclase & ↑2nd msngr cAMP & open Ca^{2+} channels; receptors: **β_1, β_2 D_1, H_2, 5-HT_4**
  - Activating Gi inhibits adenylyl cyclase ↓cAMP; receptors: α2, M2 thus drugs rel'd to these receptors
  - Activating **Gq** activates phospholipase C ↑2nd msngr IP-3 & DAG; receptors: M1, M2, α1, 5-HT-1



2 major enzymes or effector pathways in GPC receptors:
(1) Adenyl cyclase: cAMP pathway: activation of AC results in IC ↑↑cAMP func's exclusively thru cAMP dependent PK_A phosphorylates & alters func's of many enzymes, ion channels, carriers & structural proteins



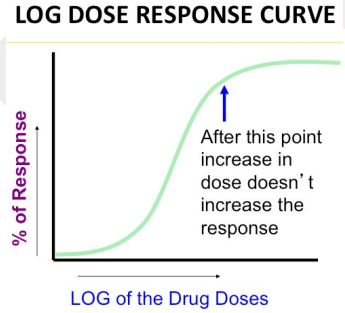


- **(2) Phospholipase C: IP_3-DAG pathway**: activation of PL_C hydrolyses memb phospholipid phosphatidyl inositol 4,5-biphosphate (PIP_2) ⎵ generates 2nd msngrs IP_3 & DAG ⎵ IP_3 mobilizes Ca^{2+} from IC depots ⎵ Cytosolic Ca^{2+} in turn acts thru calmodulin-CaM (Ca^{2+}-calmodulin complex)

- **Ion-Channel receptor (IONOTROPIC)**: cell surface has selective ion channel like Na, K, Ca, or Cl; onset of axn thru these types of receptors is fastest – millisecs; ex: Nicotinic cholinergic receptors, GABA-A & NMDA receptors
- **IC (Intracellular) receptors**: takes days to produce its axns; ex's: Steroids, sex hormones, thyroxine & Vit–D, & A use IC receptors
- **Enzyme (Kinase) linked receptors**: cell-surface receptors w/IC domains associated w/enzyme. In some cases, IC domain of receptor itself is enzyme or enzyme-linked receptor has IC domain that interacts directly w/enzyme; have large EC & IC domains, but memb-spanning region consists of single α-helical region of peptide strand. When ligand binds EC domain, signal transferred thru memb & enzyme ⎵ sets off chain of events in cell leading to resp; ex: tyrosine kinase receptor – transfers phosphate groups to tyrosine molecules; signaling molecules bind to EC domain of 2 nearby tyrosine kinase receptors, which then dimerize ⎵ Phosphates added to tyrosine residues on IC domain of receptors ⎵ transmit signal to next msngr w/in cytoplasm; onset of resp in mins
  - Tyrosine kinase linked (ANSWER): e.g. Insulin (FINAL EXAM)
  - Janus Kinase (JAK) fam e.g. GH, Interferon

⎵ Summary: drug axn & effect diff; imp 2nd msngrs are Ca^{2+}, cAMP, IP3 & DAG; 4 types drug receptors – G protein coupled receptors common targets; G protein divided into Gs (β 1,2 receptors), Gi (α-2 & M-2) & Gq (α-1 & M3)

➢ **Log DRC**: adv that you can plot as many doses as possible – QUES ON EXAM!!! Sigmoid shaped curve; (Normal DRC is rectangular hyperbola); resp proportional to log dose; wider range of drug doses can be easily shown on graph



➢ **DRC (Dose-resp curve)**: rectangular hyperbola;
- Position of DRC on X-axis indicating potency of drug PP
- Height of DRC on X-axis indicating efficacy of drug HE
- Slope of DRC indicating safety of dose range of a drug SS
  - **Steep DRC**: moderate ⎵ in dose leads to more ⎵ in resp; dose **needs** individualization for diff pt's; Unwanted & Uncommon

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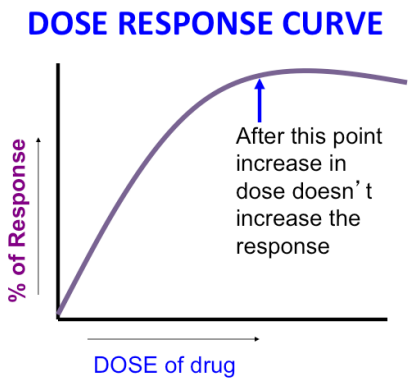
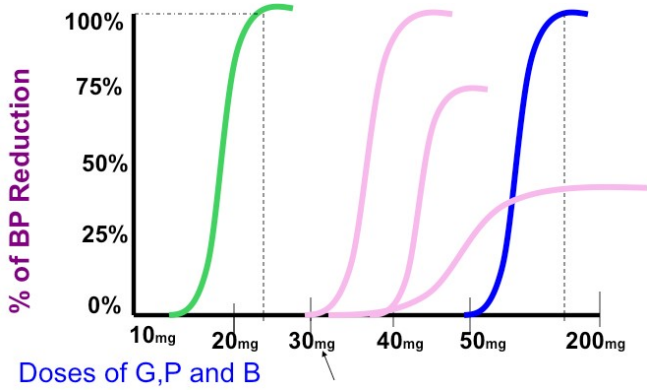
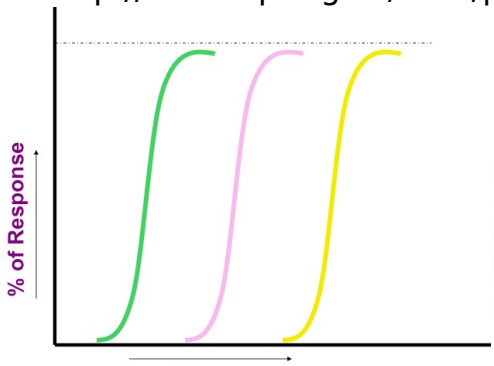
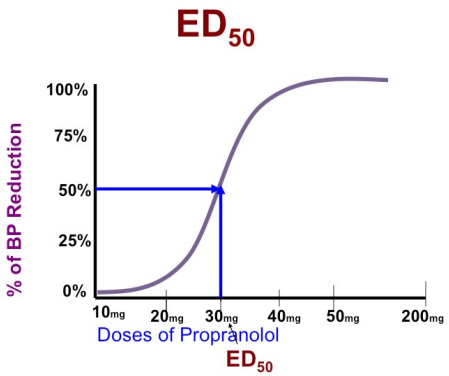
- **<u>Flat DRC</u>**: Moderate ⏚dose leads to little ⏚resp; dose ***<u>needs</u>*** ***<u>no</u>*** individualization for diff pt's; desired & Common

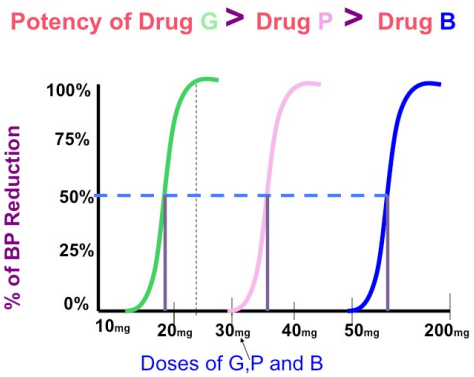




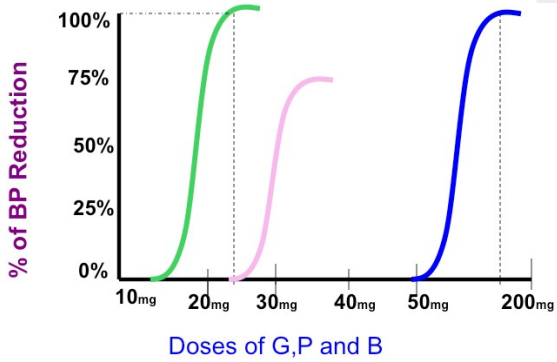
- **Drug Potency (**ED_{50}): drug amt/dose needed to produce resp aka 50%/half max resp/effect; indexed by pos of curve on dose axis; more left DRC = more potent drug; Lower ED_{50} = more potent drug is; also known as EC_{50} if you consider [plasma] instead of dose admin'd http://www.icp.org.nz/html/pharmacodynamics.htm

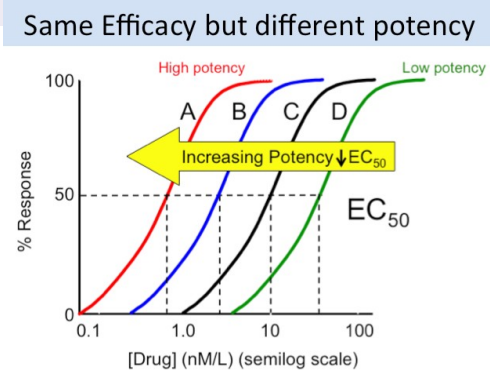


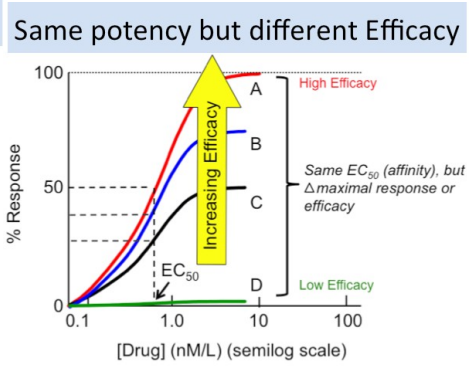


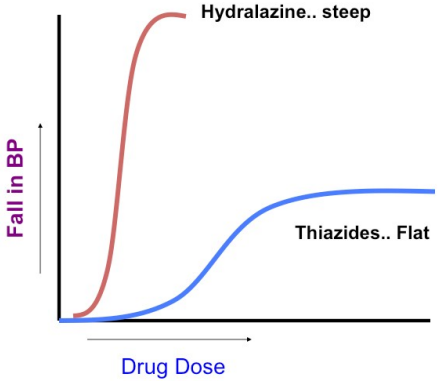


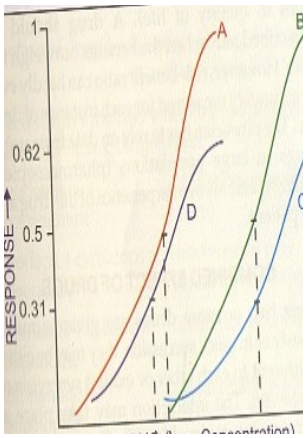
- Efficacy: Height of curve on x-axis; max resp of drug; indexed by UL of drug resp curve; Taller DRC = more efficacious drug is











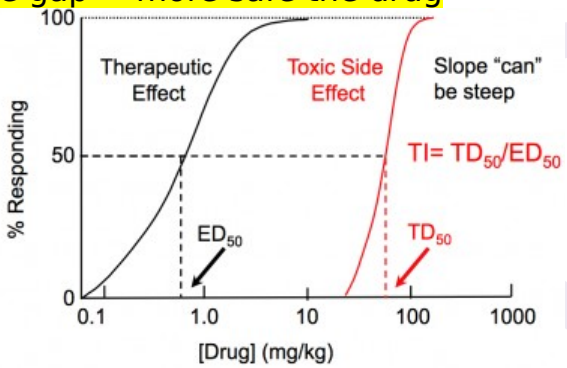
- Drug **B** less potent but equally efficacious as drug **A**
- Drug **C** less potent & less efficacious than drug **A**
- Drug **C** equally potent & less efficacious than drug **B**
- Drug D more potent than **A**, **B**, **C** & less efficacious

Q: 55-yr-old woman w/CHF is to be tx'd w/diuretic drug. Drugs X & Y have same mechanism of diuretic axn. Drug X in a dose of 5 mg produces same magnitude of diuresis as 500 mg of drug Y. This suggests that

- Drug Y is less efficacious than drug X
- Drug X is about 100 times more potent than drug Y
- Toxicity of drug X is less than that of drug Y
- Drug X is a safer drug than drug Y
- Drug X will have a shorter duration of axn vs drug Y b/c less of drug X is present for a given effect

Safety of drug

- Safety of drug assessed by measuring "**Therapeutic index**" (TI) in animal exp's;
  TI = Median lethal Dose (LD_{50}) / Median Effective dose (ED_{50})
- Since LD_{50} can't be calculated in humans, TI cannot be measured. Thus in humans, to assess safety of drugs, instead of measuring TI, we measure "safety margin" or "therapeutic window" of drug.
- **Safety/Therapeutic window:** dosage range btwn min effective therapeutic [ ] or dose, & min toxic [ ] or dose; ie. theophylline has avg min plasma [8 mg/L] & toxic efx at 18 mg/L. So, therapeutic window is 8 – 18 mg/L; Drugs w/low TI or narrow therapeutic window or narrow safety margin should be used w/caution & needs periodic monitoring (less safe) ie. warfarin, digoxin, theophylline
- DRCs for 2 diff efx of given drug will be diff. Gap btwn therapeutic effect DRC & adverse effect DRC defines ***safety margin*** Wider the gap = more safe the drug



Summary

- Pos, height & slope of DRC on X-axis indicates potency, efficacy & dose range of drug
- More left the DRC, more potent drug
- Lower ED_{50} = more potent drug is
- Safety of drug assessed by measuring Therapeutic index (TI) in animal exp's, **calculated by knowing** LD_{50} & ED_{50}. In

Qn. Drug A & B are analgesic drugs acting on same receptor. In lab animals, drug A has ED50 of 2 & therapeutic index of 10. Drug B has an ED50 of 5 mg/Kg and a therapeutic index of 20. Which of the following statements correctly defines the TD50 of drug A and drug B, in mg/Kg?
A) Drug A 30 ; drug B 50
B) Drug A 20 ; drug B 100 10 = x/2; 20 = x/5
C) Drug A 10 ; drug B 20
D) Drug A 20 ; drug B 50
E) Drug A 30 ; drug B 100

Qn. 2. 5 new antihypertensive drugs have been tested on hypertensive pt's. Each drug has unique overdose toxicity. The results are reported below.

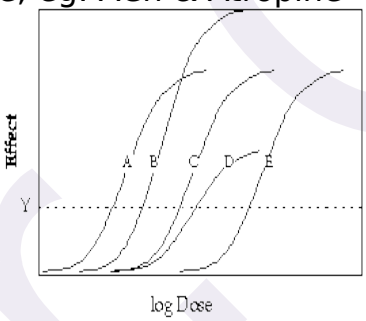
Drug	Median effective dose	TD_1 / ED_{99}
A	3 mg	2.9
B	10 mg	3.4
C	24 mg	2.2
D	35 mg	4.5
E	50 mg	3.1

TD_1 = toxic dose in 1% of patients
ED_{99} = effective dose in99% of patients

- **Which of the following drugs has the highest risk of overdose toxicity?**
- A) Drug A B) Drug B C) Drug C D) Drug D E) Drug E

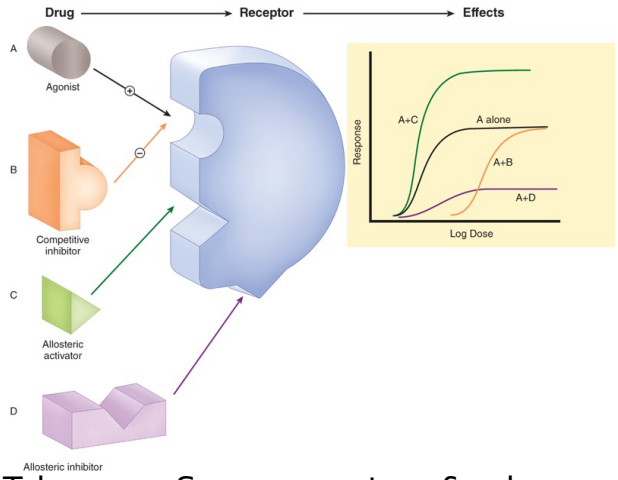
➢ Combined effect of drugs: when 2 drugs given together or in quick succession, 3 things can happen:

1. Nothing (indiff to each other)
2. Axn of 1 drug facilitated by other (synergism); *2 types of synergism* –
   a. **Additive:** efx of drugs A + B= Efx of Drug A + Efx of Drug B; Drug effect will simply add up; Eg: Paracetamol + Ibuprofen
   b. **Supraadditive (potentiation):** efx of combo greater than ind efx of components; ex. ACh + Neostigmine; OR Levodopa + carbidopa
3. Axn of 1 drug may ↓or inhibit axn of other drug (antagonism); 4 types –
   a. **Physical antagonism:** activated Charcoal used in poisoning, **absorbs** poison material, later get excreted
   b. **Chem'al antagonism (answer)**: Chelating agents used in metal poisoning, forms insoluble complexes w/metals that can be excreted; Antacids used in acid peptic diseases neutralize gastric acid; Protamine in heparin overdose
   c. ***Func'al/Physio'al antagonism***: 2 drugs act on diff receptors & produce opp efx on same physio'al system
      i. Eg. Epinephrine (Adrenaline) & Histamine axns on blood vessel & bronchial SM
      ii. Eg. Steroids & insulin axn on blood sugar lvl
      iii. Epinephrine ↓α 1 = vasoconstriction; ↓B2 = vasodilation?
      iv. Histamine ↓Vasodilation; ↓bronchoconstriction
   d. **Receptor mediated antagonism**:
      i. **Competitive antagonism**: MC type of antagonism; antagonist reversibly bind to receptors at same binding site (active site) as agonist; Competitive antagonists affect "amt of agonist" necessary to achieve maximal resp but do not affect magnitude of that maximal resp; intensity of resp depends both on antagonist & agonist [ ]; usually w/chem'al resemblance w/agonist (usually); parallel rightward shift of DRC w/no alteration of maximal resp. So, ↓potency but not efficacy of agonist; effect is surmountable; eg: ACh & Atropine



      ii. **Noncompetitive antagonism;** in both, non-competitive antagonists ↓magnitude of max resp that can't be attained by any amt of agonist. So, effect unsurmountable. No chem'al resemblance w/agonist; resp intensity depends on antagonist [ ]; flattening of DRC: depression of maximal resp of agonist dose-resp curves; 2 types –
         1. ****Irreversible noncompetitive antagonism**: antagonist irreversibly binds to active site of same receptor; Ex: Phenoxybenzamine, would be line D
         2. **Reversible noncompetitive antagonism**: antagonist reversibly binds to allosteric site of receptor. Eg: Bicuculline binds to allosteric site of Diazepam, also line D

↓ Summary: Synergism can be additive or Supraadditive. ***In competitive antagonism***, antagonist reversibly bind to receptors at same binding site (active site) as agonist. Parallel rightward shift of DRC. Effect is surmountable. Resp depends on [ ] of both agonist & antagonist. ***In Non-competitive antagonism***, antagonist irreversibly binds to receptors at same binding site or reversibly bind at allosteric site. DRC will become flat. Effect not surmountable. Resp depends on [ ] of *antagonist only*.

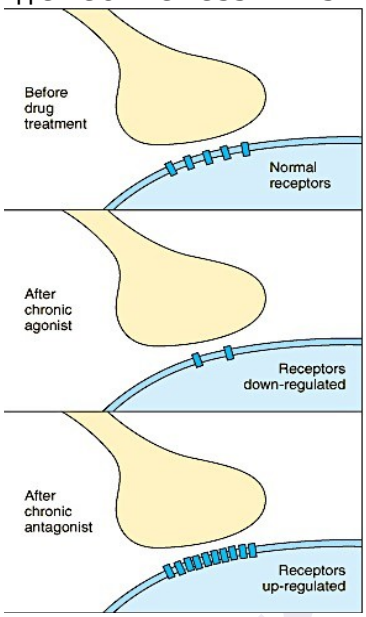


Know this graph for quiz

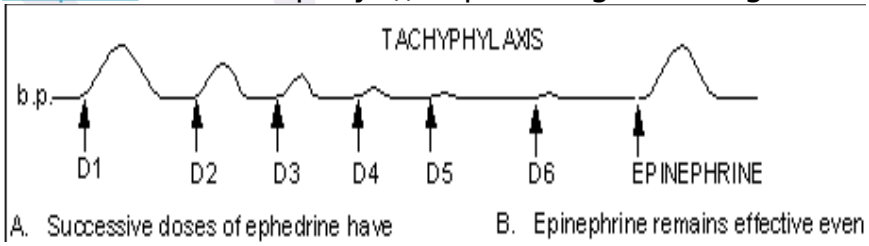
Answer: Agonist, Competitive Antagonist, Non-competitive antagonist

Tolerance, Spare receptors & adverse efx:

- **Upreg:** ↓in # of receptors on surface of target cells, making cells more sensitive to hormone or another agent; seen w/use of antagonists Eg: Prolonged use of propranolol (β_1 antagonist) can ↓ # of β_1 receptors
- **Down reg:** ↑in # of receptors; seen w/prolonged & frequent use of short acting agonists; ex: on prolonged use of short acting β_2 receptor agonists ↑# of β_2 receptors & results in ↑effectiveness in Asthma



- **Tolerance**: gradual ↑in resp to drugs & requirement of higher dose to produce given resp; occurs over period of time. E.g. tolerance to sedative-hypnotics; causes of tolerance –
  - Pharmacokinetic reasons: chronic use leads to enhanced clearance-less effective [ ]
  - Pharmacodynamics reasons: ↑# &/or affinity of receptors to drugs (down reg)
- **Tachyphylaxis**: rapid desensitization to drug produced by inoculation w/series of small frequent doses; rapidly ↑resp to drug following its initial admin; E.g. ephedrine, tyramine



- **Spare receptors**: sometimes maximal resp can be elicited at [ ] that doesn't require occupancy of all receptors in cell or tissue; in this case, system may be said to possess spare receptors (receptor pool of system is larger than # needed to evoke a full resp); ↓sensitivity to a drug.

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- **K_D** = [ ] of agonist at which 50% of receptors occupied; [agonist/drug] needed to bind 50% receptors sites; measure of affinity of drug molecule; Smaller K_d = greater affinity of drug for its receptor; if # of receptors = many fold (spare receptors) THEN: much lower [ ] of agonist sufficient to create 50% of maximal resp (EC_{50})
- Occupation of spare receptors is determined by comparing EC_{50} w/K_d
- **If EC_{50} is less than K_d, spare receptors are said to exist**
- ED_{50} = dose of agonist required to get 50% of maximal effect
- EC_{50} = [ ] of agonist required to get 50% of maximal effect
- total # of receptors bound in system is termed as B_{max}

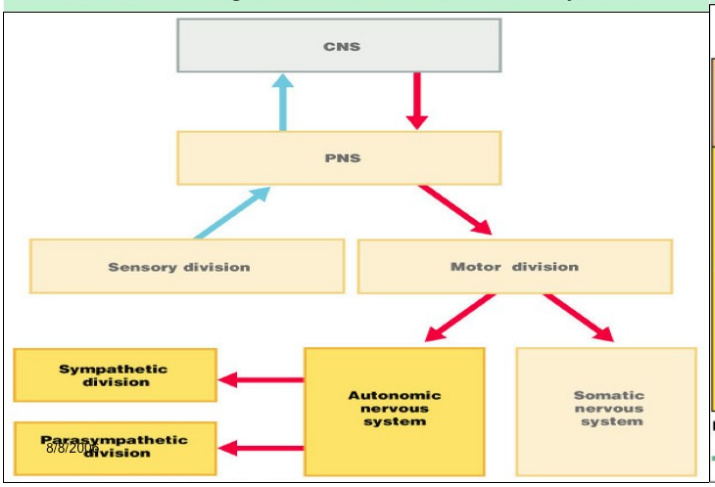
- Factors affecting drug axn: Body Size & Weight, Age (drug metabolizing enzymes very poor in extremes of ages), genetics, Pre existing health conditions (RF, HF, hepatic failure), Route of admin, Co-admin of other drugs, Diet & Placebo effect
- Adverse efx of drugs: Overdose toxicity, Side efx, Fetal toxicity, Drug abuse & dependence, Idiosyncrasy, Drug allergy, Teratogenesis, Mutagenesis & Carcinogenesis
- **Idiosyncrasy**: genetically based, abnormal resp to a drug; most often, they're dose-dependent & linked to genetic polymorphism of drug metabolizing enzymes; stop drug & treat w/antagonist
  - Eg: Prolonged apnea seen w/Succinylcholine due to Plasma cholinesterase def (BLOCK 2)
  - Eg: Malignant hyperthermia seen w/general anesthetics; AD mutation
- **Drug allergy**: immunologically mediated, adverse drug effect; only after previous sensitizing contact w/same drug or w/another drug closely rel'd in chem'al structure (latter case named ***crossed sensitization); stop*** drug & treat w/antiallergic drugs; drug must have immunogenic properties; only molecules w/MW greater than ~6000 can be immunogenic; 4 types of allergic rxns:
  - Type 1: Immediate HS rxns, IgE mediated
  - Type 2: Antibody-dependent cytotoxicity, IgG or IgM mediated
  - Type III: Immune complex-mediated rxn, IgG or IgM & IgE are involved
  - Type IV: Delayed or cell-mediated rxn, T cell mediated.
- **Teratogenicity**: drugs ability to cause abnormal dev't of fetus or appearance of malformations; morphological & func'al damage. Both generally irreversible; afx during these stages of pregnancy: stage of organogenesis (Day 17 to 80) & stage of histogenesis (Day 80 to end); mechanism: drug (or more often highly reactive intermediate such as epoxide) forms covalent bindings w/func'ally relevant macromolecules (DNA, RNA, enzymes, etc.), so provoking alterations in cellular growth & differentiation
  - **FAS** (Fetal alcohol syndrome): consists of CNS dysfunc's (such as low IQ & microencephaly), slowness in growth, cluster of facial abnormalities, & malformations
  - Teratogenic drugs: Thalidomide, Anticancer drugs, Sex hormones & antagonists, Antithyroid agents, Iodinated compounds, Anticonvulsants, Warfarin, Ethanol (high doses) & Many antibiotics

Summary: Many factors afx drugs axn. Receptors may be down reg'd OR up reg'd in some conditions. Smaller K_d = greater affinity of drug for its receptor. **If EC_{50} < K_d, spare receptors are said to exist**. Tolerance & tachyphylaxis seen w/some drugs. Idiosyncrasy. 4 types of drug allergic rxns. Cross sensitization. Some drugs teratogenic

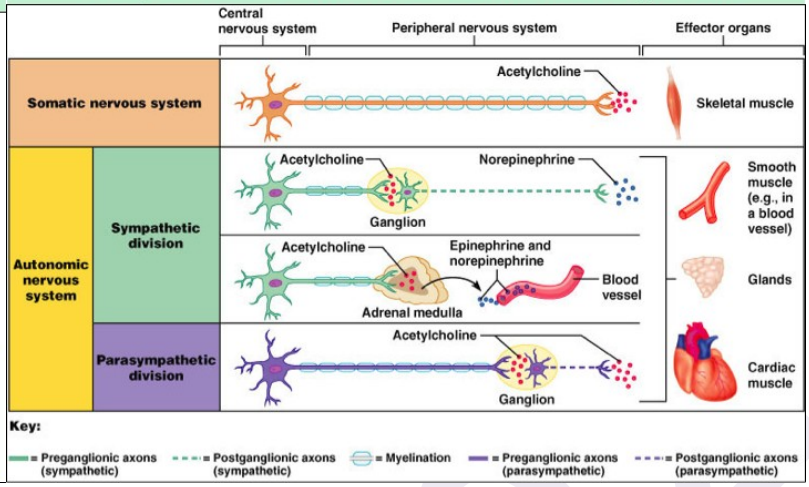
L9 ANS Intro

- **Somatic division**: concerned w/consciously controlled func's: movement, respiration & posture
- **ANS (Autonomic NS)**: largely autonomous (independent) in that its activities are not under direct conscious control; concerned primarily w/visceral func's necessary for life: CO; BF to organs, digestion

Structural Organization of the Nervous System

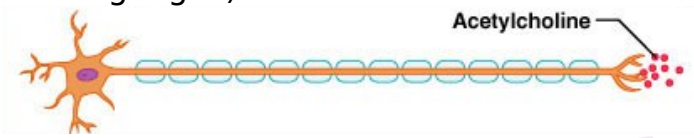


Comparison of Somatic and Autonomic Systems

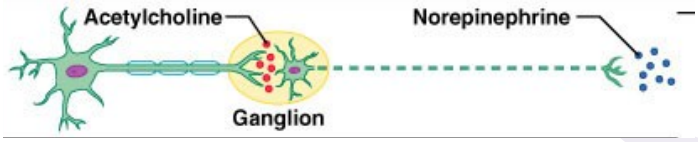


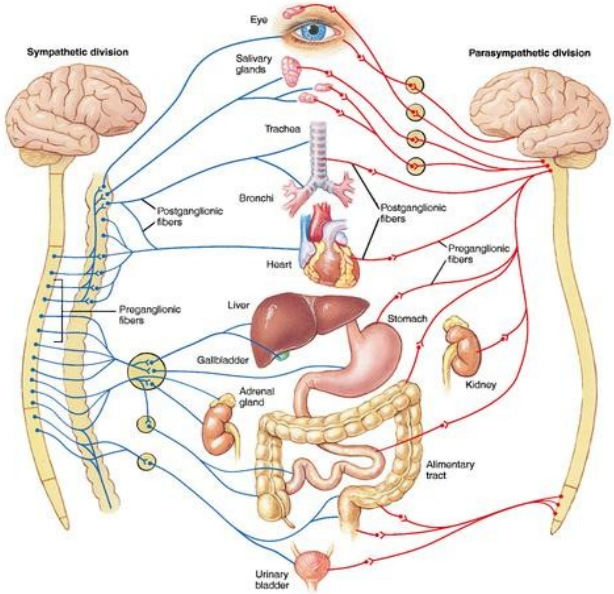
3 major differences in ANS & SNS:

1. Effectors:
   a. Effectors of somatic NS are skeletal m's
   b. Effectors of ANS are cardiac m, SM (ex. In blood vessel) & glands
2. Efferent pathways:
   a. Myelinated thick axons of somatic motor neurons extend from CNS to effector (lacks ganglia)



   b. Pathways in ANS are 2-neuron chain: preganglionic (1st) neuron has thin myelinated axon. Ganglionic (2nd) unmyelinated neuron extends to effector organ via postganglionic axon





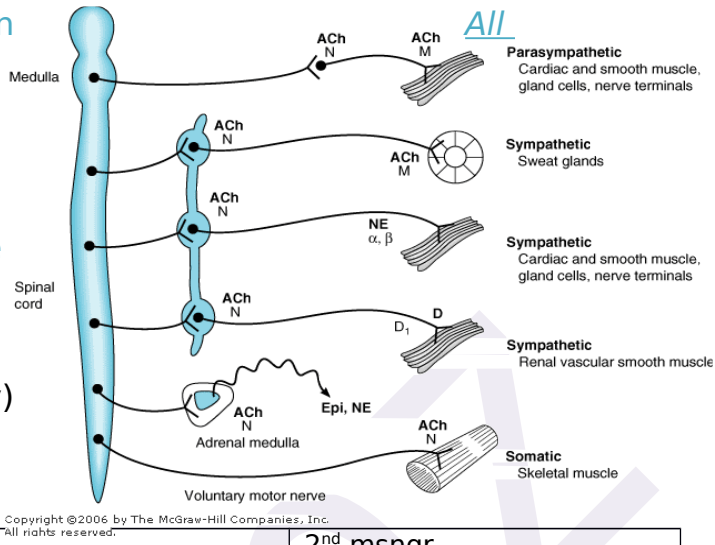
3. Target organ resp's
   a. **All somatic motor neurons** release ACh at their synapses, Ach always has an excitatory effect
   b. **In ANS:** *Preganglionic* fibers release *ACh*. *Postganglionic* fibers release *NE* (most symp) or *ACh* (parasymp) & effect is either stimulatory or inhibitory – determines efx on organ

- ANS Division into 2 major portions **Symp (thoracolumbar)** division **Parasymp (craniosacral)** division
- "symp" & "parasymp" are anatomic terms & don't depend on type of transmitter chemical released from n endings nor on kind of effect—excitatory or inhibitory—evoked by n activity

▭ ANS: NT's & 2 types of n fivers: ACh, NE, E & DA & +co transmitters

1. **Cholinergic fibers: all n's carrying** ACh NT- in *Preganglionic* fibers (Symp & parasymp n's), *all parasymp postganglionic* ~~& few symp postganglionic fibers~~; binds cholinergic receptors –
   a. Muscarinic Receptors: M1 M2 M3 M4 M5
   b. Nicotinic Receptors: N_M & N_N
2. **Adrenergic/noradrenergic fibers:** Adrenaline (E) or noradrenaline (NE) is NT; most *postganglionic symp* fibers; binds adrenergic receptors:
   a. α receptors: α1 & α2 (Gq, Gi, respectively)
   b. β receptors: β1 β2 β3 (Gs)

All receptors are G-protein coupled except Nicotinic receptors which are Ion channel mediated



Name	Type	Effector enzyme	2nd msngr
M_1, M_3, α_1, 5-HT1	Gq	↑PLC	↑IP3 & DAG
M_2, α_2	Gi	Inhibits ↑adenylyl cyclase, & ↑K^+ conductance	↓cAMP
β_1, β_2, β_3, D_1, H2, 5-HT4	Gs	↑adenylyl cyclase	↑cAMP
N_M, N_M	Ion Channel		

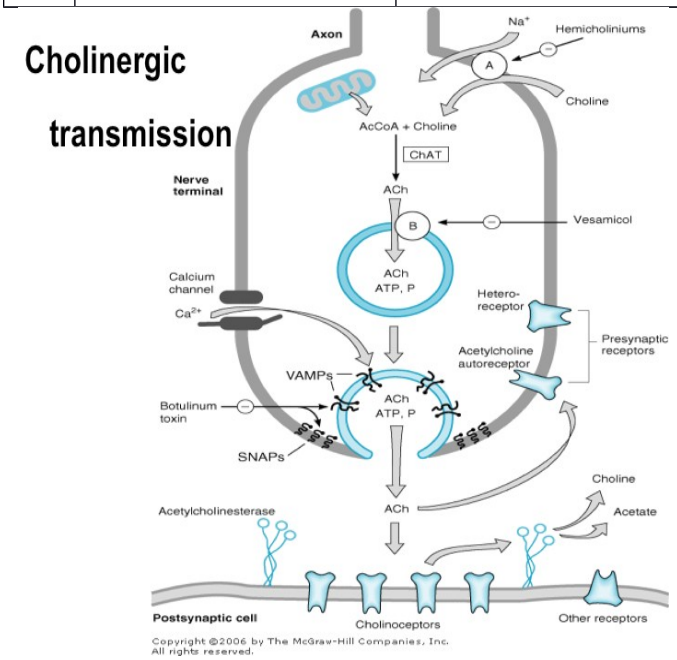
Organ	Parasymp	Symp
Heart	↓HR, FOC, CO	↑HR, FOC, CO
Blood vessel	Vasodilatation, ↓BP	Vasoconstriction, ↑BP
Smooth m	Contract, bronchospasm, diarrhea (peristalsis), urination	Relax, bronchodilation, constipation, urinary retention
Sphincters	Relaxation (LES)	Contraction
Pupil	Miosis, ciliary m contraction, ↑in lense curvature, eye fixed for near vision, cyclospasm, ↑AH drainage	Mydriasis, ↑AH production
Glands	Salivation, sweating, gastric acid	

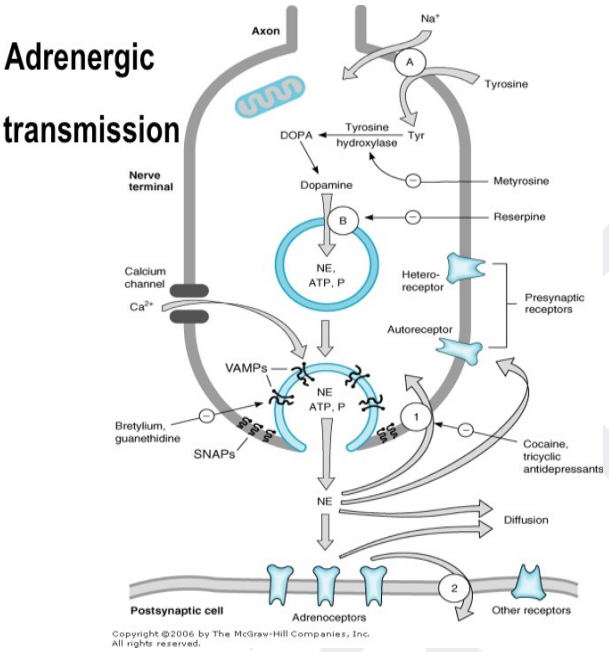
Smooth m's Sphincters Glands

M1	**Neurons**	CNS efx
M2	**Heart**	↓HR…bradycardia, FOC, CO & BP
M3	**Smooth m & glands Sphincters**	SM Contraction (except blood vessels), diarrhea, bronchospasm, urination, More Secretion – salivation, stomach acid, sweating, lacrimation, tracheobronchial secretions Relaxes all sphincters except LES
M3	**Pupil & ciliary m**	Contracts ….Miosis, ↑flow of AH
Nm	**Skeletal m end plate**	Contraction of skeletal m
Nn	**Ganglia**	Stimulation of post ganglion fibers/ ganglia
	A.medulla	Stimulation of E release from Adrenal medulla

α1	Blood vessels	Vasoconstriction ▭ ↑BP,
	Pupil (Iris)	Mydriasis of pupil (iris)
	Smooth m	SM sphincter contraction…so Constipation & Urinary retention, ejaculation
α2	Presynaptic neurons	↓release NE…bradycardia, hypotension, ↓insulin release, ↓AH production
β1	Heart	Contraction, Conduction, ↑HR, FOC, CO, ↑renin & glucagon secretion

β2	Smooth m's	Relax/bronchodilate, urinary retention, constipation, uterus relaxation, vasodilation, Gluconeogenesis & glycogenolysis, ↓AH production
β3	Fat tissue	Lipolysis
D	Renal	Vasodilation

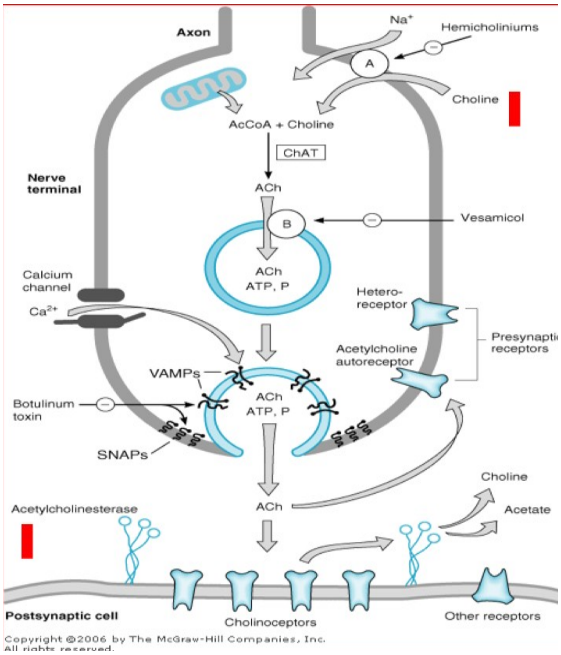




- Rate limiting step for Ach synthesis is choline uptake
- Rate limiting step for catecholamine synthesis is tyrosine hydroxylase
- Cholinergic neurotransmission is terminated by AChE
- Adrenergic neurotransmission is terminated by reuptake of NE

L10 Cholinoceptor Activating & Cholinesterase inhibiting drugs

1. ACh metabolized in synaptic junc's by enzyme AChE; acts thru receptor on diff tissues/organs aka Cholinergic Receptors 2 types cholinergic receptors –
    1. Nicotinic (N type): N_M & N_N receptors
    2. Muscarinic (M type): M_1, M_2 & M_3 receptors
2. In somatic nervous system Ach acts thru N_M receptors
3. In ANS preganglionic fibers ACh acts thru N_N receptors
4. In ANS postganglionic fibers ACh acts thru M_1, M_2 or M_3 receptors depending upon organ they're innervating



- Axns of ACh/drugs acting like ACh: (ANSWER); Note: DUMBBELSS = (<3) ↓HR (Bradycardia), FOC, CO & BP, Blood vessel Vasodilatation by releasing NO (Asked which drug releases NO & answer was ACh) & ↓BP; SM contraction & sphincter relaxation in GIT, bladder, bronchus, aka diarrhea, urination, bronchospasm, miosis & pupil ciliary m contract, ↑salivation, sweat, gastric acid, mucuous, lacrimation)
- **Cholinergic agonists**: drugs which mimic or ↑ACh; Adverse efx/OD/poisoning = exacerbated physio'al ACh efx; 2 types –

1. **Direct Cholinergic Agonists**: receptor agonists like ACh, act on receptors; ***ACh***, ***Bethanechol***, ***Pilocarpine***, ***Varenicline***, ***Muscarine*** *(alkaloid)*, ***Carbachol***, ***Methacholine***

1. **ACh**: Muscarinic & Nicotinic axns b/c non-specific & rapid inactivation by AChE's, no clinical use; Blood vessels don't have cholinergic innervations. Circulating ACh causes

vasodilatation; Vasodilation by ACh due to release of EDRF (Endothelium Derived Relaxing Factor) aka NO; **Methacholine challenge test: to dx bronchial asthma**

2. **Bethanechol**: (ANSWER) strong Muscarinic agonist (doesn't inhibit enzyme like Neostigmine) & least/ no Nicotinic axn; ↑M3 receptors ▭ ↓bowel movements & bladder contractions; vasodilation by activating muscarinic receptors on endothelium of blood vessels (can be blocked by atropine); 2 Uses: (1) Paralytic ileus (¬bowel movements, can't pass stools or flatus, in postop pt's; can also use Neostigmine that inhibits AChE) & (2) Urinary retentions (Non obstructive) in postop pt's & other neurological dis's
3. **Pilocarpine (ANSWER) (alkaloid)** – natural plant derivative): w/muscarinic activity only; lipid soluble & penetrates cornea very well; **uses**
   1. ***Glaucoma***: ↓AH outflow thus facilitating drainage
   2. ***Sjogren's syndrome***: chronic, inflammatory, autoimmune charac'd by dry mouth (xerostomia) & dry eye (keratoconjuctivitis sicca). Tx focused upon controlling sx of dry mouth & dry eye using diff strategies, ie. artificial tears, lubricant ointment & saliva substitutes commonly used

2. **Indirect Cholinergic Agonists/Cholinesterase inhibitors**: inhibit ACh metabolism by inhibiting AChE to ↓Ach in synapses & thus ↓its axns; 2 types – *Reversible* & *Irreversible* –
   1. **Reversible**: enzyme inhibition is reversible. Enzyme reactivated after some time; drugs relatively short acting & used in tx of 3 imp dis's –
      1. **Glaucoma** (↓IOP); tx w/**Physostigmine (ANSWER)**: Tertiary amine & lipid soluble; thus used in glaucoma; also for overdose of any drugs having anticholinergic properties
      2. ***Myasthenia Gravis**: autoimmune Ab mediated disruption of neuromuscular junc receptors; **Ab's** ¬func'al nicotinic ACh receptors on postjunc'al end plates & often rel'd w/thymus tumor; typical sx transient weakness, ptosis, diplopia, difficulty in speaking & swallowing, & extremity weakness – worsen w/effort & improve w/rest!!! Severe may affect all m's, even those necessary for respiration. Infection & thyroid dysfunc worsens sx. Blood ACh receptor Ab lvl is dx'ic; Tx: *AChe inhibitors* (Neostigmine, Pyridostigmine, Tensilon test), *Immunosuppressants & corticosteroids, Thymectomy, Plasmapheresis in severe refractory cases; worsened by antinicotinic meds (ie. high dose AG's – streptomycin, neomycin, gentamicin, tobramycin, amikacin), or curariform drugs (¬presynatpic ACh & ¬sensitivity of post-synaptic memb), Chloroquine, Ciprofloxacin, m relaxants, botulinum toxin, quinidine, procainamide, phenytoin, penicillamine*
         1. ******Neostigmine**: short acting for acute cases, IV'ly; quaternary amine, lipid insoluble so not used in glaucoma & little-no CNS efx; for **acute M. gravis** (emergency for short period, not for maintenance; +for post-op paralytic ileus b/c inhibits AChE (enzyme inhibition unlike Bethanechol) to ^ACh ▭ ↑SM of bowl; +reverses neuromuscular blockade & urinary retention
         2. **Pyridostigmine (ANSWER)**: longer duration of axn than neostigmine; good for maintenance/long term therapy. Given orally; not in emergency
         3. **Edrophonium (ANSWER)**: shortest acting so too brief for ~~tx~~; used in dx of M. Gravis & to differentiate myasthenic crisis from cholinergic crisis as pt of ***Tensilon test***
         4. **Tensilon test**: differentiates myasthenic crisis from Cholinergic crisis; small doses edrophonium (1–2 mg IV'ly) produce no relief or even worsen weakness if pt receiving excessive cholinesterase inhibitor therapy (Pt has Cholinergic crisis). On other hand, if pt improves w/edrophonium, ↓cholinesterase inhibitor dosage indicated (has myasthenic crisis)
         5. **Myasthenic crisis**: If drug therapy inadequate pt's develop severe m weakness
         6. **Cholinergic crisis:** If excessive amts of drugs used, pt's may become paradoxically weak b/c of nicotinic depolarizing blockade of motor end plate

7. Above 2 Clinical situations of severe/myasthenic crisis must be distinguished from excessive drug therapy (cholinergic crisis). Both crises have almost same sx; done by **Tensilon test**
8. In more resistance cases, immunomodulatory therapy (prednisone, azathioprine) combined w/1 of these above agents &/or thymectomy

3. **Alzheimer's dis: progressive neural degeneration in cortex leading to marked loss memory & ability to carry on activities of daily living; MCC of degenerative dementia; cause of unknown, but due to loss cholinergic neurons; thus tx w/ACh therapy w/AChe inhibitors like **Tacrine (ANSWER), Rivastigmine & Donepezil** DOC w/adverse efx of nausea, dizziness & insomnia

2. **Irreversible:** enzyme reactivation takes extremely long time or almost doesn't take place ⇨ leads to persistent axn of ACh; very long acting; most **OrganoPhosphates (OP);** & most from this used as insecticides or war gases; **OP poisoning** Signs & sx as acute toxic efx of irreversible cholinesterase inhibitors via *Phosphorylation (irreversible inhibition)* of cholinesterase ⇨ excess ACh ⇨ DUMBBELSS: *physio'al axns of ACh* but exaggerated; dominant initial signs due to stimulation of muscarinic receptors – abdominal cramps, vomiting, wheezing & weakness, miosis, blurred vision, bradycardia, excessive salivation, sweating, urination, bronchial constriction & diarrhea); manage OP poisoning – support ventilation & circulation, monitor ABG & ECG, Decontaminate skin, do gastric lavage & administer "Activated charcoal" to prevent unabsorbed drug being absorbed , Give IV Atropine, Pralidoxime; in severe cases, do hemoperfusion & mechanical ventilation
   1. **Atropine (ANSWER)**: most imp, life saving to treat OP poisoning; give to control signs of muscarinic excess stimulation of OP compounds; can't control nicotinic efx of OP poisoning, as this drug blocks only muscarinic receptor; given IV in large doses until you observe mydriasis, tachycardia (by ACh infusion) & dryness of mouth (3 cardinal signs of atropinization)
   2. **Pralidoxime: nucleophilic AChe reactivater, hydrolyzes/reactivates drug bound to enzyme via dephosphorylating Ache & binding organophosphate molecule; must be given at earliest possible, aka b4 ***"Aging"*** *of enzyme.* If given late, no use; Note: no role in OD of other AChe enzyme inhibitors; very high affinity for phosphorus atom in organophosphate insecticides
2. **Malathion & Parathion** used as insecticides (ie. farmer)
3. **Sarin**: used as war gas

Uses of direct acting drugs:	Uses of indirect acting drugs:
• ACh has no clinical use • Bethanechol used in urinary retention & paralytic ileus • Pilocarpine used in glaucoma & sjogrens syndrome	1. Edrophonium used in M.gravis for dx 2. Neostigmine used in M.gravis esp in clinics & emergency for short. Not for maintenance 3. Pyridostigmine used in M. gravis for maintenance (long term therapy). Not in emergency 4. Physostigmine used in Glaucoma & atropine OD (poisoning) , +TCA OD 5. Tacrine, Rivastigmine & Donepezil used in Alzheimer's 6. Malathion, Parathion used as insecticides 7. Sarin used as war gas

Organophosphorus poisoning = Miosis, Excessive salivation, Bradycardia, Bronchospasm, Abdominal cramps, vomiting, diarrhea, urination, Sweating; In OP poisoning, use atropine to reverse only muscarinic efx, not nicotinic; +Pralidoxime to reactivate enzyme

Anticholinergics & Cholinergic blockers: parasympatholytics; block ACh axns, allow SNS to dominate & thus have many of same efx as adrenergic agonists; *2 types of anticholinergics* –

➢ **Antimuscarinics/Muscarinic receptor blockers:**

- **Atropine**: long acting tertiary amine enters CNS w/CNS side efx; treats Cholinesterase inhibitors/OP (organophosphate) pesticides poisoning; to produce mydriasis in refraction error testing (but prefer short acting preps like tropicamide), heart block, bradychardia; axns/toxicity/atopinization all same: ie. kids w/consuming nightshade plant; ⇩⇩salivation,

bronchial mucus & sweat, dry mouth; Mydriasis & cycloplegia (loss accommodation reflex), Tachycardia, constipation, urinary retention, bronchodilation, excitation/hallucinations; **Toxicity tx'd by physostigmine b/c inhibits AChE (ANSWER)

- **Homoatropine**: short acting atropine prep
- **Tropicamide**: shortest acting atropine prep; acts for 4 hrs, prefer to produce mydriasis & cycloplegia in refraction error & fundoscopy
- **Pirenzepine**: to treat peptic ulcers
- **Scopolamine**: prevents motion sickness (can also use antihistaminic drugs for motion sickness)
- **Benztropine**: DOC for tx of drug induced Parkinsonism
- **Ipratropium bromide**: for COPD/bronchial asthma (not much systemic absorption, so less side efx), put graph w/line depicting ACh (this bronchoconstricts) so w/this drug, there'll be R shift curve of ACh (↓bronchoconstriction), line E (ANSWER)
- **Dicyclomaine**: treats GI spasms, spasmodic abdominal pain (ex. Menstrual pain –also tx'd by NSAIDs)
- **Tolterodine:** competitive muscarinic receptor antagonist for tx of urinary incontinence, urinary urgency & frequency; (can also use solifenacin succinate, darifenacin, oxybutynin, trospium & fesoterodine); ↓urinary urgency & improves bladder capacity; best for lesions above sacral spinal cord
- **Oxybutynin**: antispasmodic indicated for tx of overactive bladder, antagonizes ACh at muscarininc receptors, relaxing bladder smooth m, & inhibiting involuntary detrusor m contractions; worsen pt's w/BPH sx tho

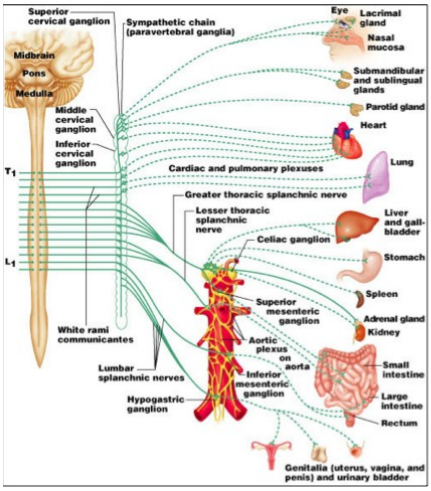
➢ **Nicotine receptor blockers:**

- **Nn/ganglionic blockers**: Hexamethonium, Mecamylamine; competitively block nicotinic receptors (Nn); therapeutic applications of ganglionic blockers virtually disappeared due to non specific efx, high toxicity ⇒severe hypotension & availability of better drugs
- **Nm blockers**: used as skeletal m relaxants

➢ **Refraction error testing**: requires dilatation of pupil for better visualization of retina (mydriasis) that can be achieved by topical application of atropine or tropicamide eye drops (anticholinergics); in old age pt's, since anticholinergics precipitate glaucoma, they're not used; alternative, α-agonists phenylephrine used –also produces mydriasis & so used only in old pt's

L11 Adrenergic Drugs

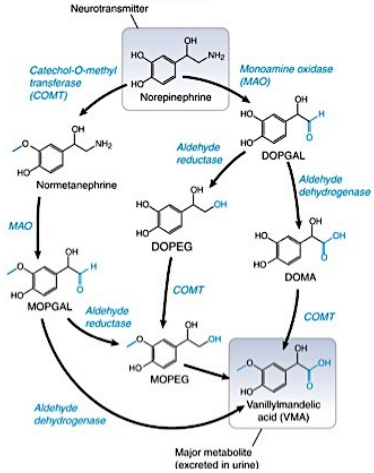
Overview of Sympathetic nervous system



Preganglionic fibers – solid lines

Postganglionic fibers – dashed lines

Norepinephrine metabolism



Classification Of Adrenergic Drugs

Class	Receptors activated	Drug
Alpha-beta agonists	α1, α2 β1 , β2 , β3	Epinephrine
	α1, α2 β1	Norepinephrine (Dopamine)
Alpha agonists	α1	Phenylephrine
	α2	Clonidine Apraclonidine
Beta agonists	β1 , β2 , β3	Isoproterenol
	β1	Dobutamine
	β2	Albuterol Salmeterol
D-receptor agonists	D1, D2	Dopamine
Mixed-acting adrenergic drugs	Direct- and indirect- acting	Ephedrine Pseudo ephidrine
	Mainly indirect-acting	Tyramine Methyldopa Cocaine Amphetamine

Relative Receptor Affinities

Drug	Receptor affinities
Epinephrine	β1= β2= β3 > α1= α2
Norepinephrine	β1> α1= α2
Phenylephrine	α1>>> α2
Clonidine	α2>>> α1
Isoproterenol	β1 = β2= β3
Dobutamine	β1> â2
Albuterol	β2 >>> β1
Dopamine	D1 = D2 >> β >> α

Comparative effects of iv infusion of epinephrine, norepinephrine, isoproterenol and phenylephrine

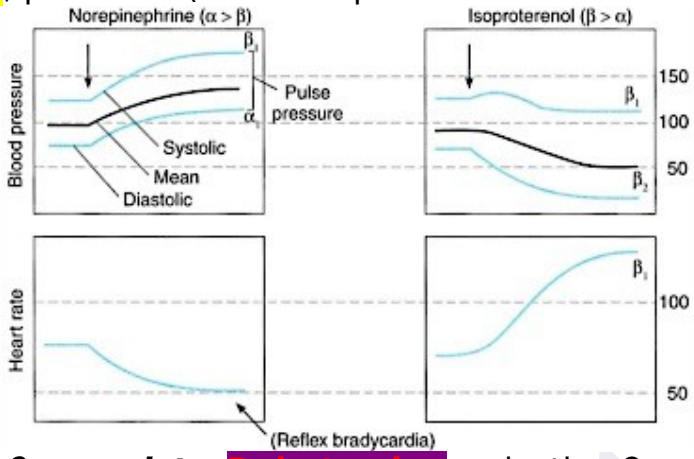
Effect	E	NE	ISO	PHE
Systolic	++	++	+	+
Diastolic	-,0	++	--	++
Mean	+	++	-	+0
Pulse	+	0	++	

NE is degraded to metabolites by 2 main enzymes –
1. **Catechol-O-methyltransferase (COMT)**: widely distributed cytosolic enzyme; in liver esp imp in metabolism of circulating catecholamines.
2. **Monoamine oxidase (MAO):** at outer surface of mitochondria metabolize NE into multiple intermediates (DOPGAL, MOPGAL, DOPEG, DOMA, & MOPEG) that are eventually excreted
3. Vanillylmandelic acid (VMA) is major metabolite excreted in urine.

Potential targets for drugs in adrenergic NS: synthesis, storage, release, activation of receptors, termination of axn/reuptake, presynaptic receptors; rate limiting step for catecholamine synthesis is tyrosine hydroxylase

Adrenergic agonists: classification –
- Direct agonists: directly activate receptors
  - α + β agonists: E & NE
    - **E (Epinephrine): β>α; for acute HSR's (anaphylaxis, angioedema WHERE hypotension & bronchoconstriction occurs due to H); to retard overall absorption of *local* anesthetics combine w/Lidocaine; vasoconstriction localizes anesthetic at desired site & systemic toxicity (ANSWER); also their duration of axn; cardiac arrest (α_1 axn) by BF to renal & splanchnic beds & VR, so aortic DP during closed chest compression, ultimately cerebral & coronary BF's enhanced (1) éHR, FOC, CO (2) **vessels w/**Vasoconstriction via α_1 & Vasodilation predominates in skeletal m due to β_2 efx (3) **BP:** Low dose BP (vasodilation by β_2 receptors predominate) OR High dose: mean BP: SBP (b/c CO) & DBP (vasodilation by β_2 receptor predominate, peripheral resistance); (4) Bronchial SM relaxation (β_2 mediated) hence why β_2 agonist albuterol & salmeterol for Asthma; (5) peristalsis (α_2 & β_2) & constipation via α_1 contraction of sphincters, (6) **Uterus** relaxation in pregnancy (β_2) to delay labor; thus β_2 agonists like terbutaline & albuterol used to postpone delivery in premature labor (7) **Urinary retention via** relaxing detrusor m & contracting trigone & internal sphincter (8) Mydriasis via α_1 contracting radial m of iris, so phenylephrine for refractive error testing in old age & kids where atropine contraindicated. IOP due to α_2 AH production. Thus Apraclonidine treats Glaucoma. In contrast, AH made via β_2 receptor. Thus β-blockers Timolol treat glaucoma. (9) β_2 **Skeletal m** tremors so use β-blocker propranolol to tremors (10) Hyperglycemia b/c inhibit insulin secretion, stimulate glycogenolysis & gluconeogenesis, Stimulate glucagon secretion & lipolysis
    - **NE: α1>α2>β1; (1) ~~direct β_1 éHR, FOC, CO~~; indirect w/N reflex baroreceptor resp to éBP overrides direct efx thus final efx is HR & no change CO ( ); **used in** Hypotension & Vasodilatory shock (due to spinal trauma, spinal anesthesia, sepsis); **No β_2 efx:** can't bronchodilatate & no use in anaphylactic rxns
      - BP: Both SBP & DBP , so pulse pressure not changed
      - BP: unlike w/E, no biphasic resp's in curves. Only α1 efx seen

- ***Selective α_1 agonists***: **Phenylephrine**** (BE ABLE TO WRITE GRAPH FOR THIS) used over atropine for glaucoma…why? +for postural hypotension & nasal decongestion, as mydriatics in old ppl (atropine ↓IOP, so contraindicated in old age), local vasoconstrictor in epistaxis; no efx on HR, can cause reflex bradychardia (requires intact vagal innervation, ie. not in cardiac transplant)
  - Xylometazoline & oxymetazoline used as topical decongestants
- ***Selective α_2 agonists***: Clonidine, Apraclonidine Tizanidine; KNOW THESE –
  - **Clonidine**: for HTN (2nd DOC) & w/drawal from tobacco, alcohol or opioids, diazepam
  - ***α*-methyldopa** – DOC in HTN in pregnancy (ANSWER: SELECTIVE ***α_2 agonists, +FINAL & B!)***
  - ↓Side efx clonidine & ***α*** -methyl dopa: Postural hypotension, dry mouth, sedation, rebound HTN
    - **Apraclonidine**: clonidine derivative used in glaucoma
    - **Tizanidine**: used in spinal cord spasticity
- ***β agonists***: **Isoproterenol**: non selective **β** agonist used in β-blocker overdoses (ie. propranolol); β_1 mediated ↑HR; β_2 mediated vasodilation & on BP: ↓↓DBP, same SBP & ↓↓mean BP; pic below (NE vs. isoproterenol efx on BP & HR)



- ***Selective β_1 agonists***: **Dobutamine**: selective β_1 agonist; given by IV infusion to pt's w/HF or cardiogenic shock who have severely depressed LV func
- ***Selective β_2 agonists***: Albuterol, Salmeterol; Uses: (1) Bronchial asthma short acting Albuterol used "as needed" & Long-acting salmeterol used together w/inhaled GC's in moderate-severe asthma, (2) COPD: often used in combo w/ipratropium, (3) Premature labor & (4) Hyperkalemia: b/c used often in combo w/insulin (both drugs shift K^+ from EC to IC space)
  - **Albuterol:** short acting & fast acting; b1>b2; used "as needed"
  - **Salmeterol**: slow but long acting; b2>b1; *Adverse efx **β**$_2$ selective agonists:* tremor, m cramps, Tachycardia, palpitations, flushing, hypotension; Hypokalemia (↑**β**$_2$ receptors leads to ↑K^+ uptake into cells, esp skeletal m ↓hypokalemia may have serious consequences in hypoxia & hypercarbia as in acute asthma); long-term admin of **β**$_2$ agonists can ↓tolerance dev't, due to down-reg of ***β***-receptors; hyperglycemia
- ***DA agonists*: DA**: ↑D receptors in low dose ↓vasodilation in renal, splanchnic & coronary beds; In high dose, also ↑α & β receptors; for shock, when associated w/poor renal perfusion; Gs; D1 = D2> **β** > α

Indirect agonists: acts by facilitating NE release:

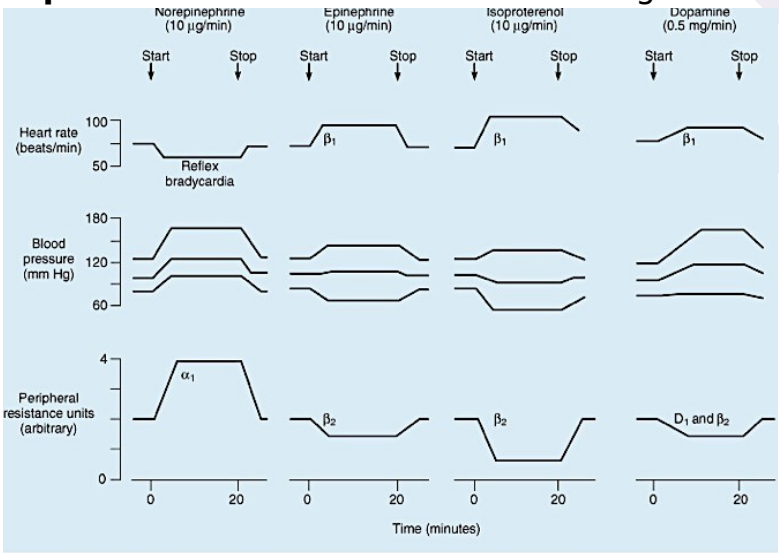
- **Amphetamine, Dextroamphetamine (Adderal) & Methylphenidate (ANSWER on FINAL)**; act by stimulating release of monoamines (NE, DA & 5-HT) & block of catecholamine reuptake; used for ADD/ADHD, narcolepsy, weight reduction. Ie. wild child out of control w/conduct disorder
  - **Narcolepsy**: daytime sleepiness, sleep attacks, difficulty concentrating, sleep paralysis, difficulty concentrating & sleep paralysis; ±hypnagogic hallucinations or hallucinations

while falling asleep; REM sleep out of control so fall into sudden state resembling REM sleep

- **Methamphetamine:** sx excitement, paranoida, random behavior, moist skin & dry mouth; can be injected (see track marks)
- **Tyramine**: false transmitter taken up by adrenergic neurons & transformed into octopamine, that displaces NE; if admin'd w/MAO I's, may cause lethal **hypertensive crisis**, due to NE release; in relatively high [ ]'s in fermented foods such as cheese, sausage, pepperoni, salami, pickled or smoked fish & yeast supplements
- **Inhibiting NE reuptake: Cocaine & TCA's:** indirect-acting adrenergic blockers of catecholamine reuptake both in CNS & PNS; central efx similar to amphetamines but shorter lasting & more intense; inhibits DA reuptake into neurons in pleasure centers of brain. Thus heavily abused. Snorted, smoked or injected; peripheral axns similar to NE; also local anesthetic axn

Indirect agonists w/additional direct efx: Ephedrine & Pseudoephedrine, α methyl dopa

- ****Ephedrine: ma huang;** *over counter nasal decongestant*, asthma, cold, & exercise enhacement; urinary incontinence & hypotension; tachyphylaxis develops w/frequent admin of small doses, anorexia, insominia, cardiac arrhythmias, HTN & psychosis; indirect agonist that releases stored catecholamines
- **Pseudoephedrine:** over counter nasal decongestant



Effects of epi, norrepi, isoproterenol and dopamine on BP , HR and PVR

L12 Glaucoma & drugs

Eye and ANS

Table II-4-1. ANS Innervation of the Eye

Target	PANS Activity	SANS Activity
Iris sphincter (circular) muscle	M_3 receptors—contraction → miosis M blockers: Mydriasis	–
Iris radial muscle	–	α_1 receptors—contraction → mydriasis (no cycloplegia) Alpha blockers: Miosis
Ciliary muscle	M_3 receptor—contraction → accommodation for near vision	–

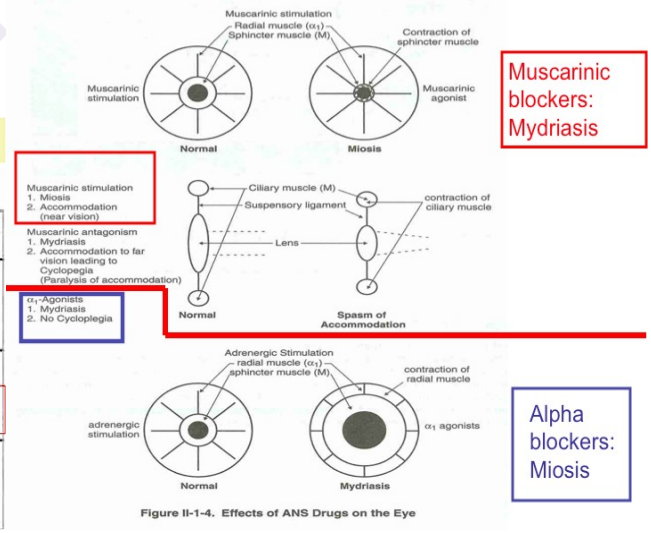


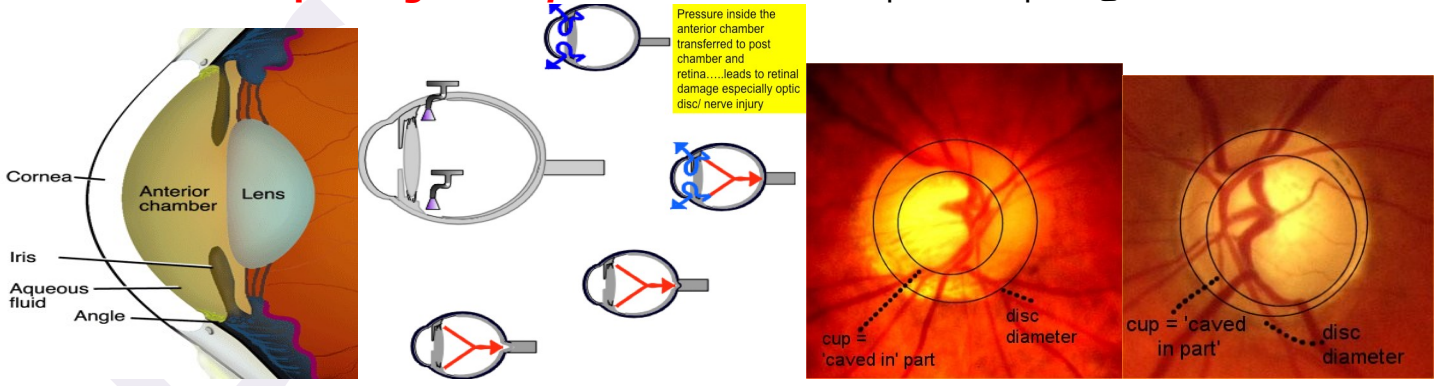
Figure II-1-4. Effects of ANS Drugs on the Eye

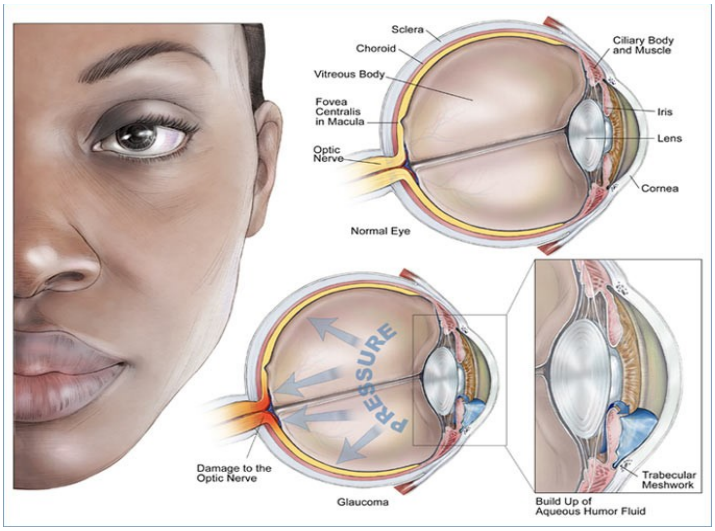
- Summary of axns of ANS drugs on eye:

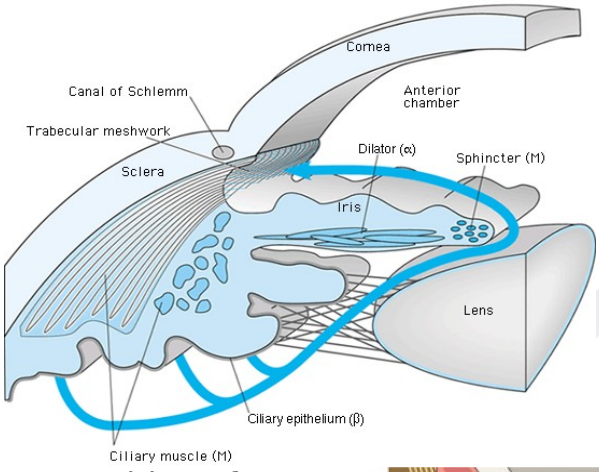
- **Cholinergic drugs**: cause Miosis & used in tx of Glaucoma
- **Muscarinic blockers:** cause Mydriasis; achieve pupil dilatation in refraction error testing & retinal exam (fundoscopy) except in old age & kids; contraindicated in glaucoma; precipitates or causes glaucoma
- **α-agonists:** ⏤Mydriasis & pupil dilatation in refraction error testing & retinal exam only in old pt's & kids
- **α-2 agonists:** stops production & facilitate drainage of aqueous humor
- **α-blockers**: causes miosis & has no use
- ***β*-agonists:** stimulate secretion of AH from ciliary epithelium
- ***β*-antagonists**: block secretion of AH

- **Glaucoma**: degenerative dis optic n associated w/painless (asymptomatic) loss vision or ⏤risk total blindness; *MCC blindness in American blacks.* 50% **not aware** having it until late. Some need laser trabeculoplasty+ incisional surgery (Yag laser iridotomy); frequently w/⇑IOP; tx aimed at ⇓IOP; 4th pic –iridocorneal angle & how its affected by iris apposition – this angle determines rate of AH efflux; **2 Problems: (1)** Excess synthesis/secretion of AH & (2) ¬¬drainage or outflow of AH; so **2 Therapy aimed at**:
  (1) ¬¬*production*: (Synthesis/Secretion) via Dorzolamide & Acetazolamide, Timolol & Apraclonidine
    1. ¬¬ *secretion or synthesis*: by **β**-blockers ⏤ b/c production/secretion of AH from ciliary body epithelium is adrenergic **β**-receptor mediated; ex. ***Timolol:*** topical eye drops (Non-selective β-blocker; also inhibited by α_2 receptor agonist ***apraclonidine***
    2. ¬¬*synthesis* by inhibiting carbonic anhydrase needed to form AH; ex: ***Acetazolamide*** (oral), ***Dorzolamide*** *(*topical*)*

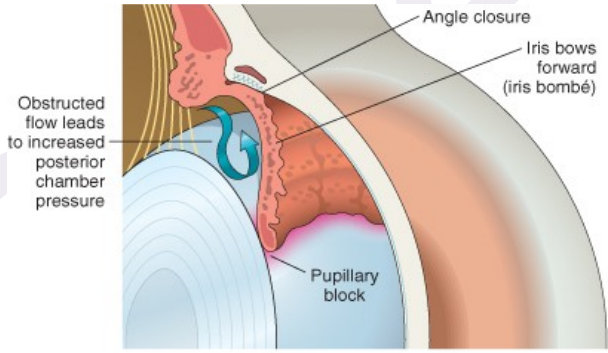
  (2) *Facilitate drainage*: Pilocarpine, Carbachol, Ecothiopate, Mannitol & Latanoprost (PG = -prost), Apraclonidine, Physostigmine
    1. **Topical *Pilocarpine, ecothiopate & physostigmine***: causes Ciliary m contraction which ⏤Irido-corneal angle & open trabecular meshwork ⏤ ⏤drainage of AH
    2. ***Latanoprost (ANSWER on FINAL)***: PG that ⏤outflow thru uveoscleral meshwork
    3. ***Mannitol*** ¬¬IOP by ¬¬vitreous volume
    4. **α_2 receptor agonist *apraclonidine*** 1%, topical drops : ⏤trabecular outflow







- **Angle closure glaucoma**: due to sudden apposition of peripheral iris w/trabecular meshwork, & leads to obstruction of *canal of Schlemm* thru which AH was supposed to be filtrated out; In anatomically predisposed eyes, transient apposition of iris at pupillary margin to lens blocks passage of AH from post chamber to ant chamber; pressure builds in post chamber, bowing iris fwd (iris bomb$\square$e) & occluding trabecular meshwork; tx: multiple drugs used; many Xs require laser therapy (iridectomy, trabeculectomy); ****2 imp drugs that causes/ Precipitates acute angle closure glaucoma are Mydriatics: Anti-cholinergic drugs; Antidepressants: SSRI drugs; So don't ever use mydriatics in glaucoma!!!; recommended 1st line therapy for acute ACG: β-adrenergic blocker (timolol), CA inhibitor acetazolamide, α-adrenergic agonist brimonidine & ophthalmic agent/miotic pilocarpine; add prednisolone ophthalmic corticosteroid if concomitant inflammation due to either infection or physical/mechanical damage; Mannitol hyperosmotic agent useful in refractory cases; E contraindicated b/c not selective a-agonist so its mydriatric efx will cause further narrowing of trabecular meshwork responsible for absorbing AH



- Some ppl w/glaucoma use marijuana b/c research found it has small efx in ↓IOP. But, no research that marijuana is anywhere as effective as legal glaucoma meds & American Academy of Ophthalmology, among others, say risky side efx of marijuana far outweigh any benefit.
- **Primary open-angle glaucoma (POAG):** MC form in US; usually afx ppl >age 40, & blacks much ↑susceptible vs whites. ~3 mil Americans w/it↑, & half of them don't know they have it. ~80,000 in US legally blind, in both eyes, from glaucoma ∴principal cause of blindness among blacks, & 2nd-leading cause (after age-rel'd macular degeneration) of blindness in whole American pop

∎ **Drugs which ↑ Drainage (Miotics): Pilocarpine,** Physostigmine, Carbachol, Latanoprost
∴ Drugs which ↓Secretion: Timolol, Apraclonidine, Acetazolamide
∴ Drugs contraindicated in Glaucoma – all Antimuscarinics which dilate pupil, ie. Atropine

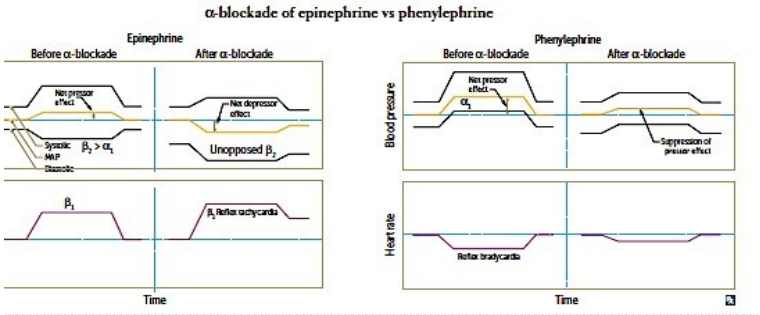
L13 Anti-Adrenergics/Adrenergic Blockers (a, b)

∎ **α-blockers**: phenoxybenzamine, Phentalamine, Prazosin, Terazocin, Tamsulosin; arterial & venous vasodilation ∴ hypotension, ↓HR due to reflex symp stimulation & ↑NE by α_2 blockade (only true for Nonselective blockers); **Adverse efx:** Postural/**Orthostatic** hypotension **b/c vasodilation,** "1st-dose phenomenon: Marked postural hypotension & syncope w/1st dose of selective agents, Reflex Tachycardia, palpitations

- **Nonselective α-blockers**:
  - **Phenoxybenzamine (ANSWER):** forms covalent bond w/receptors ∴ irreversible α-blockade; thus efx may last up to 7 days after discontinuation of therapy; treats pheochromocytoma; ID ON GRAPH

- **Phentolamine (ANSWER)**: treats hypertensive crises!!!* blocks bradychardia induced by phenylephrine; treats pheochromocytoma; + HTN due to clonidine w/drawal, cheese rxn; on GRAPH of Epinephrine, depresses its axn, so keeps ¬¬BP, even after giving more Epinephrine

	APPLICATIONS	ADVERSE EFFECTS
ective		
ybenzamine rsible)	Pheochromocytoma (used preoperatively) to prevent catecholamine (hypertensive) crisis	Orthostatic hypotension, reflex tachycardia
lamine sible)	Give to patients on MAO inhibitors who eat tyramine-containing foods	
tive (-osin ending)		
n, terazosin, osin, losin	Urinary symptoms of BPH; PTSD (prazosin); hypertension (except tamsulosin)	1st-dose orthostatic hypotension, dizziness, headache
tive		
apine	Depression	Sedation, ↑ serum cholesterol, ↑ appetite



above are the effects of an α-blocker (eg, phentolamine) on blood pressure responses to epinephrine and phenylephrine. pinephrine response exhibits reversal of the mean blood pressure change, from a net increase (the α response) to a net se (the β_2 response). The response to phenylephrine is suppressed but not reversed because phenylephrine is a "pure"

– Understand these graphs!!!

- **Selective α-blockers:**
  - **Prazosin**: treats Raynaud's Phen/PVD (but prefer CCB's more) & essential HTN; +HTN due to clonidine w/drawal, cheese rxn
  - **Terazosin** & **Doxazosin**: α-1 antagonists in vascular SM produce relaxation & subsequent dec BP & relieve urinary sx; treat both BPH (SM of bladder neck, prostate & urethra) & HTN (vascular SM)
  - **Tamsulosin**: prefer/DOC for BPH; α_1 receptors expressed in base of bladder & prostate. In BPH, contraction of these nonvascular SM's in trigone & internal sphincter of bladder responsible for obstructed flow of urine; thus α_1 receptors blockade ¬¬resistance to flow of urine & helps BPH pt's; use α_{1a} blocker…Tamsulosin preferred. Prazosin, terazosin & Doxazosin =alternatives; DOESN'T reverse hyperplasia - offers only symptomatic relief
  - **Tamsulosin & Silodosin**: selective α-1a adrenergic antagonists, for BPH but not HTN since only block α-1 receptors (selective for prostrate)
  - **Yohimbine**: α-2 selective competitive antagonist, sympatholytic, mydriatric; adjunct in managing erectile dysfunc

➢ **β-blockers**: propranolol, pindolol, timolol, sotalol, atenolol, metoprolol, esmolol; for cardiac arrhythmias (by ⏚AV nodal refractory period & sotalol has antiarrhythmic efx by blocking K^+ ion channel; ¬¬Frequency/conduction, automaticity & CT of heart are ¬¬), for IHD (Cardiac O_2 demand ¬¬in classic angina & improves exercise tolerance ⏤ prolonging survival in MI), for HTN (¬¬CO & BP, renin), Bronchoconstrict, ¬¬AH made by ciliary epithelium, ¬¬renin, for hyperthyroidism, thyroid storm & performance anxiety ("stage-fight"), glaucoma (Timolol topically, ¬¬AH produced by ciliary body), migraine headache (propranolol ¬¬frequency & intensity), HOCM, HF (mortality in chronic HF, prefer Carvedilol), Block catecholamine-induced tremor pheochromocytoma (Labetalol); adverse efx: Bradycardia, Bronchospasm b/c blocking β_2 receptors, Precipitate Peripheral vascular disorders & Vasospastic angina (block β_2 receptor mediated vasodilation may allow unopposed α_1 mediated vasoconstriction), **cautiously use CHF b/c depresses myocardial CT & excitability**, Mask premonitory sx of hypoglycemia (tachycardia, tremor, & anxiety), chronic use associated w/lipids (LDL & TG), sudden stoppage of β-blocker therapy leads to

rebound HTN due to up reg'd **β** receptors ▭can precipitate MI in cardiac pt's, or thyroid storm in hyperthyroid pt's

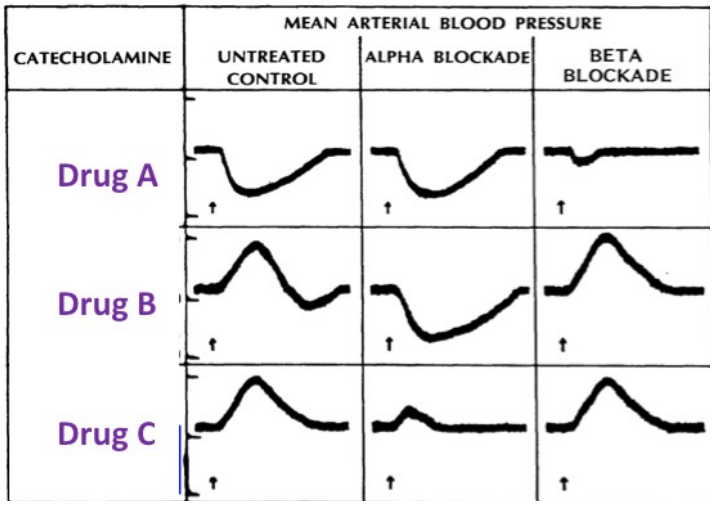
- Why few **β-blockers** preferred over other:
  - **Cardio Selective:** Relatively high affinity for **β_1** w/less blockade of **β_2**. Thus prefer over other **β**-blockers in pt's w/Bronchial asthma, Peripheral vascular disorders & Vasospastic angina
  - **β-blockers w/ISA:** Partial agonist activity, also called intrinsic sympathomimetic activity (Pindolol Acebutalol) may minimize bradycardia frequently found in elderly pt's
  - **β-blockers w/Local anesthetic axn/"memb-stabilizing" axn (MSA)**: disadv of such **β-blockers** when used topically in eye that it ¬¬protective reflexes & ▬risk corneal ulceration. **This effect absent in Timolol, hence prefer in glaucoma-**
- **Nonselective β-blockers**:
  - **Propranolol (ANSWER)**: for migraine headache by ¬¬frequency & intensity
  - **Timolol**: prefer in glaucoma (b/c has no local anesthetic efx), topically, ¬¬AH produced by ciliary body; avoids causing corneal ulceration
  - **Pindolol**: partial agonist activity aka intrinsic sympathomimetic activity ▭ minimizes bradycardia in elderly pt's; b/c partial agonist at **β-receptors**, [ ] resp curve'll show bronchodilating efx at 0 [albuterol], as [albuterol] ▬, airway dm also ▬
  - **Sotalol**: for cardiac arrhythmias (by ▬AV nodal refractory period & sotalol has antiarrhythmic efx by blocking K^+ ion channel; ¬¬Frequency/conduction, automaticity & CT of heart are ¬¬)
- **β_1 or cardio selective blockers (A-BEAM)**: relatively high affinity for **β_1** w/less blockade of **β_2**, so prefer over other **β**-blockers for Bronchial asthma, Peripheral vascular dis's & Vasospastic angina
  - **Atenolol (ANSWER)**: cardio selective beta blocker for **β_1**;
  - **Betaxolol**:
  - **Esmolol**:
  - **Acebutalol**: Partial agonist activity aka intrinsic sympathomimetic activity, may minimize bradycardia frequently in elderly pt's
  - **Metoprolol**: also used for Parkinson's tremors, b/c b1 selective, esp in pulm issues, b/c won't affect b2 in lungs

➢ **α+ β-blockers:** Labetalol, Carvedilol

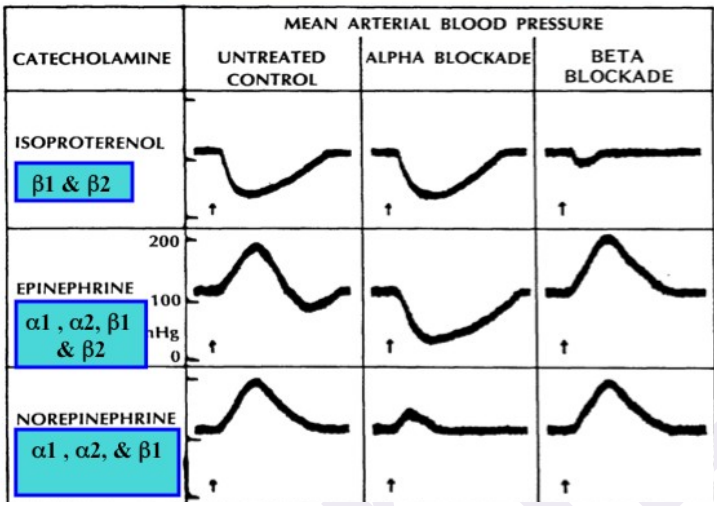
- **Carvedilol:** **α_1**, **β_1** & **β_2** receptor antagonist; treats HF (mortality in chronic HF)
- **Labetalol:** **α_1** receptor antagonist & partial agonist at **β_1** & **β_2** receptors; adv's over other **β**-blockers: marked ¬¬TPR, minimal changes in HR & CO at rest; for pheochromocytoma (blocks catecholamine-induced tremor); can cause urinary retention & difficulty in micturition so contraindicated in BPH pt's

➢ **Indirect acting antiadrenergic drug: Metyrosine:** inhibits tyrosine hydroxylase (rate-limiting enzyme in catecholamine biosynthesis)

Predicting Responses



Predicting Responses



L14 Antihypertensives

Classification of Hypertension on the Basis of BP	
Systolic/Diastolic Pressure (mm Hg)	**Category**
< 120/80	**Normal**
120–135/80–89	**PreHTN**
≥ 140/90	**HTN**
140–159/90–99	**Stage 1**
≥ 160/100	**Stage 2; emergency situations – retinopathy, epistaxis**

▭ **HTN**: silent killer, ⏚BP asymptomatic until complications develop; untx'd ▭ hypertrophy, MI, CHF, stroke, TIA, CRF, retinopathy; To treat, rule out secondary causes of HTN, begin w/lifestyle modifications. BP goal in otherwise healthy pt's is <140/<90. Goal in diabetics or pt's w/renal dis w/proteinuria is <130/<80; ie. for pheochromocytoma, treat w/phenoxybenzamine; regardless of origin, ⏚arterial BP due to ⏚PVR or ⏚CO. Rmr, BP = CO × PVR; PVR determined by vascular tone (constriction state) of systemic resistance vessels latter determined by HR & SV. HTN tx'd w/drugs that ¬¬CO, these either block β-adrenoreceptors on heart (β-blocker) or L-type CCB's ¬¬CO by ¬¬HR & ¬¬CT (inotrophy), OR use vasodilators (¬¬systemic vascular resistance, ie. α-adrenoceptor antagonist, direct-acting vasodilators, ACE I's & ARB's; To ¬¬arterial pressure -->

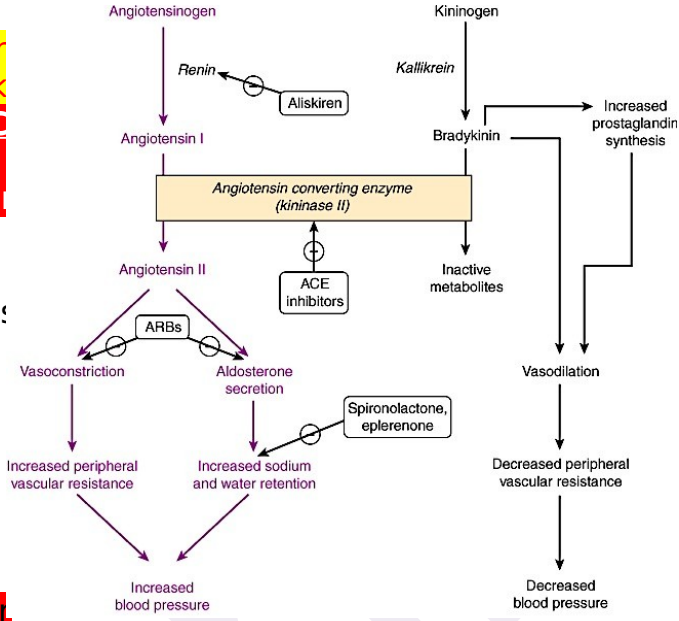
1. ᵀᴱ CO (BV, HR, SV)

- **Diuretics**: initially ¬¬CO but after few weeks may normalize, later on, losing Na^+ gives loss of stiffness to vessel walls ▭ inducing vasodilation; effective & inexpensively ¬¬venous pressure & CO by drugs ¬¬BV; act on kidney to enhance Na^+ & water excretion; ¬¬BV not only ¬¬central venous pressure, also, ¬¬CO as PL is ¬¬
  - **Thiazide** diuretics: **hydrochlorothiazide** (+for Nephrogenic DI) prefer for HTN; max antihypertensive axn at LOWER doses than diuretic dose; added benefit of ¬¬TPR w/long-term use; often achieve maximal antihypertensive effect w/doses lower than those needed for max diuretic effect; Toxicity: hypokalemia, ↓glucose tolerance & may unmask latent DM, ↑plasma LDL, cholesterol & TG's, & ↑plasma uric acid & precipitate acute gout; preferred diuretic in HTN** but N serum CK (M: 25-90 U/L; F 10-70 U/L; unlike statins)

2. & ¬¬TPR (total peripheral/systemic vascular resistance – aka dilate systemic vasculature)

▭ Note pathological efx of AGII on myocardium (& kidney) (1) Mitogenic for vascular & cardiac m cells; **(2) Remodeling**: ⏚wall-to-lumen ratio in vessels, concentric & eccentric hypertrophy, fibrosis, stenosis of intimal surface of vessel, due to ⏚migration & hyperplasia of vascular SMC's, myocytes & fibroblasts (3) *hyperplasia & hypertrophy of VSM cells & all other histo features seen w/cardiac HF cardio-myopathology produced by ATII – all slowed, prevented, & even reversed by ACE I's*

▭ RAAS inhibitors: drug that ↓↓mortality, prolongs sur
go w/drug that efx this pathway. Also includes B block
that ↓↓renin. YOU'RE REFERRING TO TX'ING **CARDIAC
REMODELLING;** toxicity – hyperkalemia esp if pt has
impairment, consuming high K^+ diet or taking other d
that tend to conserve K^+, $[K^+]$ may reach toxic lvls



- **ACE inhibitors (ACE I's)**: inhibit ACE (peptidyl dipeptidase that hydrolyzes AGI to AGII); inactivates bradykinin potent vasodilator, that stimulates NO & PCI_2 release; ↓↓BP by ↓↓PVR; *DOC** for diabetic nephropathy* b/c diminish proteinuria & stabilize renal func; improve intrarenal hemodynamics w/↓↓glomerular EA resistance & resulting ↓↓intra-GC pressure; ***Captopril***, ***Enalapril*** ***(ANSWER)***, **Ramipril, Benazepril, Fosinopril, Lisinopril, Quinapril; *Adverse efx:*** Severe hypotension after initial doses in hypovolemic pt's, Dry cough (MC adverse efx) due to ↑bradykinin?, ARF (Acute renal failure) in pt's w/bilateral renal a stenosis *(*in renovascular HTN, glomerular filtration pressures maintained by vasoconstriction of post-glomerular arterioles, efx mediated by AGII. *ACEI thus sig ↓↓GFR causing ARF),* Angioedema tho rare, potentially fatal (↑in African Americans), pregnancy category D (CONTRAINDICATED b/c severe renal pathology in fetus); DI's: ***Hyperkalemia***- if given w/K^+ sparing diuretics
- AT_1 blockers
- **ARBs (Angiotensin Receptor blockers)**: block AGII type 1 (AT_1) receptor; no efx on bradykinin metabolism & so more selective blockers of AG efx than ACE I's; provide benefits similar to ACEI in pt's w/HF & chronic kidney dis; adverse efx – noticebly lower incidence of cough, hyperkalemia, renal efx, pregnancy category D; ex: **Losartan (F ANSWER), Valsartan, Candesartan, eprosartan, irbesartan, telmisartan & olmesartan**
- **Renin antagonist/blocker: Aliskiren:** newest antiHTN, inhibit renin's axn on AGII; toxicities – headache & diarrhea
- **Aldosterone receptor inhibitor: Spironolactone, elprenone (discussed under diuretics)**

Sympatholytics/-plegics: CNS acting Clonidine & Methyldopa both for HTN; Cause ↓↓in symp outflow

- **β-blockers (-lol)**: all equally effectively ↓↓BP in mild to moderate HTN**;** in severe HTN, prevent reflex tachycardia that results from w/direct vasodilators tx; ↓↓ mortality after MI & HF; choice of β-blocker depends on how well drug is tolerated; hemodynamic/antihypertensive MOA's *(in order of ↓↓importance)/*: ↓↓*HR,* ↓↓*CO* (blocks cardiac β_1 receptor), unchanged *Venous tone,* ↓↓*PVR, negligible Postural hypotension, inhibit renin release* (via blocking β_1 receptors on JG cells)
  - ***Nonselective compounds PROPRANOLOL:*** principal toxicities include bradycardia or cardiac conduction dis, asthma, peripheral vascular insufficiency & diabetes. When discontinued, abruptly after prolonged regular use- can result in reflex tachycardia (due to hypotension)
  - ***Cardio-selective β_1 drugs*: *ATENOLOL, METOPROLOL***: most widely used b-blockers in tx'ing HTN; cause **less** bronchoconstriction than propranolol
  - ***β-blockers w/additional α-blocking activity (know 2 drugs & their indication)***
- **α-adrenergic blockers**:

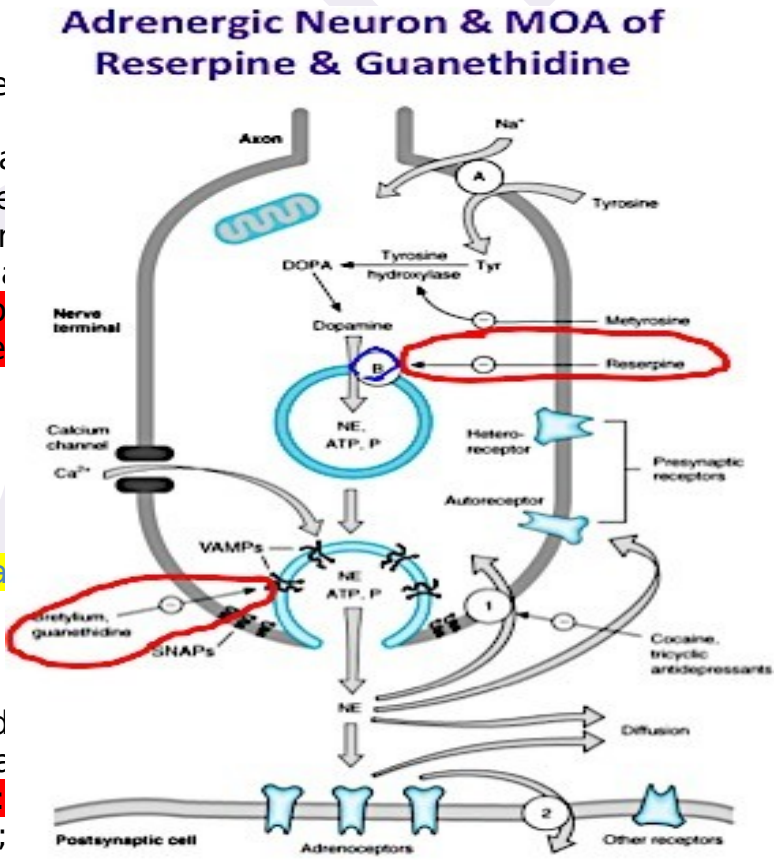
- **α_1-selective blockers**: **Prazosin, terazosin & doxazosin**; antihypertensive efx by selectively blocking α_1 receptors in arterioles & venules; side efx of postural hypotension (↓BP); for men w/concurrent HTN & BPH
- **Nonselective α-blockers: phentolamine, phenoxybenzamine**: block both presynaptic & postsynaptic receptors resulting in tachycardia; used in dx & tx of pheochromocytoma

○ **α_2-agonists (selective agents)**: (ANSWER for methyl dopa in pregnant women) activates α_2 receptors in CNS (as they readily enter CNS when given orally) ⊟⇓symp outflow ⊟↓BP (as ⇓CO &/or TPR); major compensatory resp is salt retention

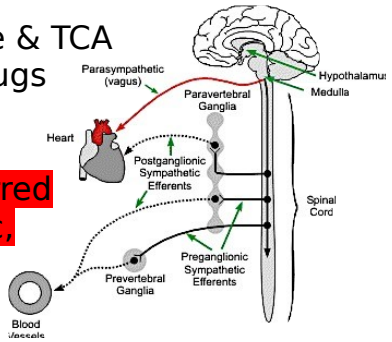
- **Clonidine****: ↓BP by ↓CO due to ↓HR & relxaing capitant vessels w/↓PVR; ⊟ dry mouth, sedation, urinary retention & difficulty micturition, sudden w/drawal causes rebound HTN (tx'd w/α-blocker phentolamine or reinstituting clonidine);
- **Methyl dopa** (ANSWER TWICE B & FINAL)**: prodrug converted into active methylnorepinephrine in brain ⊟ ↑*central* α_2 adrenoceptors; widely used in past but now for HTN in pregnancy; Toxicity: sedation, hemotologic immune toxicity (+ve Coomb's – test tube agglutination of rbc's), may progress to hemolytic anemia

○ N terminals/Adrenergic neuron blockers: guanethidine; both ↓SNS activity ⊟↓BP; compensatory resp via salt secretion; both ve effective but have more toxicities

- **Reserpine**: drugs depleting NE stores in a blocks vesicular uptake & storage of bioge amines by interfering w/uptake mechanis vesicular memb associated transporter) c serotonin & DA depletion; crosses BBB, so toxicities: depleting cerebral amines store causing sedation, mental depression & Parkinsonism sx; don't use this anymore will be tested upon, clinical sig⊟1 of earliest models understood depression thru
- **Guanethidine**: deplete & blocks NE relea from symp n endings; transported across n memb by same mechanism that transports NE (NET, uptake 1) & uptake essential for axn; once it's entered concentrated in transmitter vesicles, repla graduating NE stores depletion; toxicities: orthostatic hypotension & sexual dysfunc; if used w/cocaine & TCA, becomes blocked/useless b/c uses catecholamine reuptake pump, which is inhibited by cocaine & TCA

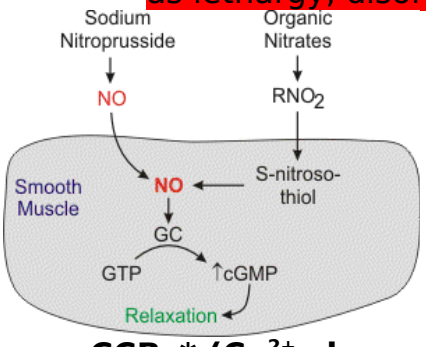


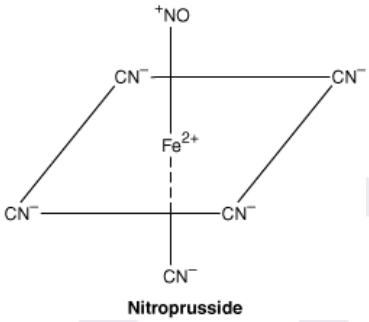
○ **Ganglionic blocking drugs**: Hexamethonium, trimethaphan; 1st drugs as antihypertensives; nicotinic Nn blockers act in ganglia severely ↓BP & block baroreceptor reflexes; not used anymore; major compensatory resp-salt retention; toxicity – parasymp blockade (blurred vision, constipation, urinary hesitancy) & symp block (sexual dysfunc, orthostatic hypotension)

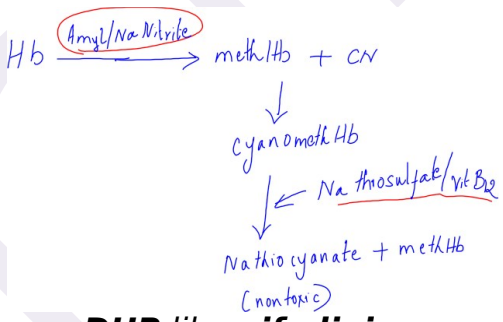


➢ **Vasodilators**: dilate vessels by acting directly on SMC's thru nonautonomic mechanisms⊟ those acting on vascular smooth m* very imp, by releasing potent vasodilator NO; focus on methyl dopa & clonidine; 4 major mechanisms;

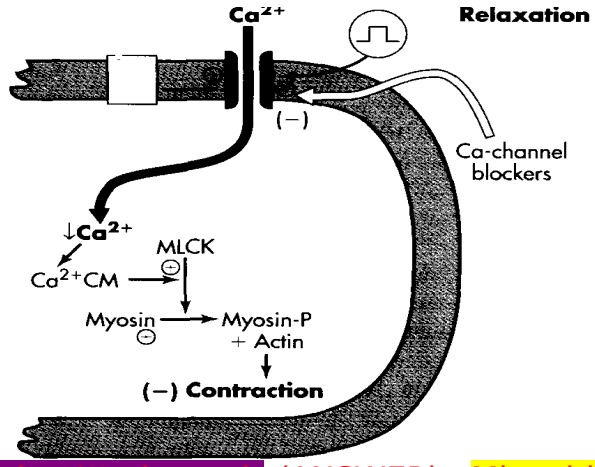
- *Release NO* – Nitroprusside, hydralazine (other drugs w/same MOA: nitrates, histamine, acetylcholine)
  - ***Hydralazine: releases NO, arteriolar vasodilator (ANSWER) (^cGMP), used in low doses b/c toxic; combo w/nitrates approved for pt's w/both HTN & heart failure, esp in African-American pt's; Major route metabolism: acetylation [pt's either "rapid acetylators" have ¬¬bioavailability (30% bioavailability) or "slow acetylators" (50% bioavailability)]; 2nd line drug for HTN in pregnancy; Toxicity: (1) Compensatory resp's-tachycardia, salt & water retention & (2) Drug induced reversible lupus erythematosus like syndrome – charac'd by arthralgia, myalgia, skin rashes, & fever (in slow acetylators)
  - **Nitroprusside**: parenteral vasodilators (both a's & v's) used in hypertensive emergencies & cardiac decompensation; ferrous iron center complex w/5 cyanide moieties & nitrosyl group (44% cyanide by weight); short acting (few mins) given as continuous IV infusion; release NO from drug (NO donor) ▭ ↑GC & ▭cGMP in SM; toxicity ▭ excessive hypotension, tachycardia, accumulating cyanide (tx'd by amyl nitrite/sodium nitrite followed by sodium thiosulfate or hydroxocobalamine), manifests as lethargy, disorientation, m spasms & convulsions;



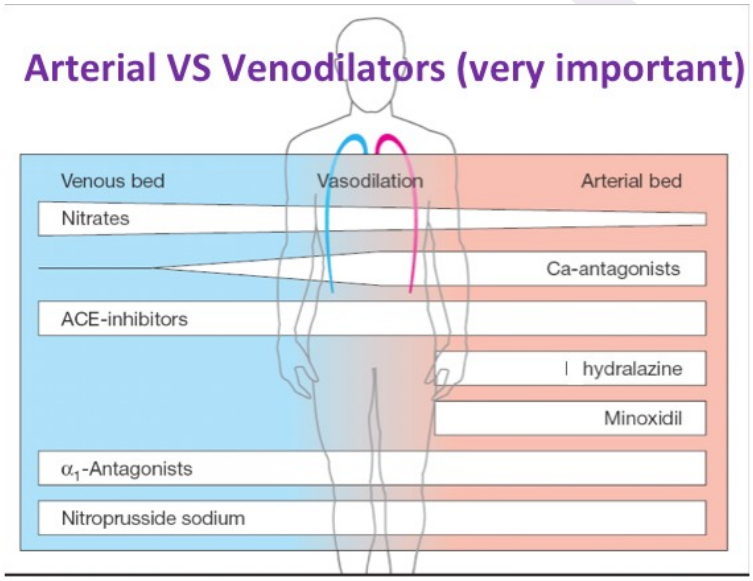


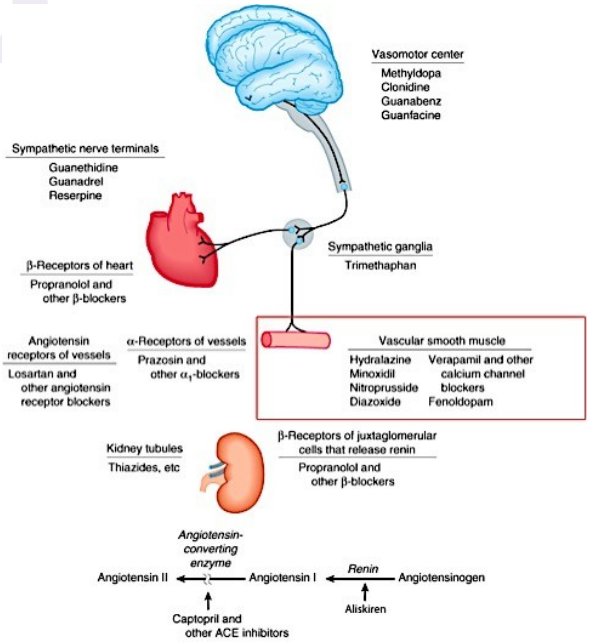


- **CCBs* (Ca2+ channel blockers)**: ***Verapamil***, ***Diltiazem***, ***DHP*** *like* ***nifedipine***, ***amlodipine***; block L type Ca^{2+} channels in blood vessels & heart ▭ ¬¬Ca^{2+} comes in ▭ ¬¬CO (verapamil & diltiazem), ¬¬TPR (all), vasodilation; all ¬¬BP; for HTN, angina & arrhythmias (verapamil & diltiazem)
  - **DHP (dihydropiridines): *amlodipine***, ***felodipine***, ***isradipine***, ***nicardipine*** (esp in HTN emergency), ***nifedipine***, ***nisoldipine***; more selective as vasodilators, can cause slight reflex tachycardia; block more in blood vessels vs. heart
    - **Nimodipine (ANSWER on B2 & FINAL):** preference for cerebral blood vessels, used to treat SAH
  - **Verapamil:** greatest depressant efx on heart & ¬¬HR & CO; affect heart >> than blood vessels; for HTN, dysrhythmias & angina; ¬¬AL & potential reflex tachy but predominant direct axn blocks slow Ca2+ channels at SA node producing bradycardia; contraindicated in CHF b/c such pt's already lack pumping blood/CT & these drugs further ¬¬CT
  - **Diltiazem:** intermediate axns; afx heart >> blood vessels; contraindicated in CHF b/c lack pumping blood/CT & these further ¬¬CT



- *Opening K^+ channels (ANSWER)* - Minoxidil, diazoxide; Innerpotassium ion [ ] is ↑(150 mM) than EC K^+ ion [ ] (3-4 mM). K^+ channel opening results in outflow of K^+ ions & hyper polarization which leads to series of cellular resp's like SM relaxation
  - **Minoxidil**: for severe HTN, arteriolar vasodilator; K^+ channel opener-causes hyperpolarization & relaxes vascular SMo; Toxicity: severe compensatory resp's (Tachycardia, palpitations, angina & edema), hypertrichosis/hirsutism (↑hair growth); also as Topical Rogaine ↑hair growth for correcting baldness [role of K^+ channel evident in pathophys of HTN. These channels traditionally for its tx. KATP channels activated by diff compounds – Minoxidil Sulphate, Diazoxide & Pinacidil +variety of benzopyran derivatives (Leveromakalim or its racemate, Cromakalim). After ↑of KATP channel, K^+ efflux occurs from vascular cell memb, ↓hyperpolarization ↓SM relaxation & ↓BP]; b/c compensatory resp's, drug directly ↓BP thru ↓PVR cause reflex ↑symp outflow, renin & ↓Parasymps↓ thus HR & cardiac force ↑; +salt & water retention will occur
  - **Diazoxide**: IV'ly infused, lasts many hrs, opens K^+ channels (hyperpolarization) – prevents/↓smooth m contraction & insulin release (used to treat hypoglycemia produced by insulinomas); toxicity: hypotension, hyperglycemia, salt & water retention
- *Activating D_1 receptors* – Fenoldopam: peripheral arteriolar dilator for hypertensive emergency & post-operative HTN; D1 receptor agonist in renal vessels ↓vasodilation; ½ life 10 mins, given continuous IV infusion





↓ Causes of Hypertensive emergency/crisis:
- Ingestion of tyramine-rich foods in pt's taking MAO inhibitors (use labetalol etc)
- Pre-eclampsia
- Recreational drug use (cocaine, amphetamine) – need to use α & β blockers
- Pheochromocytoma (massive release of endogenous catecholamines)
- Thyrotoxicosis

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- Sudden w/drawal of betablockers, clonidine

Drugs used for tx of hypertensive emergencies:

- Parenteral antihypertensive meds used to ↓↓BP rapidly
- Na^+ nitroprusside no longer 1st choice. In most cases, BP control achieved by combos of nicardipine /clevidipine plus labetalol/esmolol
- Other parenteral drugs effective: nicardipine, fenoldopam, nitroglycerin, labetalol, diazoxide & hydralazine

TABLE 2.1-14. Antihypertensive Medications Indicated in Specific Patient Populations

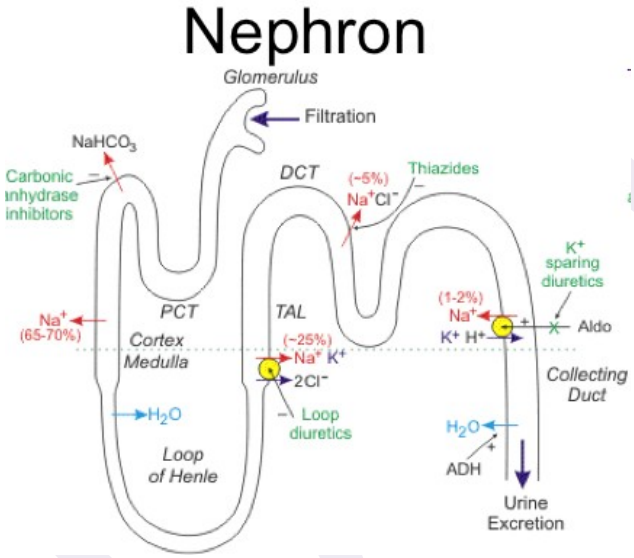
Population	Treatment
Diabetes with proteinuria	ACEIs.
CHF	β-blockers, ACEIs, diuretics (including spironolactone). CI-CCB
Isolated systolic hypertension	Diuretics preferred; long-acting dihydropyridine calcium channel blockers.
MI	β-blockers without intrinsic sympathomimetic activity, ACEIs.
Osteoporosis	Thiazide diuretics.
BPH	α-antagonists.
HT in pregnancy	methyldopa (FDA CategoryB), Labetalol(C), Hydrallazine (C), Betablockers (C)

TABLE 11–1 Compensatory responses to antihypertensive drugs.

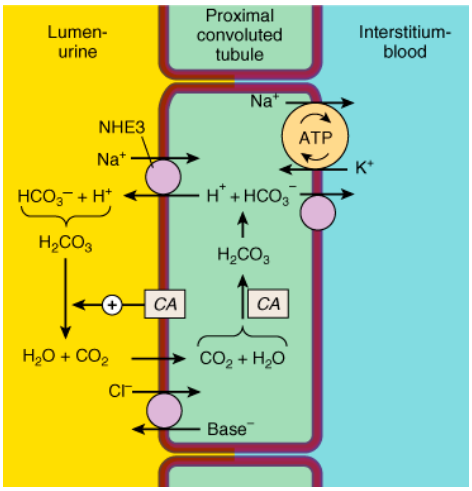
Class and Drug	Compensatory Responses
Diuretics (thiazides, loop agents)	Minimal
Sympathoplegics	
Centrally acting (clonidine, methyldopa)	Salt and water retention
Ganglion blockers (obsolete)	Salt and water retention
Alpha$_1$-selective blockers	Salt and water retention, slight tachycardia
Beta blockers	Minimal
Vasodilators	
Hydralazine	Salt and water retention, moderate tachycardia → Rx β blocker
Minoxidil	Marked salt and water retention, marked tachycardia
Nifedipine, other calcium channel blockers	Minor salt and water retention
Nitroprusside	Salt and water retention → Rx Diuretic
Angiotensin antagonists (ACE inhibitors, ARBs)	Minimal

L15 Diuretics (DRUGS acting on renal system)

- **Diuretics**: ↓rate of urine flow & sodium excretion; used to adjust volume &/or composition of body fluids in HTN, HF, renal failure, nephrotic syndrome & cirrhosis

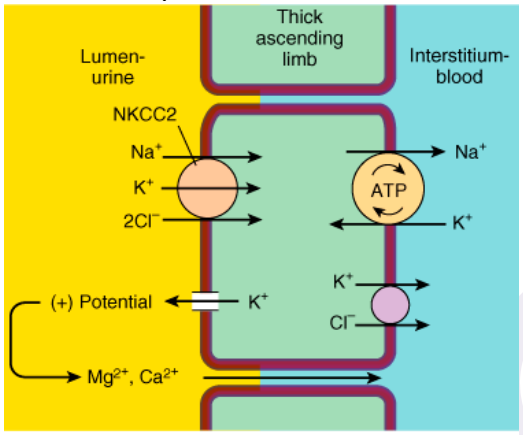


- **PCT (Proximal Convoluted Tubule):** responsible for 60-70% of total reabsorption of Na; this segment carries out isoosmotic reabsorption of AA's, glucose & many cations; **Also major site for reabsorption of Sodium Chloride & Bicarbonate; Bicarbonate itself is poorly reabsorbed thru luminal memb So it is converted to CO_2 & H_2O & this rxn is mediated by Carbonic anhydrase



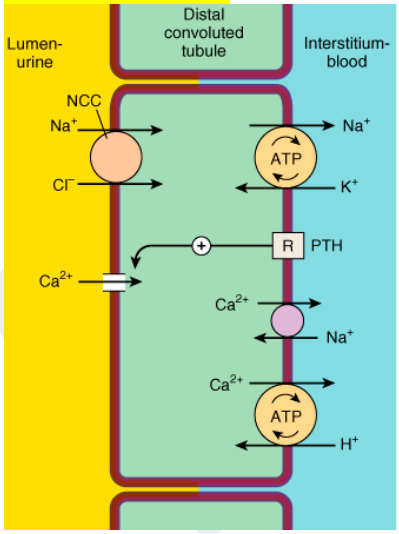
- Apical memb Na^+/H^+ exchange (via NHE3) & bicarbonate reabsorption in PCT cell
- Na^+/K^+ ATPase present in basolateral memb to maintain IC Na^+ & K^+ lvls w/in normal range
- B/c of rapid equilibration, [ ]'s of solutes ~equal in interstitial fluid & blood.
- Carbonic anhydrase (CA) is found in other locations in addition to brush border of luminal

➢ **<u>Thick Ascending Limb of Loop of Henle (TAL):</u>** Responsible for reabsorption of 20-30% of Na; this segment pumps out Na^+, K^+ & Chloride into interstitium; also major site for Mg & Ca^{2+} reabsorption; Reabsorption of Na, Cl & K accomplished by single carrier, $Na^+/K^+/2Cl^-$ cotransporter (called NKCC2); Note effect of high K^+ lvls inside cell on Mg & Ca (Diagram in next slide)



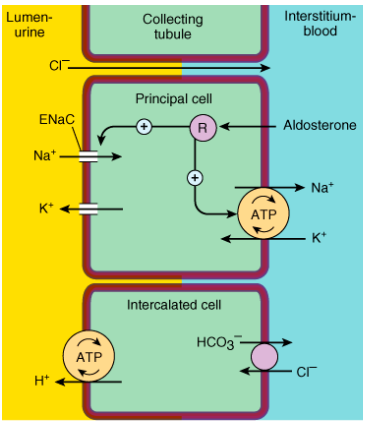
- lumen +ve elec'al potential created by K+ back diffusion drives divalent (& monovalent) cation reabsorption via paracellular pathway
- NKCC2 is primary transporter in luminal

➢ **<u>Distal Convoluted tubule</u>**: Responsible for reabsorption of 5-8% of Na; actively pumps Na, Cl out of lumen via Na^+Cl^- cotransporter; ** Ca^{2+} also reabsorbed in this segment under control of PTH

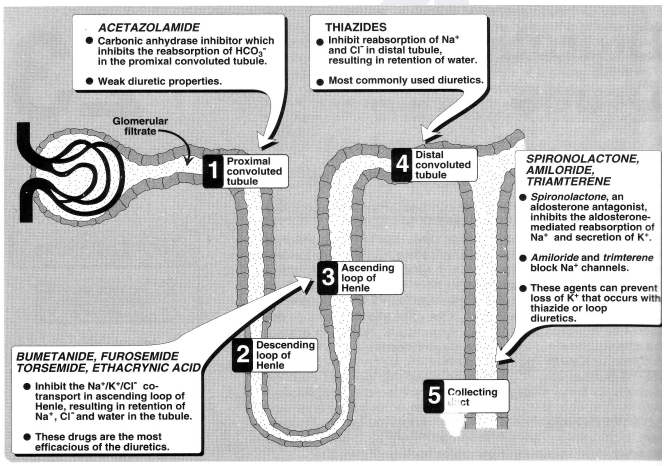


- As in all tubular cells, Na^+/K^+ ATPase is in basolateral memb
- NCC is primary sodium & chloride transporter in

➢ **<u>Cortical collecting duct</u>**: reabsorbs 2-5% Na thus its last tubular site; controlled by aldosterone; here Na reabsorption occurs via channels & accompanied by equal loss K^+ or H^+ ions; primary site of acidification of urine & of K^+ excretion; reabsoprtion of water occurs in medullary collecting tubule under control of ADH

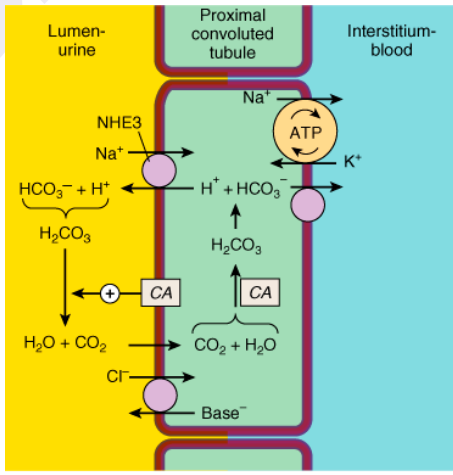


- Inward diffusion of Na+ via ENaC leaves lumen—ve potential, which drives reabsorption of Cl– & efflux of K^+. (R,

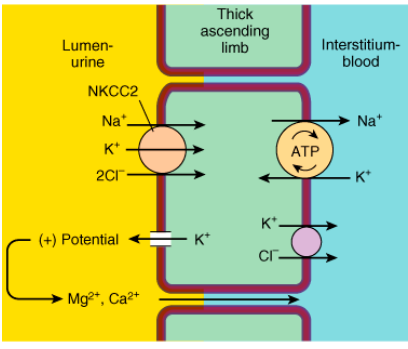


▭ GENERAL AXNS OF DIURETICS: water elimination (–sed renal Na^+ excretion), act on specific ion transporters, reaches lumen by tubular secretion, act on luminal side, so renal func determines resp, resp's depend, in part, on site(s) of axn, have ability to cause hyponatremia, hypovolemia; may undesirably alter even nonelectrolyte balance; main uses: edema, HTN & some other uses

1. **CAI's (Carbonic anhydrase inhibitors):** Acetazolamide, dorzolamide
   - **Acetazolamide**: prototype; acts by inhibiting carbonic anhydrase (CA) (both in brush border & IC CA in PCT); inhibit CA in other pts of body too; lead to Bicarbonate diuresis ▭Metabolic acidosis results; ▭Na^+ presented to CCD-some reabsorbed w/K^+ being excreted so causes sig K^+ loss in urine (hypokalemia); CA inhibition in ciliary epithelium leads to ¬¬secretion of AH (for glaucoma); Causes ***Acidosis of CSF results is hyperventilation & so used in high altitude sickness (mountain sickness); 4 Uses: Glaucoma, Urinary Alkalanization for acidic drug toxicity, Acute of mountain sickness, Sig metabolic alkalosis; Adverse efx: **Cross HSR w/sulfa drugs; Hyperchloremic metabolic acidosis, Renal stones (alkalinization of urine by these drugs cause Ca precipitation & hence stones) & Hypokalemia



2. **Loop diuretics**: inhibit $Na^+/K^+/2Cl^-$ cotransporter (NKCC2)/symporters in ascending limb of loop of Henle to block Na & Cl transport & ▭Na, Cl & fluid excretion; **Furosemide**, ***bumetanide***, ***torsemide***, ***ethacrynic acid***; ***produce massive sodium chloride diuresis, edema fluid rapidly excreted & sig'ly ¬¬BV; Note loop of Henle is diluting segment & blocking it ¬¬of this segment to dilute urine ▭also results in loss of lumen +ve potential (¬¬reabsorption of ions Ca & Mg). ▭*** Ca excretion sig'ly ▭. Again like CA inhibitors, more Na^+ presented to CCD results in loss K^+ & H^+ ▭*** may result in hypokalemic alkalosis; Uses: Tx of edematous states of HF, ascites ie. ***Acute Pulm edema (LV HF), mild-moderate CHF & severe hypercalcemia commonly in malignancy (large doses of furosemide given w/parenteral fluids & electrolytes); Adverse efx: ***Hypokalemia (so give w/K sparing drugs), Hypomagnesemia, hypocalcaemia, Hypokalemic metabolic alkalosis, Hypovolemia, ***Ototoxicity (hearing loss), ANSWER was loop diuretics in pic of Nephron pointing to Loop of Henle, ***cross HSR w/sulfa drugs



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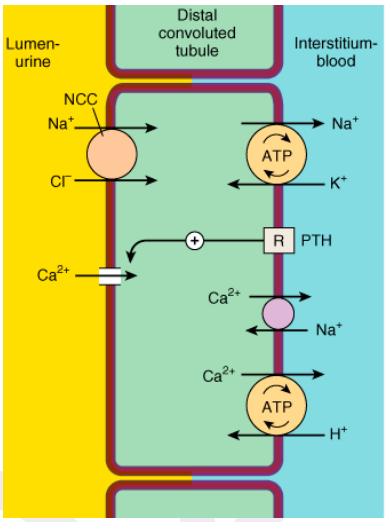
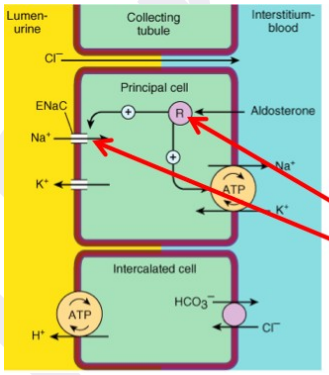
3. **Thiazides**: (Indapamide, Chlorthalidone), **Hydrochlorothiazide**: prototype; inhibit sodium chloride (NCC) transporter in early segment of DCT; cause sustained Na & Cl diuresis, ↓in transport of Na into tubular cell ↓IC Na & this promotes Na-Ca exchange ↑ ***results in ↓reabsorption of Ca from urine so urine Ca^{2+} ↓(opp to that of loop diuretics); +↓BP; for HTN & chronic renal calcium stone (b/c ↓urine [Ca^{2+}]); Adverse efx: severe hyponatremia due to excreting it, Hypokalemia due to ↓intravascular volume so body resp by ↓aldosterone & in turn excreting more K^+, Cross HSR w/sulfa, Hypercalcemia, Hyperuricemia (direct competition of thiazides for urate transport), Hyperlipidemia - serum CH, LDL & Hyperglycemia (diminish insulin secretion & peripheral uptake of glucose)



4. **Potassium/K^+ sparing diuretics**: physio'ally: Inward diffusion of Na^+ via ENaC (epithelial Na^+ channel) leaves lumen –ve potential, which drives reabsorption of Cl– & efflux of K^+; includes **Aldosterone antagonists**: **Spirinolactone & eplerenone**
    - **Spironolactone**: aldosterone antagonist in collecting tubule; binds & blocks aldosterone receptor, these drugs ↓gene expression controlling synthesis of ENaC's & Na^+K^+ATPase; used in hyperAldosteronism, CHF (long term use improves survival in pt's w/LV systolic dysfunc); Gynaecomastia (painful, enlarged breast in male), impotence (Anti-androgenic efx)



- Physiologically: Inward diffusion of Na+ via the epithelial sodium channel (ENaC) leaves a lumen-negative potential, which drives reabsorption of Cl– and efflux of K+.
1. Spironolactone is aldosterone antagonist
2. Amiloride & Triamterene-directly block the Na channels

- Na Channel blockers: **Amiloride & Triamterene (ANSWER)**- competitive inhibitors - directly block epithelial Na channels; Amiloride used in Lithium induced DI
    - **Amiloride**: also used in Little syndrome (HTN, hypokalemia, metabolic alkalosis w/low renin & aldosterone, due to constitutive reabsorption of Na^+, secretion of K^+ & H^+ in collecting duct) b/c directly blocks ENaC immediately* & still K^+ sparing
- **Efx:** ↓sodium excretion, ↓K^+ & H^+ ion excretion, May cause hyperkalemic metabolic acidosis
- Uses: Hypokalemia caused by loop diuretics & thiazides
- Adverse efx: Hyperkalemia, Extreme caution needed when given w/ACE-I (can cause…??),

5. **Osmotic diuretics: Mannitol**: prototype given IV; freely filtered in glomerulus but poorly reabsorbed (remains in lumen); holds water by its osmotic efx; acts on descending limb of Henle's loop & PCT* (where majority of isoosmotic reabsorption occurs); ↓urine volume, also ↓ICP by osmotically extracting water from tissue into blood, similar effect in eye (↓IOP); for Cerebral edema, Acute glaucoma; side efx include HA, N/V; overaggressive tx can cause excessive volume depletion & eventual hypernatremia in pt's; OD = pulm edema, caused by rapid rise in volume that can also ↓overall hydrostatic pressure in vasculature, continued rise in plasma osmolality causes more water & K+ to move out cells & brain ↑ further vol expansion & possible worsening pulm edema (b/c initial intravascular volume expansion), dilutional hyponatremia & metabolic acidosis & hyperkalemia; thus use cautiously in high-risk pt's like those w/CHF or preexisting pulm edema

Imp POINTS:

1. ****Aminoglycosides ↓ototoxicity of furosemide
2. NSAID, beta blockers, ACE inhibitors ↓risk of hyperkalemia seen w/K^+ sparing diuretics

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3. *****K+ sparing diuretics ¬¬digoxin axn where as loop & thiazide diuretics ↓digoxin toxicity
4. *****Probenecid ¬¬efficacy of diuretics by inhibiting their secretion into renal tubule
http://pharmacologycorner.com/video-animation-on-renal-physiology-and-diuretics-mechanism-of-action/

Drug	Mechanisms of Action	Urinary Electrolytes	Blood Chemistry & pH
Acetazolamide Dorzolamide	Inhibition of carbonic anhydrase in PCT	Na K HCO_3	Hypokalemia, acidosis (↓ pH), hyperchloremia
Ethacrynic acid, Furosemide, Torsemide	Inhibition of Na/K/2Cl cotransporter in TAL	Na K Ca Mg Cl ↓HCO_3	Hypokalemia, alkalosis (pH), hypocalcemia hypomagnesemia
Hydrochlorthiazide, Indapamide, Metolazone	Inhibition of Na/Cl cotransporter in DCT	Na K Cl ↓Ca	Hypokalemia, alkalosis (pH), hypercalcemia Hyperuricemia, hyperglycemia
Amiloride, Triamterene Spironolactone	Block Na channels Block aldosterone receptors in CT	Na (small) ↓ K	Hyperkalemia, acidosis (↓pH)

SUMMARY:
Hypokalemia & Metabolic alkalosis seen w/thiazides & loop diuretics
Hypokalemia & Metabolic acidosis seen w/acetazolamide
Frusemide is best for edema
Thiazides best for HTN
Acetazolamide and maniitol best for glaucoma
Mannitol is also best for cerebral edema (never used in cardiac failure)
Thiazides also used as ANTIDIURETICS!!! & causes hypercalcemia
Metalozone effective even in low GFR cases
K sparing diuretics never used alone, rather combined w/frusemide or thiazides w/purpose of preventing K^+ loss in urine
Amiloride is esp used in lithium induced nephrogenic DI & CF
Nephrolitiasis w/hypocalcemia best tx'd w/thiazides
Frusemide causes hypocalcemia & ototoxicity that can be ↓by other drugs like aminoglycosides
Spiranolactone causes Gyancomastia

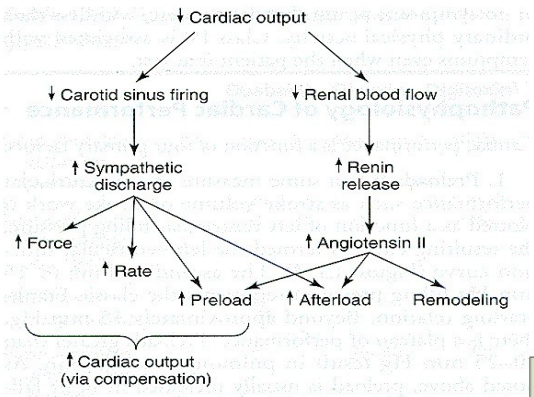
Uses of diuretics:
1. CCF – DOC should be thiazide rather than Loop diuretics.
2. HTN – mild to moderate HTN - diuretics alone or w/combo w/other drugs.
3. Hepatic ascites – Thiazides w/potassium supplements or Thiazides & K-sparing diuretics.
4. Pulm edema of cardiac origin – Loop diuretics.
5. ↓ICP– Osmotic diuretics.
6. Renal edema – Nephrotic syndrome – Thiazide & K-sparing or Loop diuretic & K+ sparing.
7. Chronic renal failure – Loop diuretics.
8. Acute renal failure – Osmotic diuretics.

- **ADH (Antidiuretic Hormone) agonists: Vasopressin & desmopressin**; facilitates water reabsorption from collecting tubule by activation of V_2 receptors (Gs)- ↑cAMP causes insertion of additional aquaporin water channels into luminal memb (of tubule); Used in Neurogenic (pituitary) DI; ¬¬urine volume & ↓its [ ]

- **ADH antagonists: ***Demeclocycline, Conivaptan** (Lithium has ADH antagonistic efx but never used for this purpose); these oppose axns of ADH & other peptides, which act on V_2 receptors; ADH such peptides secreted by certain tumors (ie. small cell carcinoma of lung) & can cause sig water retention & hyponatremia. **SIADH** Tx'd w/demeclocycline & conivaptan
  - Note: Lithium used for tx of Mania can cause Nephrogenic DI (Li interferes w/normal resp to ADH)
  - Rx of Lithium induced DI- Amiloride

L16 Drugs for CCF (Congestive Cardiac Failure)

- **Heart failure**: heart can't provide adequate perfusion of peripheral organs to meet their metabolic requirements; charac'd by: ↓↓CO
  - Systolic dysfunc- ↓↓in cardiac CT
  - Diastolic dysfunc- inadequate filling of ventricles during diastole
  - Acute HF: short-term aim is stabilization by providing symptomatic tx thru IV interventions
  - Chronic HF: management multifaceted, w/long-term aims of: relieving sx, improving hemodynamics, improving QoL & ↓↓mortality
  - Compensation in HF accompanied by ↑SNS, Chronic up-reg of RAAS & efx of aldosterone on heart, vessels & kidney; CHF should be viewed as complex, interrel'd sequence of events involving hemodynamic & neurohormonal events; In failing heart, loss of contractile func ↓↓CO & arterial BP. Baroreceptors sense hemodynamic changes & initiate countermeasures to maintain support of circulatory system. Activated SNS is compensatory mechanism to maintain adequate CO by:
    - ↑myocardial CT & HR (β1-adrenergic receptors)
    - ↑vasomotor tone (α1-adrenergic receptors) to maintain systemic BP
  - Consequences of hyperadrenergic state:
    - Over long term, hyperadrenergic state leads to irreversible myocyte damage, cell death & fibrosis
    - In addition, augmentation in peripheral vasomotor tone ↑LV afterload
    - This places added stress upon LV & ↑in myocardial O_2 demand (ventricular remodeling).
    - frequency & severity of cardiac arrhythmias enhanced in failing heart



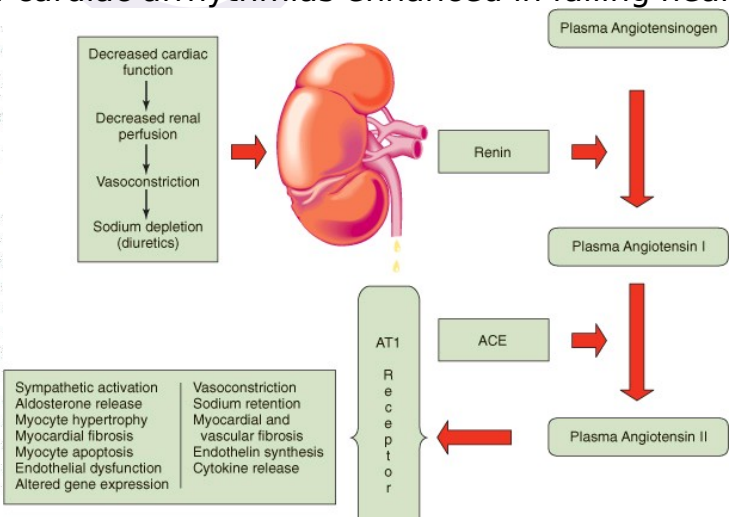
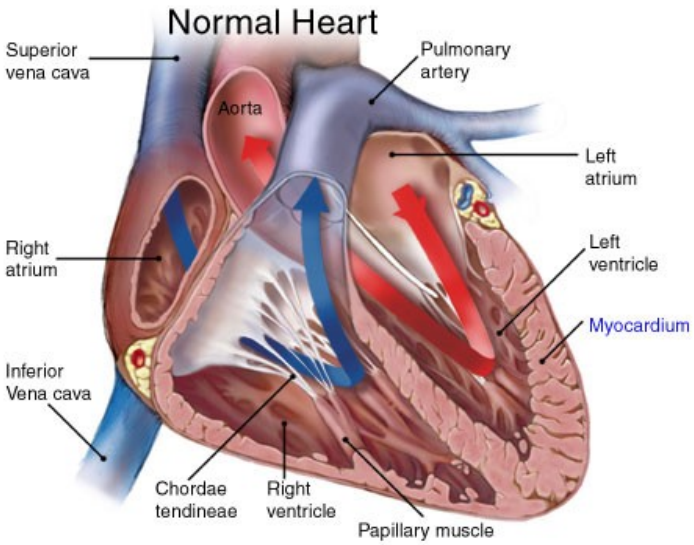
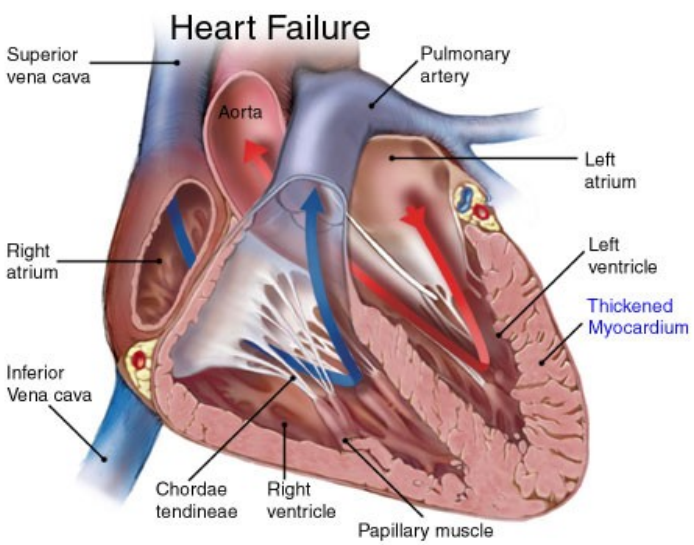


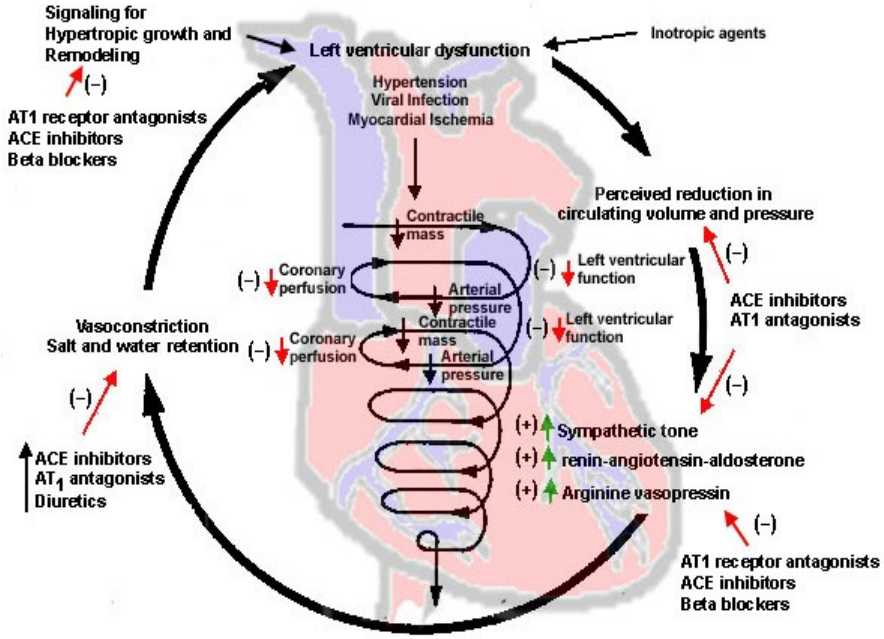
Figure 13–2. Some compensatory responses that occur during congestive heart failure. In addition to the effects shown, angiotensin II increases sympathetic effects by facilitating norepinephrine release.

- RAAS: Baroreceptor mediated activation of SNS leads to ↑in renin release & formed AG II
- AGII acts thru AT1 & AT2 receptors (most axns thru AT1 receptors) ↓ causes vasoconstriction & ↑aldosterone production; so RAS remains most imp target of chronic CHF therapy





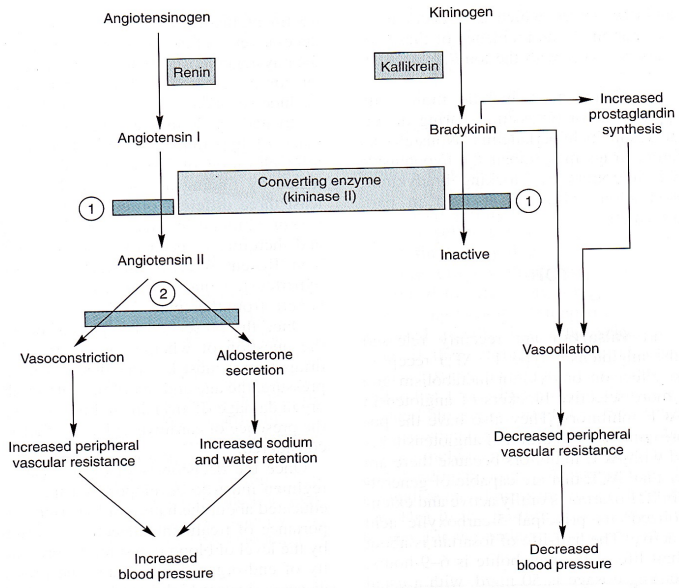
- Goal to alleviate sx, improve QoL, arrest ventricular remodeling, prevent sudden death, reduce cardiac work, w/rest, weight loss, low Na+ diet & drug therapy (diuretics, vasodilators, beta-blockers, digoxin, other cardiac inotropes – dobutamine, milrinone)



▭ ***Diuretics***: useful in ↓↓sx of volume overload by ↓↓EC volume, ↓↓VR; Adverse efx: Both Loop diuretics & thiazides cause hypokalemia

- Loop diuretics: frusemide & bumetanide most affective & commonly used
- Thiazides effective in mild cases ONLY.
- Potassium sparing diuretics: help in ↓↓hypokalemia due to these loop & thiazide diuretics.
  - ***Spironolactone***: Aldosterone inhibitor, minimize K^+ loss, prevent Na^+ & water retention, endothelial dysfunc & myocardial fibrosis; added to loop diuretics to modestly enhance diuresis; more imp'ly, improve survival

▭ ***ACE I's for CCF***: block ACE ▭ ↓↓AGII, ↓↓aldosterone, ↓↓fluid retention, ↑vasodilation, ↓↓arterial resistance (AL), ↓↓venous tension (PL), slows cardiac remodelling; **Captopril, Lisinopril, Enalapril, Ramipril, Quinapril**; Adverse efx: Cough (Bradykinin), postural hypotension (vasodilation by bradykinin), hyperkalemia (possible DI's?), contraindicated in pregnant women (1st trimester), rarely angioedema (facial swelling/puffiness)



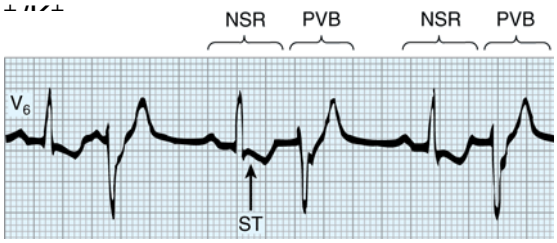
▫ ***ARB's***: competitive antagonists of AGII, no ACE inhibition (so no cough); Losartan, Irbesartan, Candesartan

▫ ***Vasodilators***: venodilators, arteriolar dilators, or both

- **Venodilators**: **Isosorbide dinitrate**: ↓↓PL; for Acute & chronic HF & angina
- **Arteriolar dilators (ANSWER)**: **Hydralazine**: ↓↓BP & AL; use of it w/nitrates (BiDil) have ↓↓mortality
- **Sodium nitroprusside**: both arteriolar & venodilator for hypertensive emergencies (malignant HTN)

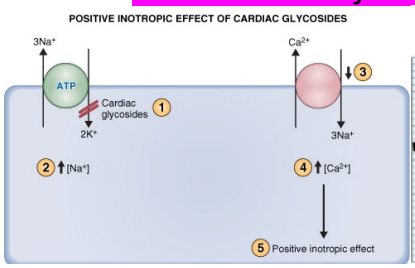
▫ ***Inotropes***: ↑FOC, ↑IC Ca^{2+}

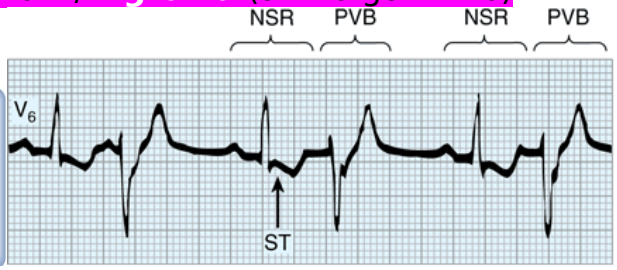
- **Cardiac glycosides**: **Digitalis** (from foxglove plant), **Digitoxin** & **Digoxin**
  - ****Digoxin:** only cardiac glycoside available for use in US (1) for CCF b/c ↑cardiac CT (+ve inotropic effect) –inhibits Na/K ATPase pump ↑IC $[Na^+]$– eventually ↑cytosolic Ca^{2+} & (2) ↓↓rapid ventricular rate in atrial flutter & fib by enhancing vagal tone (cardiac parasympathomimetic efx) slows sinus HR & AV conduction; Uses: Severe LV systolic dysfunc (CCF), Manages pt's w/chronic Atrial fib; Note: can't stop progressing pathological changes causing HF & doesn't prolong life in pt's w/CHF
    - *Toxicity*: b/c narrow therapeutic range 0.5-1.5 ng/ml, must be monitored; Malaise, confusion, depression, vertigo, vision (abnormalities in color vision); Anorexia, nausea, intestinal cramping, diarrhea; Palpitations, syncope, arrhythmias, bradycardia, AV node block, tachycardia. On EKG Bigeminy (Premature Ventricular Beats); contraindicated in WPW syndrome b/c ↑anterograde conduction across accessory pathways that bypass AV node ▫ v fib – MOST DEATHS in WPW syndrome due to digoxin use; also contraindicated in v fib; factors/drugs ↑toxicity –
      - B/c K+ competes w/digoxin for binding sites on Na^+/K^+ ATPase, hypokalemia results in ↑digoxin binding & thereby enhances its therapeutic & toxic efx.
      - Hypercalcemia enhances digitalis toxicity as it ↑in IC Ca^{2+}
      - Hypomagnesemia also sensitizes heart to digitalis-induced arrhythmias



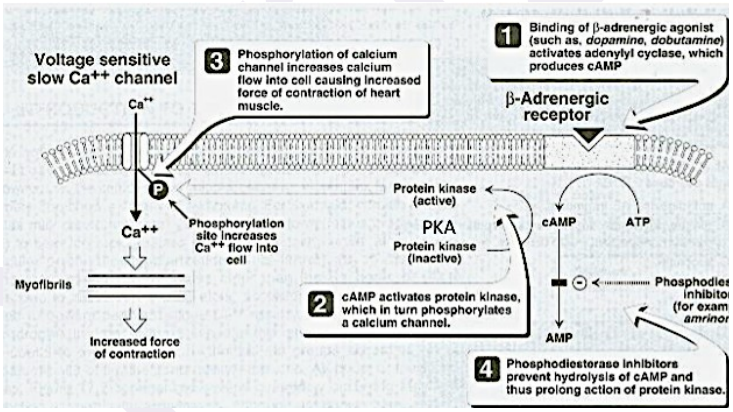
- Ex: 96 y/o woman to ER w/complaints of abdominal pain, dizziness, confusion & double vision for 5 days. She was discharged from hospital just 4 days ago when she was dx'd w/atrial fib & tx'd w/digoxin to control of tachycardia. On admission her plasma digoxin lvls was 2 ng/mL. PMH: HTN, atrial fib, CAD, stroke, CHF. Meds: Metoprolol, Digoxin, ASA, lisinopril, Furosemide, Coumadin, omeprazole

- **loop & thiazide diuretics*****, K+ depleting diuretics - ?? Quinidine, Amiodarone & verapamil ↑digoxin plasma lvls (by depressing renal digoxin clearance)
  - Management of toxicity: K^+ supplementation or spironolactone (K^+ sparing diuretics ↓digoxin axn), For digoxin induced arrythmias: lidocaine, Phenytoin or propranolol; Severe toxicity tx'd w/**Digibind** (anti-digoxin Ab)

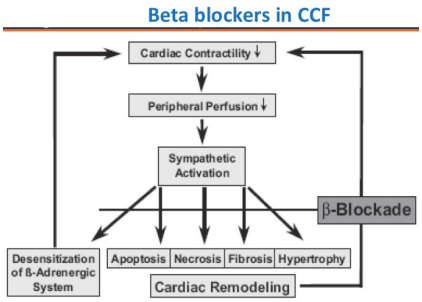




- **DA**: acts at variety of receptors (dose dependent)
- **β-adrenergic agonist**: **Dobutamine**: **(β1 stimulant)** b1 >b2, a ↑β-adrenergic receptors & produces +ve inotropic resp; useful in acute HF w/marked systolic dysfunc



- **PDE Inhibitors**: Inamrinone (amrinone) & Milrinone (ANSWER) (bipyridines); inhibit PDE (Phosphodiesterase) ↓ causing ↑IC [cAMP] ↓↑Ca^{2+} entry into cell; ↑myocardial CT by ↑Ca^{2+} influx during AP; also have vasodilating effect; selective for PDE isoenzyme-3 (found in cardiac & smooth m)
- Niseritide/recombinant **human BNP:** for tx of *acute* decompensated CHF; binds receptors in vasculature, kidney & other organs ↓potent vasodilation by ↑cGMP; effective in HF b/c ↓PL, AL & diuresis; ADR- hypotension
- **β-blockers**: slow HR & ↓myocardial O_2 consumption; also ↓remodeling; Carvedilol & Metoprolol MC'ly used for CCF amongst β-blockers; recent ↓mortality in pt's w/these drugs



Conclusion

- ACE inhibitors are cornerstone in tx of CCF, helps in long term survival
- Digoxin useful in CCF w/systolic dysfunc
- Loop Diuretics very useful agents for ↓pulm edema, K sparing diuretics have long term benefits
- Beta blockers used in selected pt's (mild/moderate failure, low dose)

35 from Autonomics, Pharmacodynamics & Pharmacokinetics
15-18 Cardiovascular – HTN, Heart Failure, Diuretics

L1 Antianginal drugs

- **Angina pectoris**: form of paroxysmal (sudden onset) chest pain felt beneath sternum & commonly radiates down L arm &/or shoulder; can also radiate or originate in neck or upper back as well; cardinal sign of CAD (ischemic heart dis); **caused by imbalance of O_2 supply vs demand**, resulting in myocardial ischemia

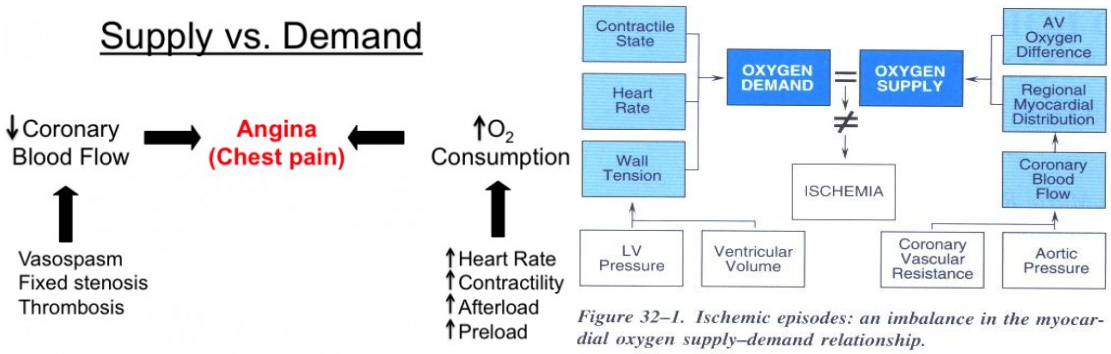
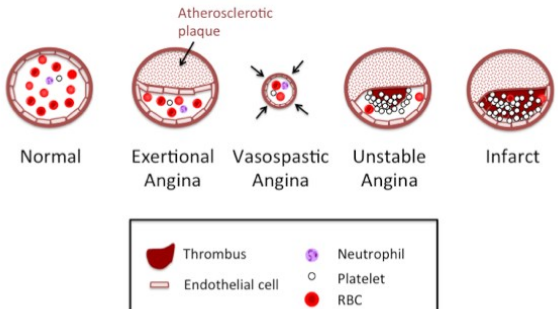


Figure 32–1. Ischemic episodes: an imbalance in the myocardial oxygen supply–demand relationship.

- **Ischemia Heart Dis classification:** Know Mechanism of anti-angina for Nitrates, CCBs & B-Blockers

Coronary artery pathology in Ischemic heart disease

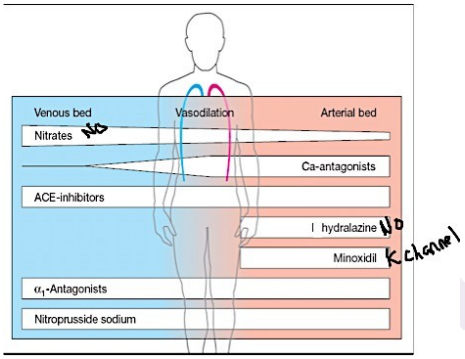


Want to treat underlying factors! (PL, AL, Antiplatelet)

1. **Typical/Classical/Exertional Angina**: when chronic Coronary A Occlusion due to AS, occurs if coronary a is narrowed ↓BF thru narrowed a's cannot meet ↓O_2 need; sx occur w/ ↓emo'al or physical exertion
2. **Coronary Vasospasm (Prinzmetal's/Rest/Variant Angina):** due to reversible spasm of large coronary a's, at AS plaque site; anytime, irrespective of physical/emo'al exertion; use vasodilators – CCBs or Nitro b/c these ↓O_2 delivery

3. ACS's (Acute Coronary Syndromes):

- **Unstable Angina**: due to ruptured plaque & platelet aggregation; charac'd by ↓frequency & severity, from combo of AS plaques & vasopasm; anginal sx occur even at rest; might signal impeding MI & tx'd as medical emergency
- **NSTEMI (Non-transmural infarct)**
- **STEMI (Transmural infarct)**



Capacitance of blood **vessels** describes distensibility of blood **vessels** w/in body; it's inversely proportional to elasticity.

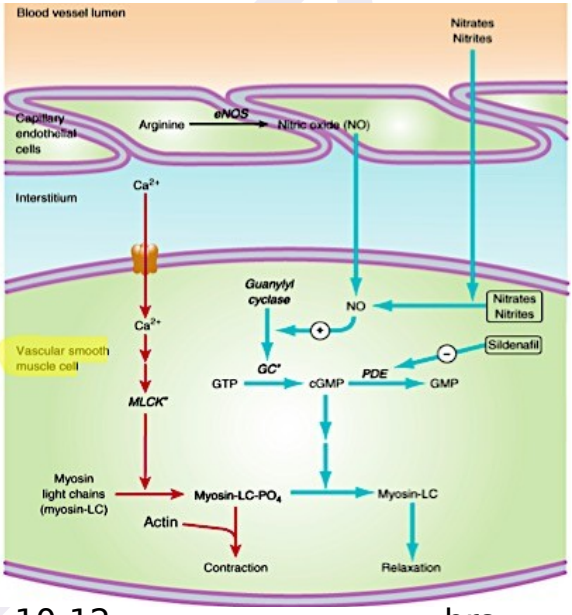
Thus, greater amt of elastic tissue in blood **vessel** = greater elasticity, & smaller ..

↓ **Strategies for ANGINA tx:** inadequate coronary O_2 delivery for myocardial O_2 needs; corrected by 2 ways:

1. ↓O_2 delivery by vasodilators: Nitrates (& CCB's) **may also ↑ myocardial O_2 delivery in variant angina by reversing coronary arterial spasm**
   - **Nitrates**: prefer v's but some act on a's; powerful vasodilators release NO/EDGF (NO pathway) w/GC (guanyl cyclase) converts GTP to ↓ cGMP ↓ smooth m relaxation; effective due to axn on capacitance vessels to ↑↓cardiac PL, +dilate collateral coronary vessels; **treat vasospastic angina*****
     - Altho **venous efx predominate at low doses**, ***nitroglycerin*** produces **dose-rel'd dilation of BOTH arterial & venous beds.** Venodilation MORE DOMINANT promotes peripheral pooling of blood & ↑↓VR, ↑↓LV EDP (↓↓ **PL**). Arteriolar relaxation

↓systemic vascular resistance & arterial pressure (↓AL) ↓**Myocardial O_2 consumption or demand ↓ by both arterial & venous efx** & get more favorable supply-demand ratio; may cause redistribution of coronary BF from N to ischemic tissue

- **Nitroglycerine (GTN/glycerol trinitrate):** MC'ly used short acting & sublingually, rapidly absorbed gives ~instantaneous high [serum]'s; also available as transdermal (ointment/ patch); not orally b/c ~completely metabolized by liver (high 1st pass metabolism), low oral bioavailability 10-20%
- **Isosorbide dinitrate:** long acting for chronic use, better oral
- **Isosorbide Mononitrate (ANSWER)**: long acting for chronic use, better oral
- Rmr other drugs that trigger NO formation: ACh, Bradykinin, histamine & serotonin
  - **Contraction** of vascular SM **triggered by Ca^{2+} influx** ↓Ca^{2+} combines w/calmodulin to form complex that converts enzyme myosin light chain kinase to active MLCK ↓ phosphorylates myosin light chains, initiating interaxn of myosin w/actin ↓**Nitrates via cGMP *dephosphorylates* Myosin light chains to prevent interaxn w/actin ↓ relaxation! Ie. Histamine, nitroprusside, Hydralazine, ACh – all act by releasing NO; + PDE inhibitors have interaxn w/Nitrates à both ↑ cGMP**



- ****NITRATES Adverse efx & contraindication**: headache (2% b/c vasodilate extra cranial vessels), tolerance if doses given w/in 10-12 hrs, reflex tachycardia, CONTRAINDICATED w/type 5 PDE inhibitors (sildenafil for erectile dysfunc) b/c these potentiate axn for angina by inhibiting PDE5 that metabolizes cGMP in SM ↓ ↓cGMP in erectile SM relaxes it allowing greater inflow of blood w/better & prolonged erection but this also happens in vascular SM ↓ combo of nitrates (thru ↓cGMP (ANSWER)) causes synergistic relaxation of vascular SM w/potentially dangerous hypotension & inadequate perfusion of critical organs ↓thus, co-admin w/in 24 hrs of sildenafil produces severe hypotension via ↓vasodilation****

– **CCB's (Calcium channel blockers):** block VG L-type Ca^{2+} channels in cardiac & smooth m; *Note Imp differences in vascular selectivity exist among these CCB's (note below)

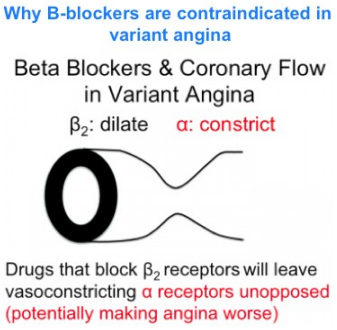
- **DHP (Dihydropyridines) aka Nifedipine, Amlodipine,** Nicardipine, **Nimodipine:** have greater ratio of vascular SM efx relative to cardiac efx than nonDHP's; may differ in their potency in diff vascular beds; ex. nimodipine esp selective for cerebral blood vessels so used in SAH
  - **Nifedipine**: rmr DHP, so more vascular selective, for classic angina, prinzmetal's & HTN; **ADR: flushing, headache, hypotension (w/reflex tachycardia), peripheral edema**
    - **Classic angina**: **dilates peripheral *arterioles*** which (↓ **AL**) against which heart works ↓↓heart work ↓ **myocardial energy consumption & O_2 requirements**
    - **Prinzmetal's/Vasospastic angina**: **dilates main coronary a's & its arterioles**, both in normal & ischemic regions; can also be caused by DHE
    - **HTN**: **directly dilates peripheral resistance arterioles**, leading to ↓TPR & ↓arterial BP
  - **Amlodipine**: **esp cause ankle swelling** (peripheral pooling)

- ❖ **Nimodipine (final answer)**: cerebro-selective vasodilator aka esp selective for cerebral vessels so used in SAH where body compensates to hemorrhage by vasoconstriction (could cause hypoxia & ischemia b/c constriction & no BF); no other DHPs used for SAH!

- **Non DHP's (Verapamil, Diltiazem):** affect heart more than vessels, prefer L type Ca^{2+} channels
  - ❖ **Verapamil**: nonDHP CCB (prefer L type Ca^{2+} channels in <3), ↓↓AV conduction; used for PSVT*, chronic atrial fib/flutter*, vasospastic & exertional angina
    - **Paroxysmal Supraventricular Tachycardia (PSVT)**: DOC for prophylaxis or chronically, drug of 2nd choice after adenosine for acute tx
    - **Control of ventricular rate in chronic atrial fib/flutter**.
    - **Vasospastic & Exertional angina**: as prophylactic & tried in refractory cases of unstable angina, but otherwise not drugs of 1st or 2nd choice in this condition
    - **HTN:** preferred in HTN
    - ***Contraindications: DON'T GIVE in Severe hypotension, 2nd or 3rd degree AV block, Cardiogenic shock, & Severe CHF (b/c don't want to ↓↓FOC even more); **Side efx:** Constipation, Bradycardia (b/c afx heart), AV conduction block; **DI w/digoxin (↑↑ digoxin lvls by blocking p-Glycoprotein channels)**
  - ❖ **Diltiazem**: used for **Vasospastic & Classic Angina** (prophylactic), **HTN**, & **Control of ventricular rate** in atrial fib/flutter; **Side efx: Hypotension, AV conduction block, Bradycardia**, Constipation

– Myocardial revascularisation (Coronary angioplasty)

2. By ↓↓O_2 requirement
   – **β-adrenergic blockers (Non selective: Propranolol & b1 or cardioselective: Atenolol, Metoprolol (ABEAM))** – ↓↓workload being done by blocking cardiac β1 receptors to produce ↓↓ **HR** (so improve tolerance), ↓↓ **CT** & ↓↓ **BP**; combo of these efx ↓↓ **myocardial O_2 demand at rest & in exercise** (**don't have any efx on myocardial O_2 supply)**; for **Angina of effort (classic angina)** but **NOT** vasospastic angina; **used in combo w/other antianginals (nitrates & CCB which cause tachycardia)**



   – **Contraindications: in Vasospastic Angina** (b/c **blocking B_2 ↑↑ more constriction, when vasospasm already problem** (unopposed α affect) Not even cardio-selective if we don't have to. (does not only affect B1)**, & in WPW syndrome (b/c drug blocks AV node b receptors)
   – **tx of Beta Blocker OD: (**blocked Gs ↓↓ ↑↑cAMP) so give **Glucagon b/c has its own cardiac receptors which ↑↑ IC cAMP)**

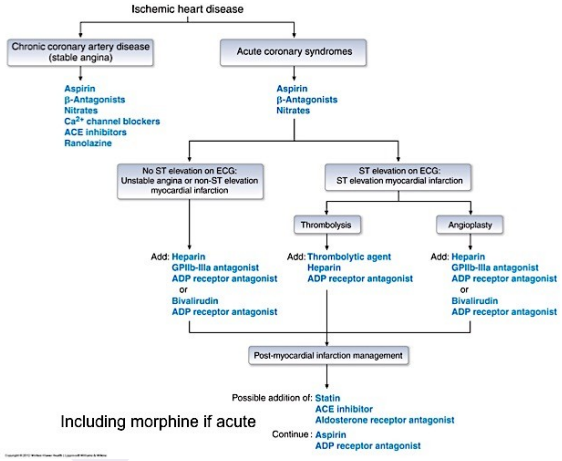
3. Antiplatelet drugs: Low dose aspirin, or Abciximab
4. **Ranolazine**: not 1st line, new alternate drug for angina ↓↓CT by blocking late Na^+ current (in phase 2) in <3 ↓↓ facilitates Ca^{2+} entry into cell via sodium-calcium exchanger ↓↓ efficiency of O_2 utilization by partial **FA oxidation inhibitors (pFOX inhibitors);** newer drug for those who can't tolerate other antianginals

➢ **Useful drug combo = Nitrate + b blocker**: diff mechanisms of axn cause additive efficacy & ↓↓each others unwanted side efx; **β blocker prevents reflex tachycardia & +ve inotropy** (due to nitrates) & ↓↓cardiac workload; adding **nitrate ↑↑ |--| EDV** (due to β blockers) by ↓↓venodilation (↓↓venous capacitance)

➢ **Tx of various types of angina recommended by AHA**
  - **Acute Emergency tx of angina: MI = MONA**
    - *Oxygen*: ↓↓ST elevation & limits ischemic injury

- *Nitroglycerin*: causes coronary dilation, greater perfusion, ↓↓PL & AL
- *Aspirin*: low dose only, 160-325 mg orally ASAP, chewed absorbed faster & preferred; Anti-platelet
- *Morphine*: opioid ↓↓central anxiety & relives pain (afx systolic output & pressures) that afx HR, CT & SBP which ↓O_2 demand; rmr to monitor pain & vitals b/c can cause respiratory depression or hypotension; +produces venodilation ↓↓VR & PL (O_2 demand); analgesic for MI (CNS depressant);

- **Chronic Stable Angina of Effort**: mono or combo antinginal therapy w/Long-acting Nitrates (isosorbate mononitrate & dinitrate), CCB's, b-blockers, alternative 2nd line drug Ranolazine; HOWEVER more complete tx includes: ABCDE
  - **A**spirin, **A**CE inhibitors (helps against cardiac remodeling) & **A**ntianginals (listed above)
  - **B**eta blocker & **B**P control
  - **C**holesterol drug (Lipid lowering drugs – management) & **C**igarette cessation
  - **D**iabetes & **D**iet management
  - **E**xercise & **E**ducation
- **Vasospastic (Variant) Angina**: use **mono or combo therapy w/: Nitrates, CCB's,** NOT Beta-blockers
- **Unstable Angina Management:**
  - **Antiplatelet agents (aspirin, Plavix, Gp3b-2a inhibitors)** (325 mg aspirin initially) b/c in unstable, thrombus full of platelets partially occludes vessel ↓ at ↓risk MI or non-STEMI
  - **Anticoagulants (heparin)**
  - **Nitroglycerin** (sublingually or by buccal spray; IV if pain persists; topical or oral for maintenance)
  - **Beta-blocker** (↓↓HR to 50-60 beats/min; caution in pt's w/evidence of HF)
  - **ACE-inhibitor**
  - **Statin or other lipid-lowering agent if applicable** (prophylactic therapy) for maintenance
  - **In high-risk pt's: catheter-based myocardial revascularization (PCI)**
  - **Thrombolytics contraindicated in absence of ST segment elevation**; streptokinase or TPA – choose for STEMI (not for NSTEMI, b/c absent ST segment elevation)



Bivalirudin: specific & reversible direct

L2 Antiasthmatics

Receptor Physiology of Bronchus

- Innervation: M_3 Receptors located in bronchial smooth m, β_2 Receptors in airways.
- Stimulation of cholinergic receptors (ACh, $M_{3\ receptors}$) = bronchoconstriction; Opposing force is Muscarinics à cholinergic M3 cause bronchoconstriction
- Stimulation of adrenergic receptors (β_2 receptors) = bronchodilation; In bronchus, have B_2 (bronchodilation) à adenylyl cyclase à ↓cAMP – cause smooth m relaxation

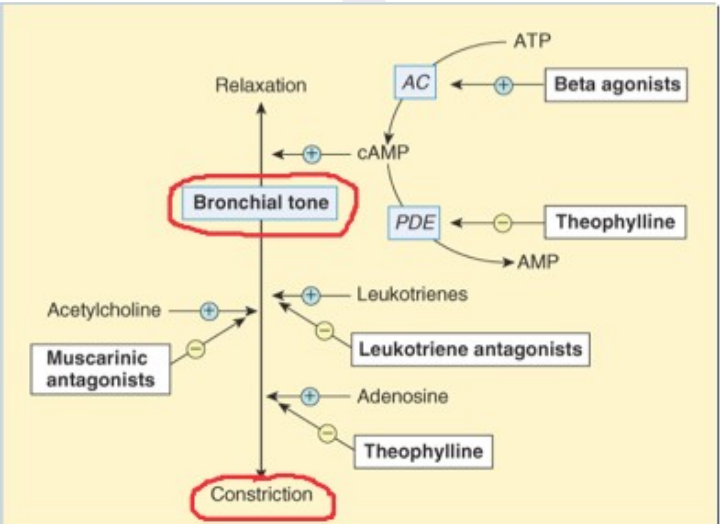
- Axn of inflammatory mediators on bronchial smooth m - bronchoconstriction
- In asthma there is lung changes – main pathology is bronchoconstriction (narrowing)
- In allergies à release of inflammatory mediators (PG's, LT's, Histamine) à also mediate bronchial smooth m; In bronchus the important one are **leukotrienes**. (LTs)
- Drugs we have that antagonize histamine do not really help asthma much.

4 features of Bronchial Asthma

1. **CF's:** recurrent bouts of SOB, chest tightness, & wheezing, often associated w/coughing; Cough not always pt of asthma. Wheezing dx'ic – sign in a young child (they don't complain about other sx). Reversible bronchoconstriction – can be reversed, so treated easily
1. **Physiologic features:** marked ⬇bronchial responsiveness to inhaled stimuli leading to widespread, Reversible bronchoconstriction ;
1. **Pathologic features:** lymphocytic, eosinophilic Inflammation of bronchial mucosa causing "remodeling" of bronchial wall, hyperplasia of bronchial vasculature, smooth m, secretory glands & goblet cells
1. **Immunologic features:** direct correl'n btwn IgE lvls & prevalence of Asthma we don't deal w/this pt well. But there's new drug **mab** (**Monoclonal Ab**)

Clinical classification of drugs

- Relievers/Bronchodilators: help immediate complication. (Asthma attacks are on & off)
  - PG's & LT's come from arachadonic acid.
  - Arachadonic acid (from cell memb) produce **LT's w/help of LOX** & PG's from COX. PG's (Prostacyclin, PGE, PGF)
  - **Ppl using NSAIDs** à **inhibit COX (stop fever & inflammation)** à **but by doing so ⁊ LT's b/c there's more Arachadonic acids being acted on by Lipoxygenase** à **more LT's (Bronchoconstriction) – diversion of AA. THUS NSAIDS are precipitating factor for Asthma**. Avoid NSAIDs in Asthmatic pt's
  - **Adenosine** cause constriction. **cAMP causes relaxation**. – can use a **B agonist. Or can use Phosphodiesterase Inhibitors** (Type 5 PDE)
  - **Theophylline** – coffee, tea à inhibit PDE à ⬇cAMP à relaxation. (same as β-agonist)
  - But also acts as anti Adenosine.
  - **Muscarinic antagonist:** ipratropium bromide, inhibit constriction (relax)
  - LT antagonists – inhibit inflammation but can also afx



- **Adrenergic agonists (B2 agonist): MOA:** stimulation of β_2 receptors ⬇ cAMP ⬇↓m tone ⬇bronchial smooth m relaxation; Albuterol, Terbutaline (selective b2 agonist), Salmeterol, Formeterol; side efx: tremor, hypokalemia, tachycardia, headache. Inhalation makes this not happen as much

- **Short acting (SABA) eg: Albuterol/Salbutamol:** used **only** for symptomatic relief in acute management; given for everybody, no matter how severe, in immediate attacks. (B2 agonist) – cause bronchodilation; relieves sx immediately. (inhalation); Short-acting beta-2 agonist w/short duration used As-needed in maintenance of chronic asthma & *tx of acute asthma b/c of its quick onset of axn; chances of tolerance dev't is higher*
- **Long acting (LABA) eg: Salmeterol**: used for prophylaxis: long-acting beta-2 agonist, Duration 12 hours; *Used for Prophylaxis* (inhalation); *Not used for tx of acute asthma due to delayed onset of axn; Chances of tolerance development is lesser; prevents* Mucocillary axn
- **Adverse drug rxn:** tolerance, fine tremors, palpitation, dizziness, restlessness, agitation, hypokalemia
- **Inhaled β_2 Agonists have minimal or no adverse drug rxns**
- Agonists à cause downregulation. Antagonists cause upreg
- Inhalation can cause same side efx – but much less than systemic delivery (IV)

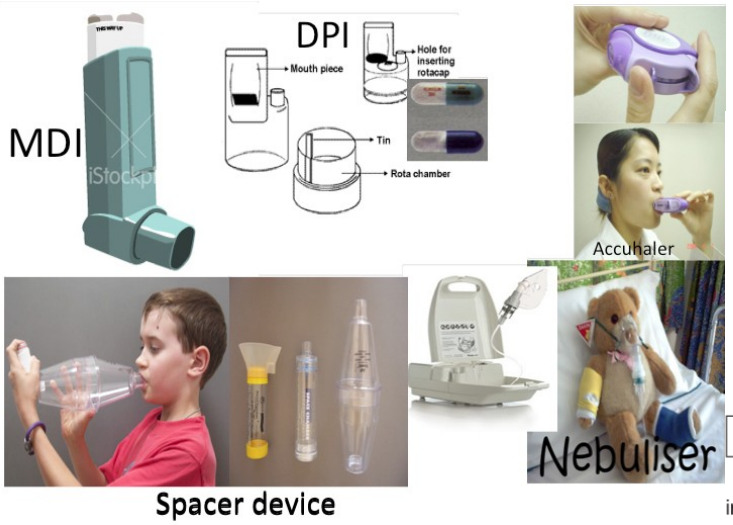
- **Methylxanthines**: **Theophylline: given orally**; inhibit PDE ↓ cAMP [ATP ↓ cAMP ↓ 5-AMP] +[GTP ↓ cGMP ↓ 5-GMP]; **Bronchodilator**, but CNS stimulant - insomnia, tremor, convulsions; & in Heart- +ve chronotropic & inotropic efx; also Weak vasodilator, Weak diuretic
  - **Aminophylline** – not as good any more but another drug that stops PDE.
  - Narrow therapeutic margin - bronchodilator efx at 5-20 mg/L : ↑side efx when give >25mg/L thus needs drug monitoring (TDM); eliminated by CYP450 enzymes in liver so can be **substrate for drug inducers/inhibitors** à drug **affected by P450 inducers** (rifampin, barbs, phenytoin, Carbamazepine, alcohol, GC's) **or inhibitors** (Cimitidine, SSRIs, KTZ, macrolides, antibiotics, Grape fruit juice); can be used as last resort à add on (**adjuvant**)
  - In asthma - Slow release theophylline useful in nocturnal asthma, as add on drug, where inhaled steroid plus beta agonists are ineffective
  - Side efx: Anxiety, **tachycardia**, insomnia, tremors, Vomiting, diuresis, Arrythmia, shock, convulsions all b/c ↑cAMP
- **Muscarinic antagonists**: **Ipratropium bromide & Tiotropium**; ↑mucociliary clearance, used as solutions in nebulisers or inhalers, used in COPD***; also used as adjuvant to β_2 agonists & corticosteroids in Asthma
  - ***Ipratropium bromide*** **(ANSWER)** (Muscarinic blocker) à for COPD as opposed to salmeterol; inhaled; short acting, slower resp
  - ***Tiotropium****:* long-acting muscarinic antagonist for 24 hr

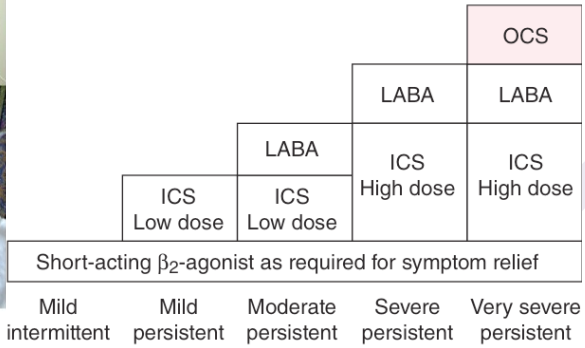
- Controllers (¬¬inflammation)
  - **GC's (Glucocorticoids)**: only anti-inflammatory efx, no *direct* bronchodilator efx (indirect); no role in tx of *acute* bronchoconstriction; intermediate steps Arachadonic acids intermediates on way to PG's & LT's affected by GC's; Eventually have to give steroids – ¬¬inflammation (but not immediately); modulation of cytokine & chemokine production, inhibit eicosanoid synthesis, inhibit accumulation of mast cells, ¬¬vascular permeability; axns: ¬¬Bronchial hyperactivity, ¬¬Mucosal edema & ↑**responsiveness of beta receptors on airway*** [Use steroids in asthma à above all efx. ¬¬ responsiveness of beta receptors to any EPI in body or any Beta agonists we give (Albuterol, EPI, Salmeterol).]**
  - **Inhaled Cortico Steroids (ICS):** very few adverse efx such as: Dysphonia (more around n's that innervate m's of speech – due to myopathy of laryngeal m's & mucosal irritation) & **Oropharyngeal Candidiasis (via immunosuppression) can be prevented by advising pt's to gargle mouth w/saline water; high topical & low systemic activity
    - Beclometha**sone**
    - Budesonide*** WILL BE TESTED

    - Flutica**sone**
    - Triamcino**lone**
- **Systemic Cortico Steroids:** >>systemic side efx; for severe chronic asthmas – recurrences: prednisolone oral, Status asthmaticus (**Status = Severe & Acute, must be both** (like Status epilepticus); ie. **Hydrocortisone i.v**, **Prednisolone oral**
- **LT receptor antagonists**: **Montelukast (kids >1), Zafirlukast (kids <5)**; competitively block LTD_4, LTE_4 receptors to block bronchoconstriction, ↓↓edema & ↓↓mucus production; **for Prophylaxis & chronic asthma; Lukast** à block LT receptors à cause bronchodilation by blocking.
- **LT synthesis inhibitor**: **Zileuton**: 5-LOX inhibitor so ↓↓ **LT synthesis**; for **Aspirin induced asthma**-but Toxicity: Elevation of liver enzymes; block COX so LOX breaks arachadonic acid to more LT'sà so Zileuton would be DOC; Added for last resort options: not as great as what emphasized. Efficacy not great so must wait & watch (take time); lot of off label uses. – reduce LT's
- **Mast cell stabilizers**: **Cromolyn** & **Nedocromil** (Sodium cromoglycate, Nedocromil Sodium); not bronchodilators & don't cause smooth m relaxation; only anti-inflammatory efx; stabilize mast cell from degranulation & inhibit further release of inflammatory mediators from mast cell; given orally & usually very safe, poor bioavailability; for prophylaxis of asthma, allergic rhinitis & conjunctivitis
    - Mast cell is mediator of inflammation à release Histamine; drugs stabilize mast cell à**prevent disintegration** of mast cell (these drugs do not allow mast cell to degranulate) à **no Bronchodilation associated**. Just alternative drugs. Not great.
    - Oral route for rhinitis & conjunctivitis –inhalational route will not help these.
- **Anti-IgE monoclonal Ab**: **Omalizumab**: new humanized monoclonal Ab to human IgE; **inhibits binding of IgE to mast cells**; prevents release of mediators **for Prophylaxis of asthma**

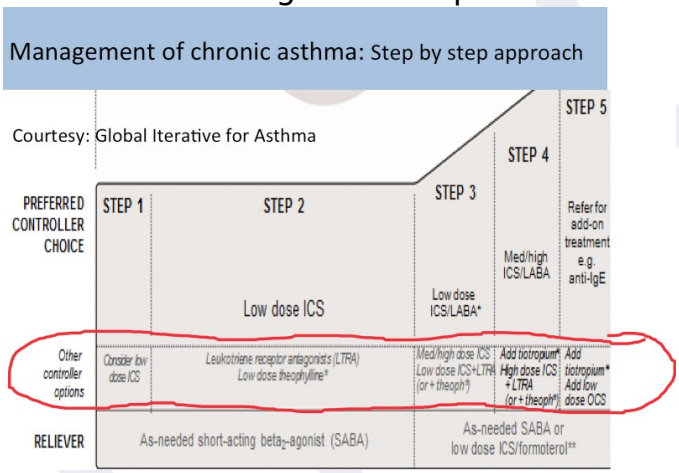
Mode of delivery of drugs

- Oral or IV route (Systemic delivery): Very uncommon
- Inhalation route (Aerosol delivery): MC
    - High local (bronchial tree) concentration of drug
    - Low systemic delivery of drugs
    - Sig'ly less side efx: **adv of inhalation**: b/c it is such local affect*** (**test question**)
- Types of inhalers:
    - Metered dose inhalers (MDI), where metered dose is delivered from canister in form of spray
    - Dry powder inhaler (DPI), where active drug is in form of fine powder which has to be inhaled
    - Nebulizer – used to think it delivered better than MDI but this is not true; they're equally effective; will still be used on COPD, for Children – easier using nebulizer b/c MDI takes coordination.
    - Spacer – allow you to inhale at your own time. You press at your own time & you inhale at your own time. Don't need to coordinate movement.





- Mild intermittent – someone who get it once in a while.
- Persistent – frequent attacks.
- Pt's categorized. Mild/moderate/severe – based on how often, how severe attacks are, how responsive to drugs. (no direct criterion)
- No matter what you are, **Albuterol** is short term relief à B2 agonist.
- If they don't respond – add **inhalational corticosteroids (ICS)**.
- Give albuterol to begin. Then #s of attacks ⥥as child gets older – add in ICS. Once you start ICS – must be given months to yrs (**ICS is prophylactic**) – not used for immediate relief.
- **Steroid receptors are inside cell and cause gene transcription.** à **takes time. Not immediate.**
- If getting worse, when steroids are no longer helping (LABA = Long Acting Beta Agonist)
- **Salmeterol** – long acting. But still give albuterol for emergency attacks.
- **OCS** = Oral Corticosteroids. à Very bitter drug.
- Dr. Gowda gave example of a child returning back to mild intermediate after OCS tx.



- Same chart & tx as last slide. (top & bottom are same as before)
- But red is new: Physicians have right to choose diff drug tx. Do have a choice. (these drugs not very good)
- Long term corticosteroids – can lead to cushings à but inhalation acts so locally it is very rare.

➢ **Acute, Severe Status Asthmatics:** could be brought on by Emotion/stress: asthma exacerbations (usually triggered by viral URIs) are periods of acute worsening of asthma sx that may be life-threatening. w/Sx: ⥥dyspnea, wheezing, & chest tightness; PE w/pulsus paradoxus, tachypnea, tachycardia; Pulm func test w/¬¬FEV1 & PEF; Hypoxemia & Pco2 usually ¬¬due to hyperventilation. Normal or rising Pco2 can signal impending respiratory failure.

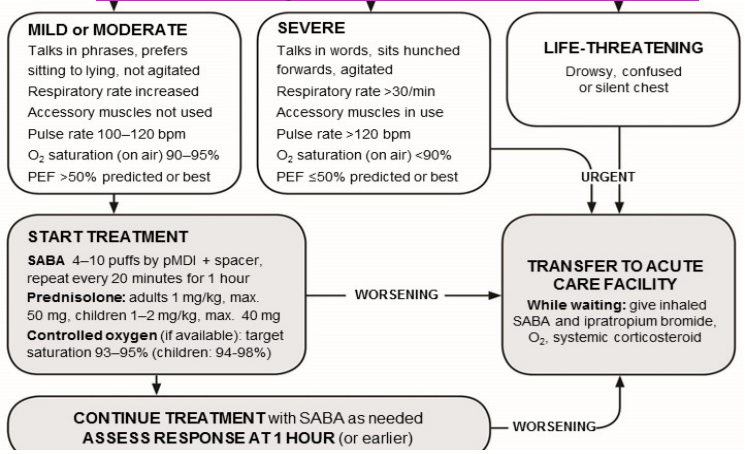
- **PEF(R) = peak expiratory flow rate**; person's max speed of expiration, as measured w/**peak flow** meter, small, hand-held device used to monitor person's ability to breathe out air.

Management of Status Asthmaticus

- High doses of **SABAs q1h**

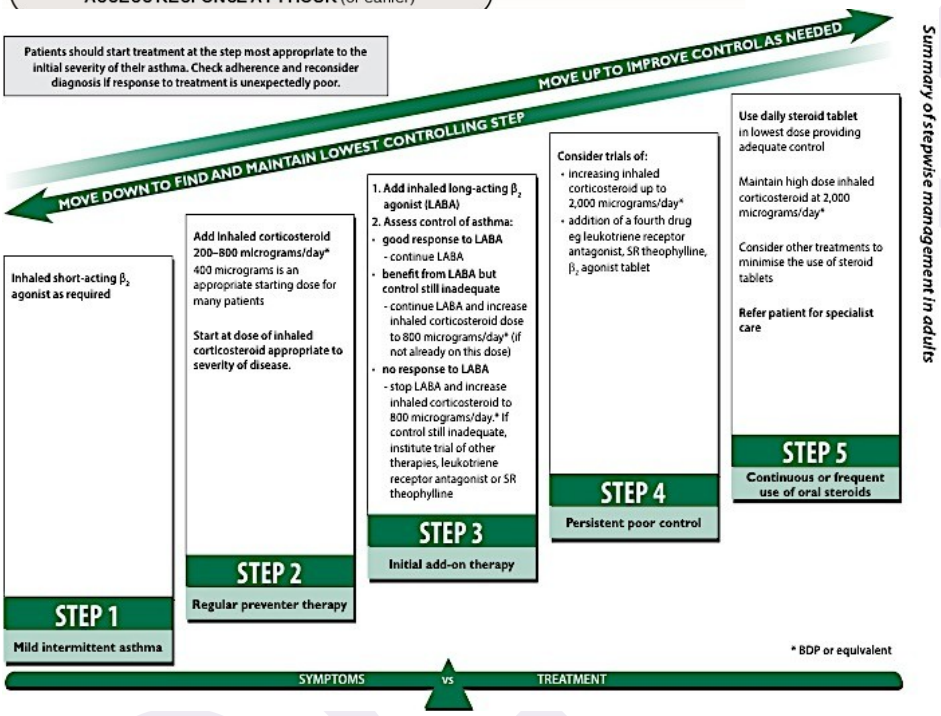
Dr. Chanz

- Systemic corticosteroids: Eg: **methylprednisolone** 80 mg IV q8h
- **Oxygen**: Supplemental oxygen should be provided to maintain adequate oxygen saturation (>90%).
- **Ipratropium**: Inhaled anticholinergic bronchodilator medication can be added to SABAs
- **Mechanical ventilation**: If respiratory failure occurs
- **Antibiotics**: If Pneumonia occurs
- Correct dehydration & acidosis- fluids



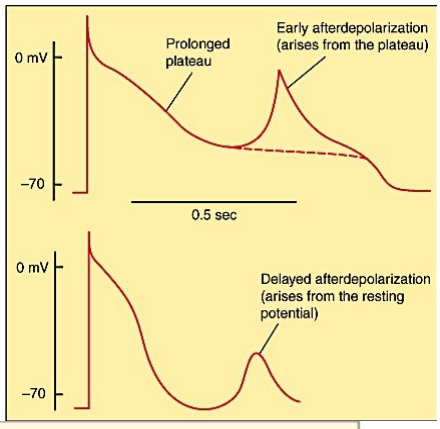
Summary:

- Asthma best tx'd by learning classification based on CF' Viz. mild intermittent, mild persistent, moderate persistent, & severe
- In chronic management of asthma, reliever used as needed & controller used prophylactically
- Relievers: SABA ie. Albuterol is best. LABAs ie. salmeterol considered in moderate persistent cases
- Controllers: ICSs are best.
- Other drugs added only if above therapy fails to

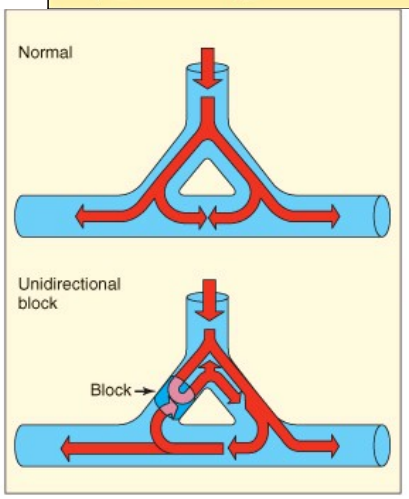


L3 Antiarrhythmic drugs: all can suppress cardiac contractions

- To func efficiently, heart needs to contract sequentially (atria then ventricles) & have adequate time to fill btwn contractions
- **Arrhythmias:** may cause heart to beat too slowly (sinus bradychardia), beat too fast (tachycardia), to respond to impulses from other sides other than SA node, respond to impulses traveling along extra pathway (A-V reentry, Wolff-Parkinson White Syndrome); consist of cardiac depolarizations that deviate from normal pattern via abnormality in impulse formation (automaticity) &/or impulse conduction (reentry)
  - *Disorders of impulse formation involve* (1) no change in pacemaker site (eg. Sinus bradycardia or tachycardia) &/or (2) dev't of ectopic pacemaker activity (anywhere outside SA node)
  - *2 forms of abnormal activity*, **early & delayed after depolarizations**. In both, abnormal depolarizations arise during or after a normally evoked AP. Thus often referred to as "triggered" automaticity



- **<u>Early after depolarization</u>** *<u>in phase 3</u>* – ie. Torsade des pointes; arises from prolonged plateau
- **<u>Delayed after depolarization</u>** *<u>in phase 4</u>* – w/more IC Ca^{2+} ▭ digoxin induced, esp when given w/enzyme inhibitors (ie. Cemitidine, Macrolides (ie. Erythromycin) ▭ causing delayed after

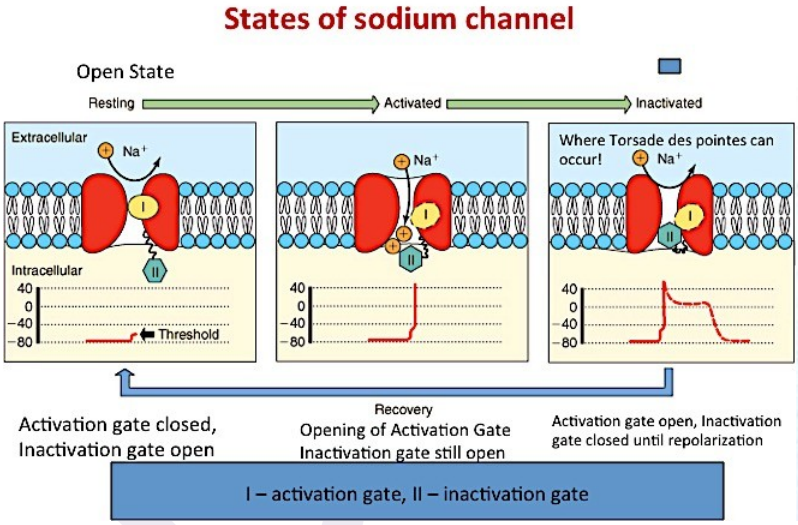


➢ Disorders of impulse conduction can result in
1. **Bradycardia**, as occurs w/AV block;
2. **Tachycardia**, as when a reentrant circuit develops; retrograde impulse conduction will once it turns back, excite that pt of myocardium repeatedly ▭ creating **<u>reentrant circulation</u>** in ischemic zone ▭ responsible for major cardiac arrhythmias ▭ esp PSVT

▭ Ionic Basis: transmemb potential of cardiac cells is determined by
1. [ ]'s of Na^+, K^+, Ca^{2+} & Cl^- on either side of memb

▭ Cardiac AP: movements of these ions produce currents that form basis of cardiac AP.
- At rest, most cells not permeable to Na, but at start of each AP, they become permeable to Na^+
- Similarly, Ca^{2+} enters (phase 2) & K^+ leaves (phase 3) cell w/each AP

▭ States of Na^+ channel:



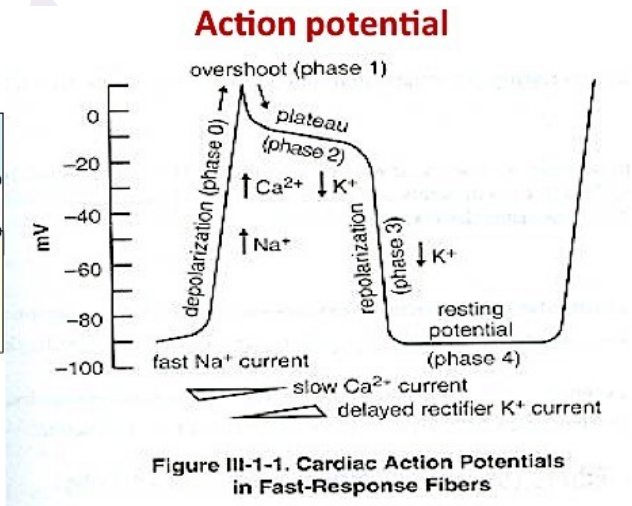
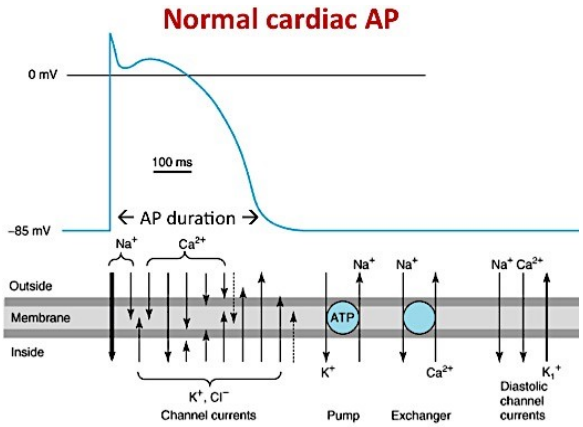


Figure III-1-1. Cardiac Action Potentials in Fast-Response Fibers

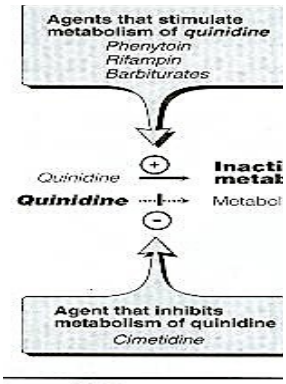


AP of ventricle: 01234 (from physio!)

- Phase 0) rapid depolarization: opening VG Na^+ channels, inwd Na^+ current, MP reaches +20 mV; slow VG Ca^{2+} open; open Ik
- Phase 1) initial brief repolarization: closing VG Na^+ channels, outward K^+ current b/c high electrochem'al gradient for K^+
- Phase 2) Plateau: long stable depolarization at 0 mV; opening VG slow (L-type Ca^{2+} channels) ∴ slow ***inwd*** Ca^{2+} current (max) balances outwd K^+ current (thru ungated channels)
- Phase 3) Rapid repolarization: opening VG K^+ (IK1 – inwd rectifier) channels (*always closed in depolarization & plateau*) VG Ca^{2+} channels start closing; STRONG outwd K^+

∴ Classification of drugs: signifies major effect caused these drugs (some overlap in class!):

1. **Class 1:** fast Na^+ channel blockers! Preferentially Block VG Na^+ channels (activated & inactivated) as LAs) ~~aka slow phase 0 depolarization or phase 1~~ in cardiac pacemaker cells & myocytes; b/c block Na^+ entry ∴ ↓↓Na entry rate ∴ ↓↓excitability & conduction velocity; more effective in abnormal tissues than channels in normal tissue b/c ****use-dependant** (more effective when tissue(s) highly depolarized, ie. dis'd/ischemic myocardium prone for arrhythmias b/c have many alternate pathways generating them) or *state-dependant* phenomena (affect Na^+ channels aka bind more readily when channel open or inactivated than when fully repolarized/resting); use dependence b/c Na+ channels in rapidly depolarizing tissue spend more time in activated & inactivated states allowing more binding time for drug; dissociation from channel occurs during resting state (conformational state distinct from inactivated state that occurs following repolarization); *3 subtypes* (reflect efx on AP duration (APD) & kinetics of Na^+ channel blockade) *– (w/sodium-channel-binding strength 1C>1A>1B) hence 1C w/more pronounced use dependence*
   a. **Class 1A**: **Quinidine**, **Procainamide**, **Dysopyramide**; ****Primary Block I_{Na}** aka Na^+ channel blocker ∴ slows phase 0 depolarization ∴ prolong APD b/c **Secondary Block I_{Kr}**** so additional efx on K^+ channels (class 3 axn!) ∴ **slow AP's rate of rise ∴ slows conduction ∴ prolongs AP*** ↑↑ ventricular ERP ∴ prolonging QT interval**; block cells that discharge at high frequency w/out interfering w/N low frequency impulse in heart; treat both atrial & ventricular arrhythmias; toxicity can cause Torsade des pointes/**QT prolongation syndrome!!! w/sudden syncope episodes & dangerous ventricular arrhythmias (b/c also block K^+ channels,** your **next AP interrupts phase 3 repolarization ∴ abnormal automaticity);** KNOW SPECIFIC TOXICITIES FOR EACH DRUG*; adv of being relatively nonselective (binding myocytes diffusely) & dissociating slowly, providing blockage in WPW syndrome
      i. **Quinidine**: class IA Na^+ channel blocker; oral antimalarial obtained from syncona alkaloid plant; binds to inactivated Na^+ channels & prevents Na^+ influx ∴ slows rapid upstroke of phase 0; treats (1) atrial, AV junc'al & ventricular tachyarrhythmias & (2) maintains sinus rhythm after cardioversion of atrial flutter or fib; not used clinically b/c toxic! In [high]'s precipitate arrhythmias (fatal VF); DI's: ***↑↑ steady state [digoxin]** (displaced from binding sites & ↓↓renal CL of it); ***Toxicity: Large doses ∴ **cinchonism***** (blurred vision, tinnitus, headache, disorientation & psychosis), Syncope, prolonged QTc & torsades des pointes

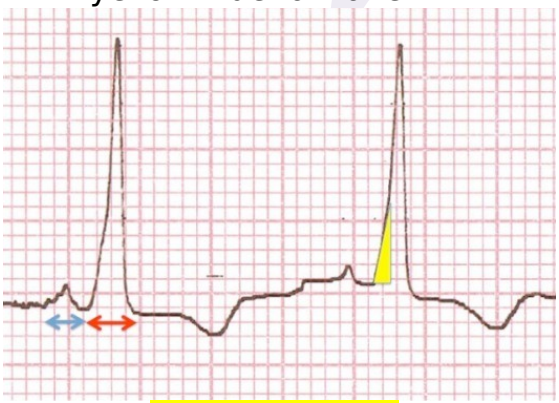


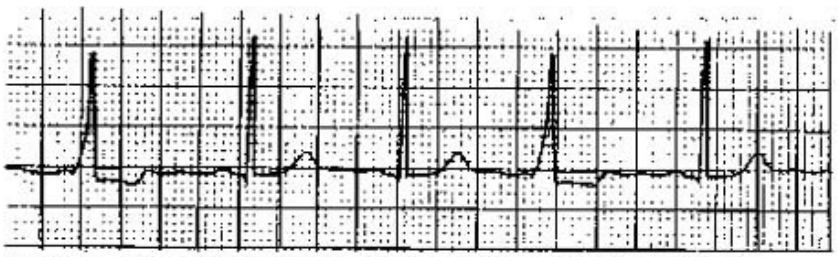
Agents that *stimulate* metabolism of quinidine: Phenytoin, Rifampin, Barbiturates

Agents that *inhibit* metabolism of quinidine: Cimetidine

ii. **Procainamide**: Class IA, LA procaine derivative, given oral & metabolized by acetylation to N-acetylprocainamide (**NAPA**)*** - prolongs APD (class III properties); for slow acetylators, develop toxicity; ADR: Chronic use = more ADR, ***reversible lupus like syndrome (facial rash, ANA Ab's, fever); high doses ↓CVS efx of systole or ventricular arrhythmias & CNS efx (depression, hallucination, psychosis); prevents v. fib in pt w/**WPW syndrome w/a fib** caused by accessory elec'al pathway to ventricle —> 2 separate elec'al pathways to ventricle; 1 of normal conduction thru AV node & conduction tissue & other/2nd purely of myocytes forming bundle of Kent. accessory pathway lacks AV nodes ability to limit # of atrial impulses that pass thru to ventricle, so atrial transmission thru this route proceeds unabated to ventricles in WPW

1. Tx in WPW w/atrial fib - make sure these erratic atrial signals travel thru normal conduction pathway ONLY, thus controlling rate so ANY BLOCKER OF AV NODAL TRANSMISSION CAN'T BE USED b/c pushes more atrial impulses thru accessory route to ventricles —> rapid deterioration into v fib. so can't use adenosine, digoxin, propranolol, verapamil
2. **WPW syndrome/Ventricular preexcitation syndrome**: caused by abnormal connection btwn atria & ventricles via 'bundle of Kent' bypass tract – causes ventricles (either R or L, depending on which side abnormal tissue is) to be activated early, causing dec PR interval & slurred QRS upstroke (delta wave) causing QRS complex widening; occasionally exp serious arrhythmias caused by reentry – MC reentry in WPW is AV reentry tachycardia where impulses travel down AV node & back up thru bundle of Kent to atrium – b/c atria being stimulated after ventricles in retrograde fashion, ECG shows inverted P waves immediately following QRS complexes – ie. RR interval 0.4 sec, prev ECGs w/PR interval of 0.09 sec & widened QRS; blue – short PR interval, red – wide QRS complex, yellow – delta wave





Intermittent Wolff-Parkinson-White syndrome (first and fourth beats). By comparison with the normal beats, it can be seen how the delta wave both broadens the ventricular complex and shortens the PR interval.

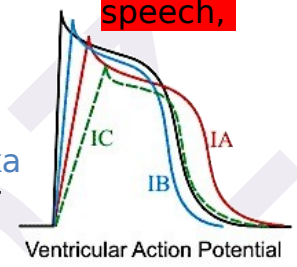
iii. **Disopyramide:** Class IA w/–ve inotropic efx (↓myocardial CT); for ventricular arrhythmias; anti-muscarinic acts like atropine ↓***ADR- anticholinergic/*antimuscarinic* aka signs & sx↓ constipation, urinary retention, dry mouth, dry eye, pupillary dilation, bronchodilation, tachycardia

b. **Class 1B**: **Lidocaine**, **Phenytoin**, **Tocainide** & **Mexiletine**; bind less avidly to Na+ channels so weak Na^+ channel blocker (**Block** I_{Na}) so shorten phase ***3*** repolarization ↓shorten ↓APD, (also b/c doesn't affect K^+ channels as much) & ↓ERP; dissociation from

channels occurs so rapidly that there's minimal cumulative efx over multiple cardiac cycles, resulting in little use dependence; more selective for ischemic myocardium b/c reduced RMP delays Na+ channel transition from inactivated to resting state, resulting in ⏚drug channel binding; useful for tx'ing ischemia-induced ventricular arrhythmias, 1 of MCCODs in short term following acute MI

i. **__**Lidocaine**__: local anesthetic esp useful for ventricular **__arrhythmias post MI's__*****; shortens phase 3 repolarization & ¬¬APD; abolishes ventricular reentry, give IV [never oral b/c 1st pass metabolism], eliminated by liver via dealkylation; dosage adjustment needed in liver damage; Toxicity: CNS efx: drowsiness, slurred speech, **__paresthesia followed by tremors__**, agitation, confusion, convulsions, may precipitate arrhythmias

ii. ***__Phenytoin__**: anti-epileptic



- Class IA: e.g., quinidine
  - Moderate Na^+-channel blockade
  - ↑ ERP
- Class IB: e.g., lidocaine
  - Weak Na^+-channel blockade
  - ↓ ERP
- Class IC: e.g., flecainide
  - Strong Na^+-channel blockade
  - → ERP

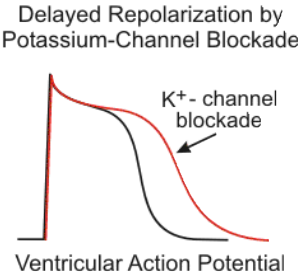
c. **__Class 1C (*Flecainide, Propafenone*)__**: strong Na^+ channel blocker aka block I_{Na} ▭ markedly slows phase 0 depolarization ▭ no efx on APD or ventricular ERP; suppress phase 0 upstroke, sig –ve inotropic efx; more pronounced use dependence b/c their slow dissociation from sodium channel that allows their blocking efx to accumulate over multiple cardiac cycles – enhanced w/tachycardia & resulting ⏚in Na+ channel blockade helps slow conduction speed & terminate tachyarrhythmias; but these stronger use-dependence efx can cause delay in conduction speed out of proportion to prolongation of refractory period; this can promote arrhythmias esp in pt's w/ischemic or structural heart dis; NOT USED clinically b/c cause highly dangerous arrhythmias**;** approved only for tx'ing refractory ventricular arrhythmias b/c huge safety concerns;ADR: ***__Dizziness, blurred vision, headache & nausea__***, Aggravates CHF, can aggravate preexisting arrhythmias; can induce VT, which is resistant to tx

2. **__Class 2__: __Propranolol__, __Metoprolol__, __Nadolol__, __Atenolol__, __Acebutolol__, __Pindolol__, __Esmolol__;** sympatholytic β-adrenoreceptor blockers in heart ▭ suppress Ca^{2+} conductance & diminish phase 4 depolarization ▭ depresses automaticity, prolongs conduction & ¬¬HR; treat tachyarrhythmias caused by ⏚symp activity/ hyperadrenergic state (ie. hyperthyroidism) b/c ¬¬AV conduction, & for Atrial flutter & fib & AV nodal __reentry__ tachycardia/arrhythmias aka chronic tx of PSVT (Paroxysmal SupraVT/AV reentrant arrhythmias)

a. Propranolol (nonselective B-adrenergic blocker, ¬¬chronotropy & inotropy via β1 blockade), Metoprolol, Nadolol, Atenolol, Acebutolol, Pindolol, ~~Sotalol, Timolol;~~

b. **__Esmolol__**: short acting β -blocker (short half-life b/c its metabolism by plasma esterases) **__treats arrhythmias intra-operatively__*** or short term control of acute arrhythmias

3. **__Class 3:__** (BASID = **__Bretylium__**, **__Amiodarone__**, **__Sotalol__**, **__Ibutillide__** & **__Dofetilide__**) K^+ channel blocker aka block I_K potassium channels ▭ prolongs phase 3 repolarization ▭prolong APD (by altering K^+ current) ▭ prolong ERP ▭ prolonged QT interval (can also cause Torsade des pointes)***; block K^+ channels & diminish outward current in repolarization; I_{kr} (Inward rectifier K current);



a. **__Amiodarone__***: 40% iodine & structural rel'n to thyroxine, class IA, II, III & some IV axns, dominant efx prolong APD & ERP; insig antianginal; fully absorbed after oral admin w/prolonged ½-life of many weeks so full efx achieved only after 6 weeks hence more maintenance drug; **for refractory SVT & VT;** *****side efx on long term use ~½ pt's discontinue b/c ▭ thyroid abnormality (monitor for hypo or hyper; peripheral conversion of thyroid hormone lvls), Interstitial pulm fibrosis (cough, dyspnea, requires periodic CXR), corneal microdeposits, GI intolerance, tremors, ataxia, dizziness, Neuropathy & iodism blue skin discoloration (to skin of mucous memb b/c iodine accumulation); inhibits CYP3A4 so contraindicated w/warfarin otherwise warfarin ^ ▭ excessive anticoagulation & bleeding

b. **Sotalol**: Class 3 tho b-blocker, prominent efx on K^+ channels; w/potent β-blocking activity ↓blocks rapid outward K^+ current ↓ prolongs both repolarization & APD, lengthens ERP; for long term therapy to ↓↓rate of sudden death following MI & strong antifibrillary efx in ischemic myocardium
c. **Bretylium:** class 3 K^+ channel blocker
d. ***Ibutillide**: favorable pharmacokinetics

4. **Class 4**: **NONDHP** CCB's (**Verapamil, Diltiazem**) block cardiac Ca^{2+} channels ↓ delay depolarization by slow conduction in tissues dependant on Ca^{2+} - SA & AV node depolarize in resp to slow inward current of Ca^{2+} & Na^+ ↓ All other cardiac cells depolarize in resp to rapid inward current of Na^+ ions ↓shorten APD; don't use DHP's b/c vasodilate ↓ ↓↓BP ↓ reflex symp tachycardia not so good in pt's w/tachy arrhythmias; >>axn on heart than vasculature, treat atrial dysrhythmias, reentrant SVT, IV'ly for PSVT/AV nodal re-entrant arrhythmia

↓Others:

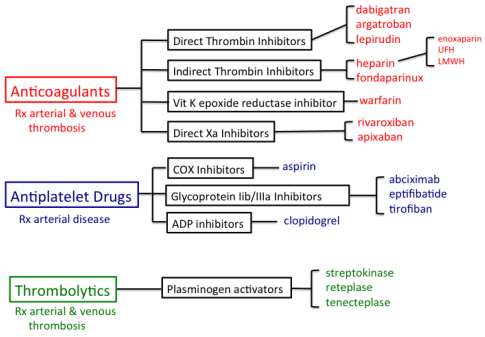
- **Digoxin**: enhances vagal tone* (parasymp)↓↓AV conduction for arrhythmias & control atrial flutter/ fib (↓↓ventricular rate); prolong ERP so In emergencies used IV, rmr ADR (ectopic ventricular beats)
  - ↓ AV nodal conduction (parasympathomimetic effect)
  - ↓ ventricular rate in atrial flutter and fibrillation
- **Adenosine**: natural nucleoside, ↑A- Adenosine receptors; **DOC in acute PSVT & AV reentrant nodal arrhythmias;** IV'ly, plasma ½ life <30 sec so short acting; In high doses (1) ↓↓AV conduction velocity, (2) Prolongs refractory period & (3) ↓↓SA & AV nodal activity; ADR-flushing (b/c mild vasodilator), sedation, dyspnea; contraindicated in WPW b/c accelerates accessory conduction rate (↓degenerating atrial fib into v fib)
- **Magnesium**: used in torsades des pointes (QT prolongation syndrome via class IA & III), interferes w/Na/K ATPase, Na^+, K^+ & Ca^{2+} channels, given IV (slow), used w/extreme caution

- Set of investigations you would order if you start a pt on amiodarone? Thyroid func, CXR
- CCBs predominant efx on cardiac tissue & less efx on peripheral blood vessels? Verapamil, Diltiazem aka non DHP CCB's
- How is atrial flutter & fib managed? Need to give anticoagulants to prevent thrombus formation, any K+ blockers esp Ibutilide, b-blockers & digoxin for rate control, amidarone for rhythm control
- DOC for PSVT (Paroxysmal SupraVT/AV reentrant arrhythmias)?
  - Acute = Adenosine IV
  - Chronic = b-blockers/CCB's (non DHP's –verapamil or diltiazem)
- DOC for VT ? DOC Cardioversion, Amiodarone, Lidocaine
- VF – DOC cardioversion

- Certain drugs will cause cardiac arrhythmias, including anti-arrythmics! :O
- ***Torsade de pointes**: imp b/c *caused by drug toxicity, w/abnormality in indirect K^+ channels, see prolonged QT interval due to early after depolarization; tx by w/draw meds causing it (Class IA & III), correct electrolyte, IV Magnesium sulfate (act like CCB's in myocardial cells ↓ correcting arrhythmia) w/B-blockers

L4 Drugs Affecting Hematopoietic System:

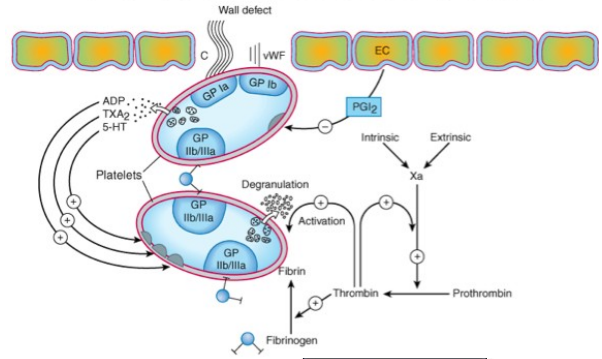
Drugs Used to Treat Clotting Disorders



Focus more on Heparin & Warfarin*

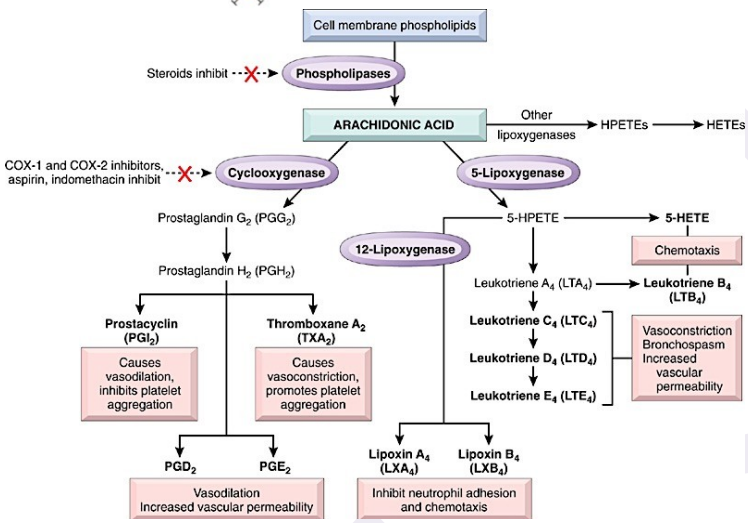
GpIIbIIIa inhibitors: inhibit this receptor

Thrombus formation at site of damaged vascular wall & role of platelets & clotting factors



TXA2, ADP & 5-HT promote coagulation cascade ⊔ platelets adhere w/fibrinogen receptors aka Gp2b3a (imp for aggregation)

Thrombin will activate Fibrinogen to fibrin to stabilize platelet



LO ⊔ LTC_4, D_4, E_4's for bronchospasm in asthma

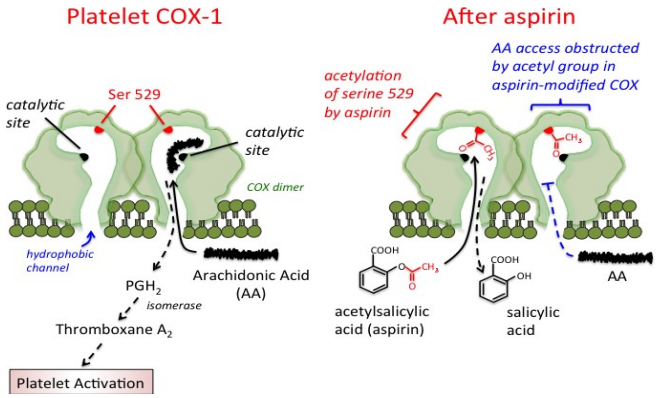
COX responsible for platelet aggregation thru TXA_2

⊔ ***Bosentan****:* endothelin-receptor antagonist vasodilator blocks endothelin (potent vasoconstrictor that ↑endothelial proliferation) so ¬↓pulm arterial pressure for pulm HTN sx & lessens progression of vascular & RVH

⊔ ***Antiplatelet drugs****: for arterial dis's! COX inhibitors (aspirin), ADP inhibitors/antagonists (clopidogrel, Ticlopidine), Gp2b3a inhibitors (abciximab, eptifibatide, tirofiban)*

- ****Aspirin (acetylsalicylic acid):** acidic antiplatelet COX inhibitor for arterial thrombi/dis; *acetylates serine* residue in active sites for both COX-1 & COX-2, irreversibly inhibits them
  - **Low doses aspirin (81-325 mg/d) selectively inhibit COX-1 in platelets permanently** for **platelet's lifetime,** since platelets lack DNA & can't make new enzyme ⊔This enables selective antiplatelet efx; Low dose daily prevents ischemic attack & MI, Thus, prophylactic antiplatelet benefit always in low dose
  - **Higher dose aspirin inhibits both COX's so** inhibits PGI (prostacyclin) synthesis (PGI prevents platelet aggregation) & *antiinflammatory dose* (>1000 mg/day but *NO ANTIPLATELET efx)*; side efx: peptic ulcers (¬↓PG's = ¬↓protective mucosal effect in stomach), metabolic acidosis (tx'd w/alkalinization w/sodium bicarbonate or acetazolamide diuretic)

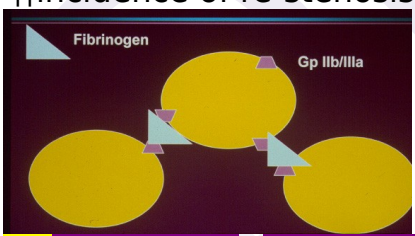
Dr. Chanz



ADP receptor antagonists: inhibit ADP mediated platelet aggregation; used after percutaneous coronary intervention & for tx'ing unstable & NSTEMI; for arterial thrombi w/acute/recent MI (2ndary prevention for those allergic to aspirin - replaced in aspirin allergic pt's post MI for anti platelet benefits), ACS or stroke, or *to re-establish coronary perfusion after stent* (¬risk of stenosis), or in PAD (Buerger's); ***Clopidogrel, Ticlopidine, Prasugrel, Ticagrelor (reversible)***; diff tolerabilities

- **Clopidogrel**: prodrug metabolized by CYP2C19 to active metabolite, **irreversibly blocks ADP receptor on platelets**, thus ¬platelet aggregation, no efx on PG metabolism (unlike aspirin); ¬incidence neutropenia or thrombocytopenia hence prefer; used in AS'ic ischemic dis & prevents acute stent thrombosis after percutaneous coronary interventions; good for outpt therapy
- **Ticlopidine**: **irreversibly blocks ADP receptor on platelets**, thus ¬platelet aggregation, no efx on PG metabolism (unlike aspirin); not preferred b/c side efx: as immune mediated rxn severe neutropenia* & thrombocytopenia (TTP – thrombocytopenic purpura needs reg monitoring blood counts hence lmtd value)
- **Cangrelor**: reversible $P2Y_{12}$ inhibitor inhibits ADP-induced platelet aggregation; **fast acting**; doesn't need metabolization to active metabolite (vs clopidogrel); immediate efx when infused & maintained w/continuous infusion, always IV, only for selective cases – for adult undergoing PCI (percutaneous coronary intervention) to open blocked/narrowed coronary a & improve ^BF to myocardium; **Side efx:** potential for autoimmune rxns manifesting as **dyspnea**
- **CYP2D6:** metabolizes Codeine (mild opioid used as cough suppressant) to morphine
- **CYP3A4:** metabolizes majority of drugs
- **CYP2C9:** metabolizes Warfarin; high [Warfarin] can cause bleeding/hemorrhage so genetic polymorphism in CYP2C9 can induce that
- **CYP2C19:** metabolizes Clopidogrel

GPIIb/IIIa RECEPTOR antagonists: Abciximab, Eptifibatide, Tirofiban; inhibit fibrinogen binding to GPIIb/IIIa receptor thus inhibit final common pathway of platelet aggregation; given along w/aspirin & heparin during coronary angioplasty (PTCA) – markedly ¬incidence of re-stenosis; adverse: bleeding, thrombocytopenia



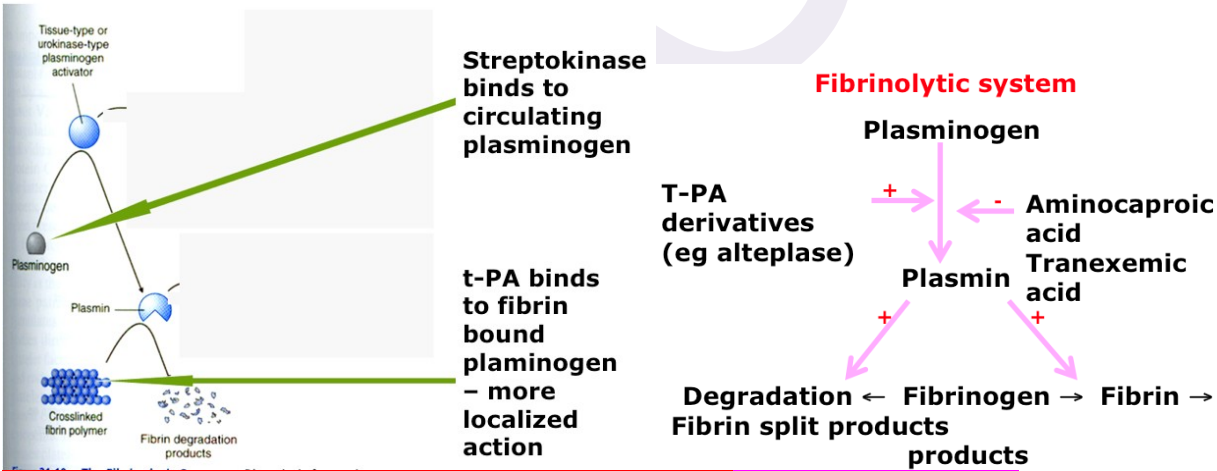
- **Abciximab:** GPIIb/IIIa RECEPTOR antagonist (ANSWER); monoclonal Ab's against gpIIb/IIIa receptor complex
- **Eptifibatide:** GPIIb/IIIa RECEPTOR antagonist; **given along w/aspirin & heparin during coronary angioplasty (PTCA) – markedly ¬ incidence re-stenosis**
- **Tirofiban:** GPIIb/IIIa RECEPTOR antagonist
- What is the receptor is acts on?? Clinical indication???****

- **Vorapaxar**: PAR-1 antagonist (protease-activated receptor-1) blocks thrombin-mediated platelet activation w/out interfering w/thrombin-mediated cleavage of fibrinogen; ↓↓tendency platelets to clump together & form clot; **for Recent MI, or established PAD (peripheral a dis);** +used w/other anti-platelet agents (aspirin or clopidogrel)
  - **What is PAR-1?**: 4 types of PARs: PAR-1 & PAR-4 expressed on human platelets. PAR-1 mediates platelet activation at low [thrombin]'s, & PAR-4 mediates activation at high lvls of thrombin. Once PAR-1 activated by thrombin, various phenotypic efx occur, including production of thromboxane, release of ADP, serotonin & E & platelet activation.

↓ **Thrombolytics/Fibrinolytics:** only for STEMI. Exclude intracranial hemorrhage? **still very imp for tx'ing coronary occlusion but for situations where coronary catherization not readily available;** overdose tx'd by antifibrinolytics (aminocaproic acid, tranexamic acid); **alteplase (tPA), reteplase (rPA), streptokinase, tenecteplase (TNK-tPA); clot lysis for acute MI, PE & arterial thrombosis**

- **Streptokinase:** protein (not enzyme) *made from streptococci*, combines w/plasminogen & ↓its conversion to active plasmin; still available for use; BUT Clinical trials shown **coronary catherization better than this drug b/c ↓↓ mortality sig'ly better than thrombolytics** in pt's suffering from MI caused by CAD; **side efx: Bleeding, allergic rxns, hypotension, fever**
- **Urokinase:** derived from human tissue; **(no longer commonly used)**
- **tPA (Tissue plasminogen activator: alteplase, reteplase – recombinant DNA technology:** t-PA binds to fibrin in thrombus & converts entrapped plasminogen to plasmin ↓ initiates local fibrinolysis w/lmtd systemic proteolysis (acts selectively on thrombi); **for acute MI** (STEMI) in adults to improve ventricular func after acute MI; NOT indicated for NSTEMI that result from incomplete blockage of coronary a by platelet aggregation (antiplatelet meds indicated instead), acute massive **pulm embolism, acute ischemic stroke; Notes:** When used to treat stroke - should only be initiated w/in 3 hrs after onset stroke sx, & after exclusion of intracranial hemorrhage (will just end up bleeding more); Coronary occlusion due to thrombus present in infarct-rel'd coronary a in ~80% pt's exp'ing STEMI evaluated w/in 4 hrs onset of sx

Fibrinolytics mechanism



↓ Thrombolytics can cause bleeding, tx'd by **antifibrinolytics**: inhibits plasminogen activation to treat excessive bleeding due to OD of fibrinolytics; **Aminocaproic acid, Tranexamic acid**

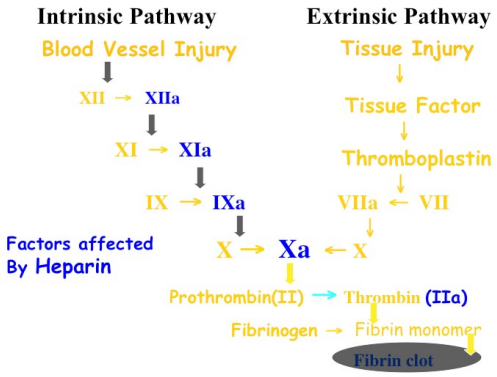
↓ **Anticoagulants:**

↓ ***Indirect thrombin inhibitors:***

- ****Heparin**: IMMEDIATE ANTICOAGULANT **for DVT, PE, Acute MI, coronary angioplasty w/fibrinolytics, atrial fib w/embolization, cerebrovascular dis, vascular surgery & prosthetic heart valve**; highly ionized (hence given IV or subcutaneous, not absorbed orally) strong acidic activates AT III ↓ affecting XIIa, Xia, IXa, Xa & IIa (all in intrisic pathway

& common – IIa); indirect axn; dose monitored by aPTT (activated partial thromboplastin time; testing intrinsic pathway aka blood vessel injury) to maintain it btwn 45-75 secs (means there's adequate anticoagulation; N = 25-39 secs), if prolonged = overdose = toxicity – bleeding tx'd by basic substance antidote ***protamine***** to neutralize & stop bleeding; +suspected tetratogenic (Pregnancy Category C) & only given to pregnant pt's if needed. Hence LMWH (along w/aspirin) used in pregnancy when needed; adverse efx – hemorrhage – nose bleeds, hematuria, tarry stools as 1st bleeding sign, petechiae & easy bruising may precede frank bleeding, ***HIT (*Heparin induced Thrombocytopenia* – Ab-heparin-PF4 complex activates platelets ⊏ thrombosis & thrombocytopenia) ***Immune mediated in 25% pt's ⊏ must switch to direct thrombin inhibitor &*** Osteoporosis- on prolonged use

- **UFH (Unfractionated heparin):** large MW anticoagulant, afx all clotting factors; straight chain large MW mucopolysaccharide⊏ ↑ATIII⊏ inactivates clotting factors ⊏(in intrinsic pathway – thrombin IIa, IXa, Xa)



- **LMWH (Low molecular weight heparins - Enoxaparin, Dalteparin, tinzaparin**: selectively inhibit Factor Xa, less efx on Factor II Thrombin; given subcutaneously, longer half life (⁊ **bioavailability =** ⌐¬frequency of dosing), less monitoring needed b/c less efx on aPTT, less complications like hemorrhage, thrombocytopenia tho **equally efficacious;** for (1) **prophylaxis DVT,** (⊏PE) *in pt's at risk*: undergoing abdominal surgery at risk for thromboembolism, undergoing hip replacement surgery during & after hospitalization, knee replacement surgery b/c severely restricted mobility in acute illness; & for (2) **prophylaxis ischemic complications of unstable angina & non-Q-wave MI (NSTEMI)**, concurrently ***admin'd w/aspirin***; +suspected tetratogenic compound (Pregnancy Category C) & only given to pregnant pt's if "clearly needed". Hence (along w/aspirin) used in pregnancy when needed
- **Fondaparinux**: binds ATIII w/high specificity ⊏inactivating factor Xa; doesn't cross react w/pathologic HIT (Heparin-induced-Thrombocytopenia) Ab's in most; for **Prophylaxis DVT** (could lead to PE, ie. undergoing hip fracture or knee replacement surgery), **tx of either acute DVT or acute PE** when admin'd w/warfarin, **anticoagulation in pt's w/HIT b/c** these pt's can't use heparin anymore & so they're tx'd w/either fondaparinux or direct thrombin inhibitor

⊏ **DTI's *Direct thrombin inhibitors***: inhibit thrombin (serine protease that enables conversion of fibrinogen to fibrin in coag cascade); axn independent of ATIII; directly inhibit free & clot-associated thrombin; used for venous thromboembolism, atrial fib, HIT, doesn't require lab monitoring; adverse efx: bleeding, no specific reversal agent (can try using activated PT complex concentrates (PCC) &/or fibrinolytics (ex. tranexamic acid)

- **Lepuridin**: recombinant form of **Hirudin**, specific, irreversible inhibitor of thrombin in saliva of **leeches**
- **Argatroban**:
- ***Lepuridin, Argatroban*: as alternatives to heparin in HIT (Heparin induced thrombocytopenia)**

- **Dabigatran**: inhibits thrombin-mediated fibrin formation; ↓↓ **risk stroke & embolism from DVT in pt's w/non-valvular atrial fib** (FDA 2010); in Canada, also prevent forming harmful blood clots (ie. in legs & lungs) after hip or knee replacement surgery; helps ↓↓risk stroke & MI
- **Bivalirudin:** specific & reversible direct thrombin inhibitor (DTI), rel'd to hirudin, anticoagulant used by leeches

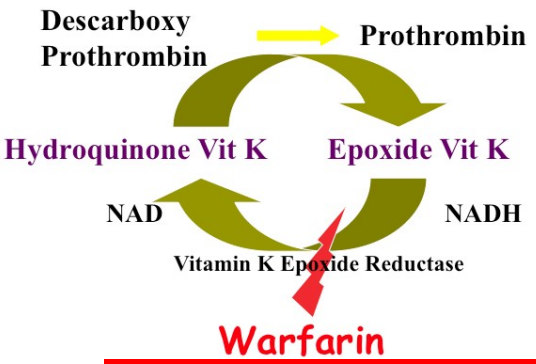
↓ ***Direct Xa inhibitors***: don't need monitoring for dosage adjustments vs. warfarin; directly bind & inhibit factor Xa; tx & prophylaxis for DVT/PE (rivaroxaban), stroke prophylaxis in pt's w/Atrial fib; oral agents; adverse efx: bleeding

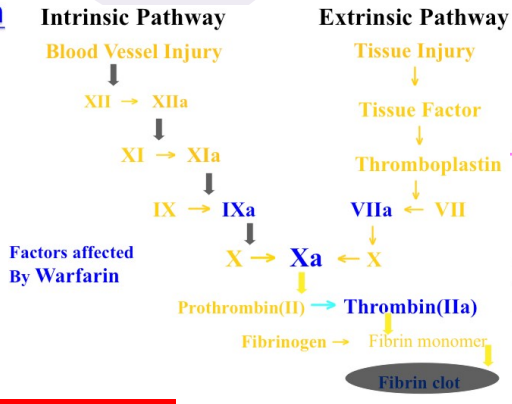
- **RivaroXaban**: **prevents VTE following hip or knee surgery** (FDA 2010).
- **ApiXaban**: Prophylaxis to ↓↓risk stroke & systemic embolism in nonvalvular atrial fib

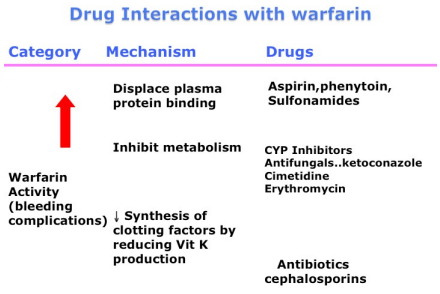
↓ ***Vit K Epoxide reductase inhibitors (Oral anticoagulant):***

- ***Warfarin**: Vit K Epoxide reductase inhibitor (Oral anticoagulant); synthetic analog of active ingredient in spoiled sweet clover that caused outbreak of hemorrhagic dis in cattle; ↓↓hepatic synthesis of Vit K dependent clotting factors –prothrombin, VII, IX, X & endogenous anticoagulant proteins C & S – by preventing gamma carboxylation of glutamate residues of clotting factors; via inhibiting Vit K Epoxide Reductase↓ prevents regeneration of hydroquinone Vit K form; **orally w/8-12 hr delay in axn** due to time taken for degrading clotting factors in circulation; **highly bound to plasma proteins- 99% & monitored by INR (International normalised ratio);** used for long term anticoagulation for maintenance in DVT, PE, acute MI, coronary angioplasty along w/fibrinolytics, Atrial fib, cerebrovascular dis, vascular surgery, prosthetic heart valves, *rmr contraindicated in pregnancy (↓ bone deformities, fetal haemorrhage, abortion, ophthalmologic abnormalities – "Do not wage warfare on baby; keep it HEPpy w/Heparin"); [high] ↓ bleeding/ hemorrhage so genetic polymorphism in CYP2C9 (its metabolizer) can induce+
  - INR **(Recommended INR: 2-3)** = **PT time (test)** /prothrombin time **(control); (22-39/11-13 secs] b/c** Normal PT time (indication of extrinsic & common pathway +factors X, V, VII): 11-13 secs
  - **Coumarins**: anticoagulants w/chem'al structures similar to original compound isolated from clover, & include **dicumarol**, **warfarin** & **phenindione**

Mechanism of action of warfarin

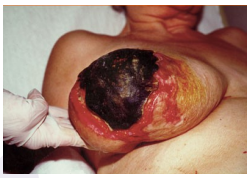






  - Warfarin contraindicated in pregnancy FDA category X b/c can cause miscarriage, still birth, birth dfx or fatal bleeding in unborn baby; can cross placenta & cause hemorrhagic disease in fetus
  - ***Warfarin DI's w/these drugs ↑ Warfarin (bleeding):**
    - *Aspirin, Phenytoin, Sulfonamides*: by displacing plasma protein binding
    - *CYP Inhibitors (Antifungals KTZ, Cimetidine, Erythromycin/Macrolides):* inhibit metabolism
    - *Antibiotics like cephalosporins*: ↓↓Vit K production thus ↓↓synthesis of clotting factors

- ***Warfarin DI's w/following drugs ↑↑ Warfarin (↑↑ anticoagulation): Any ques on DI's regarding anticoagulants – TALKING ABOUT WARFARIN, ie. when you give plasma protein drug what happens? When you give enzyme inducer what happens?
  - *CYP enzyme inducers RBCGAP -* Rifampicin, Barbiturates, ~~Phenytoin~~, Carbamazepine, GC'S & Alcohol chronic admin: by inducing Warfarin's metabolism
- **Adverse efx**: hemorrhage (ecchymosis, epistaxis, hematuria) so must monitor PT time; tx w/stopping drug, giving vit K1(ANSWER) & fresh frozen plasma; also rare complication is skin necrosis in 1st week therapy due to ↓↓protein C synthesis – manifests as dermal necrosis of extremities or breast



Summary of properties anticoagulants		
Nature	Large polymers like **Heparin**	Small molecules like **Warfarin**
Route of admin	IV, SC (Parental)	Oral
Onset of axn	Immediate	Delayed 8-12 hrs
Duration of axn	4-6 hr	3-6 days
Antidote	Protamine sulfate	Vit K
Mechanism	Activate AT III	Inhibit synthesis of Vit K dependent clotting factors
Monitoring	aPTT 45-75 secs for unfractionated heparin but not LMWH's (intrinsic pathway)	PT time (prothrombin; INR) 2-3 PT/INR (extrinsic pathway)
DI's	Few, nonteratogenic	More – 99% highly plasma protein bound, teratogenic (contraindicated in pregnancy)
Use	Mostly acute, over days	Chronic, over weeks

> Dipyrimadole: antiplatelet for prophylaxis of thromboemboli in pt's w/prosthetic heart valves; in combo w/warfarin; may ↓↓stroke incidence in prior stroke or TIA pt's but not used in acute stroke setting

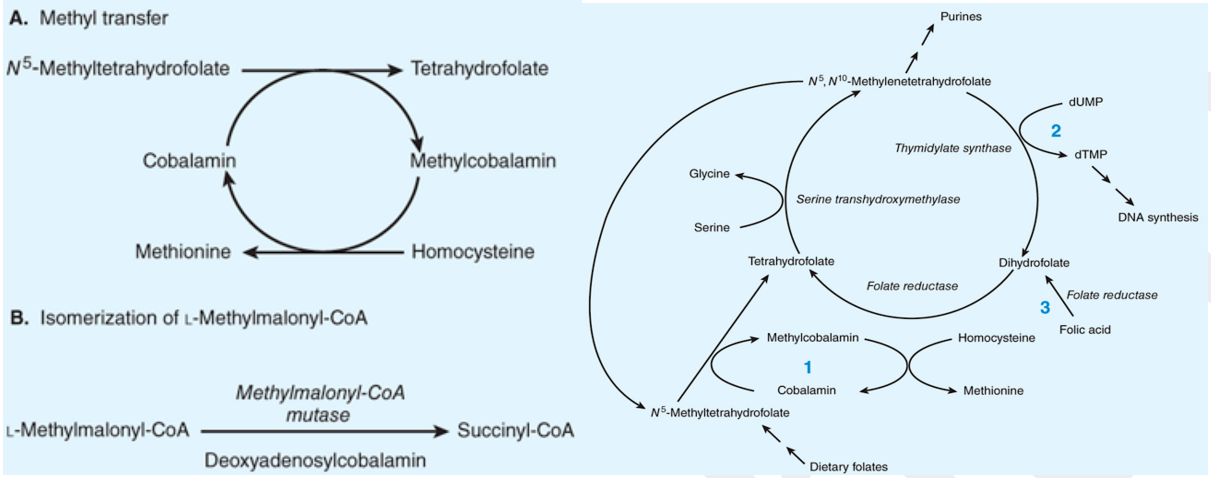
Haemopoietic Agents used in tx of anemias & Hemopoietic growth factors

- **Iron Fe^{3+} (ferric) ⇌ Fe^{2+} (ferrous) easily absorbed; Max absorption in duodenum**
  - **Factors ↑↑ iron absorption:** acid, acsorbic acid (orange juice), AA's, Meat
  - **Factors ↑↑ iron absorption:** antacids, phosphates, phytates & Tetracyclines* (b/c have chelating property à binds to certain metal cations like Ca^{2+}, iron, Mg^{2+} preventing their absorption), so there should be gap of at least 1-2 hrs btwn ingestion of each; physical interaxn), presence of food
  - **Oral iron preparations: Ferrous sulfate, Ferrous gluconate, Ferrous fumerate;** adverse efx: Epigastric pain, N/V, constipation, staining teeth, metallic taste
  - **Parental iron [Iron dextran (IV/IM), Sodium ferric gluconate complex (only IV) & Iron sucrose (only IV)]:** given when oral iron not tolerated b/c side efx or severe def, malabsorption or noncompliant
  - **Treats:** Iron def anemia, Nutritional def (premature infants, growing children), Anemia of pregnancy, Blood loss (GI bleeding), Malabsorption, Pregnant & lactating women-prophylaxis
- **Lead poisoning: tx'd w/BAL (dimercaprol, crosses BBB so DOC for lead encephalopathy) & chelation therapy w/EDTA (ethyelenediaminetetracetic acid) for high blood lead lvls; can also give succimer oral chelator – chelating agents enhance lead excretion in urine**
  - **BAL (dimercapol):** chelating agent forms stable chelates, enhancing metal secretion, for tx of lead, arsenic, antimony & mercury poiosining, used to be 1st agent for Wilson's dis but b/c difficult to administer (IM, 10% oil) & may cause discomfort, used only as adjunctive tx; SE: N/V, tachycardia & burning sensation of lips & mouth

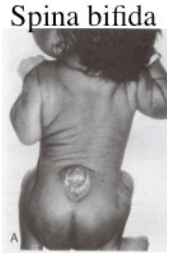
- **Succimer:** for lead poisoning, & arsenic & mercury poisoning if admin'd shortly after exposure

➢ ***Acute iron poisoning:** common in infants & children; w/vomiting, hematemesis, bloody diarrhea followed by shock, can progress to severe metabolic acidosis, coma, death; **tx w/deferrioxamine (ANSWER)** – iron chelating agent that'll bind to iron & help excrete it

➢ **Vit B 12:** cyanocobalamine, hydroxocobalamine; N absorbed w/IF (gastric parietal cell) + B12 ▭ absorbed in distal ileum; treats Megaloblastic & pernicious anemia; needed for conversion of homocysteine to methionine & to convert N-5-methyl THF to THF for DNA synthesis ▭ hence def ▭ neurological sx ▭ **megaloblastic anemia** ▭folate accumulates aka folate trap as N-5-methyl-THF, tx w/folic acid but doesn't correct neurological sx; also needed for converting methylmalonyl-CoA to Succinyl-CoA



➢ **Folic acid:** converted by folate reductase to DHF (dihydrofolic acid) ▭ converted by DHFR to THF (tetrahydrofolic acid), aids in pyrimidine synthesis, N-5-10-methylene THF needed to convert dUMP to dTMP by thymidylate synthase; used to treat Megaloblastic anemia caused by nutritional def, alcoholics, liver dis, pregnancy, malabsorption & esp drugs* - **phenytoin, sulfonamides, methotrexate toxicity (**causes Megaloblastic anemia so give w/Leucovorin/citrovorum factor/folinic acid**), INH (isoniazid for TB), OCPs, pregnancy & when maternal folic acid def (w/NTD ie. spina bifida)**



- **Methotrexate:** inhibits DHFR, so giving Folic acid supplement not effective, give folinic acid (formyl TH_4) **aka Leucovorin/citrovorum factor** (active folic acid) as Leucovorin Rescue (rescuing bone marrow cells from MTX toxicity)

Hematopoietic GF's: EPO, G-CSF & GM-CSF

➢ **Recombinant human EPO (Erythropoietin)**: glycoprotein that ↑**RBC production**. Epoetin alfa, 165 AA glycoprotein made by recombinant DNA technology; given SC or IV to treat anemias in chronic renal failure caused by bone marrow suppressant drugs like zidovudine tx'd HIV pt's, cancer pt's on chemo, treat EPO def when ↓allogeneic blood transfusion in surgery pt's
  - **Hypoxia**: primary physio'al stimulus for EPO production in body ▭EPO def can result from compromised renal func (it's primary site of production) ▭ causes **normocytic anemia**

▭Colony stimulating factors:

➢ ***Myeloid GF's:** used to **treat neutropenia** caused by anti-cancer drugs***
  - **G-CSF (Granulocyte Colony Stimulating Factor): *filgrastim***
  - **GM-CSF (Granulocyte/MO Colony Stimulating Factor): *Sargramostim***

➢ **Megakaryocyte Growth Factors**
  - **Interleukin 11 (oprelvekin):** ↑formation of megakaryocytes & ▭their # in peripheral blood; **for Thrombocytopenia after cancer chemo cycle**

➢ **Platelet growth factor**

L5 Hypolipidemic drugs

- Dyslipidemia: associated w/high cholesterol &/or high TG lvls in plasma.
- Cases where both cholesterol (>200 mg/dL) & TGs elevated, considered Combined Dyslipidemias.
- Cholesterol & TG's normally in body & needed for normal cell func (steroids, digestion, cell memb's)
- 2 major clinical sequlae of hyperlipidemia are acute pancreatitis & AS.

NCEP ATP III Classification of LDL, Total & HDL Cholesterol (mg/dL)

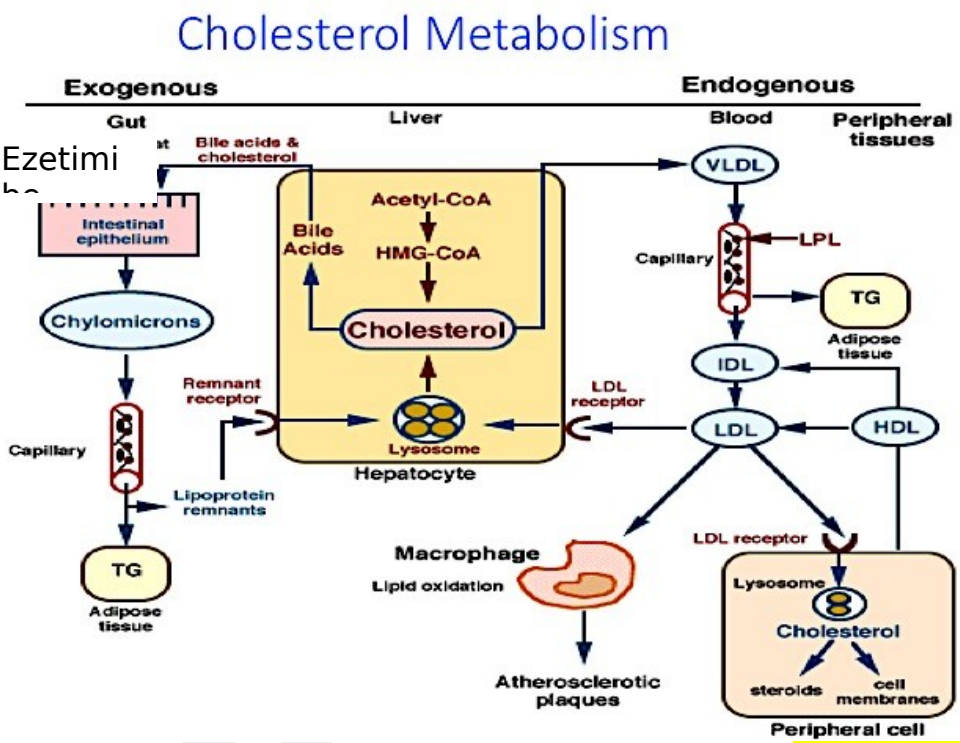
LDL Cholesterol - Primary Target of Therapy; <100 = Optimal; 100-129 = Near Optimal/Above Optimal; 130-159 = Borderline High; 160-189 = High; >190 Very high

Total Cholesterol <200 = Desirable; 200-239 = Borderline High; >240 = High

HDL Cholesterol <40 = Low; >60 = High;

- Chylomicrons: largest of lipoproteins, formed in intestines & carry TG's of dietary origin.
- Very Low Density Lipoproteins (VLDL): secreted by liver, provide means for TG's from liver to be exported to peripheral tissues; (mostly TG's); liver synthesizes cholesterol & secretes it as VLDL (→IDL→LDL)
- Low Density Lipoproteins (LDL): "bad cholesterol" transports cholesterol from liver to blood stream; High lvls in blood associated w/ ↑risk of AS & CAD. (Normal is <100 mg/dL)
- High-Density Lipoprotein (HDL): "good cholesterol", HDL's acquire cholesterol from peripheral tissues i.e. arterial walls. Low HDL lvls are risk factor for cardiovascular disease (< 40 mg/dL)
- LP(a) Lipoprotein: formed from LDL-like moiety & LP(a) protein. Highly homologous to plasminogen but lacks ability to be activated by tPA (repair of vessels)

Ezetimi
be

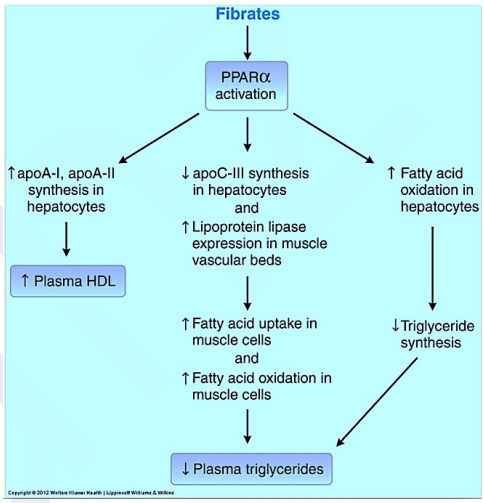


Statins (HMG-CoA Reductase inhibitors): primary therapy for dyslipidemia; competitive inhibitors of HMG-CoA (hydroxy-methyl-glutaryl coenzyme A) reductase (catalyzes conversion of HMG-CoA to mevalonate) ↓*** induction/↑high affinity LDL receptors (imp pt of mechanism!) ↓↑LDL uptake ↓ more break down of it↓ thus lower serum LDL lvls; +standard therapy to initiate immediately after MI, irrespective of lipid lvls; Side Efx: **1st**, Elevations of serum aminotransferase (**AST/ALT**) & hepatotoxicity; 2nd, *Myositis (m pain), marked by ↑CK activity. If drug not discontinued, rhabdomyolysis may occur producing myoglobinemia - may lead to acute renal failure. 3rd, New-onset Type 2 Diabetes; Contraindications: Pregnancy category X;

Major DI's: CYP inhibitors (erythromycin, KTZ, Grapefruit juice) ↓[statins plasma]. Concomitant use w/amiodarone or verapamil or fibrates (other hypolipidemics) ↓risk myopathy

➢ **Simvastatin, Pravastatin, Lovastatin, atorvastatin, fluvastatin**

↓ **Nicotinic acid/Niacin (ANSWER)**: water soluble Vit B_3, inhibit VLDL synthesis in liver which ↓↓LDL made & ↓↓catabolic rate for HDL; used in combo w/resin or statin to normalize LDL in heterozygous familial hypercholesterolemia & other forms of hypercholesterolemia; **clearly most effective agent for ↑↑ HDL lvls**; Side efx: harmless **cutaneous vasodilation** (pretx'd w/aspirin or ibuprofen to prevent it aka NSAIDs otherwise can lead to **pruritus**), carb tolerance may be impaired, Hepatotoxic (long term use in [high]), Hyperuricemia/Gout (↑uric acid), nausea



↓ **Fibric Acid Derivatives (Gemfibrozil, Fenofibrate)**: agonists at peroxisome PPARα (proliferator-activated receptor α; intranuclear receptor) ↓ transcribes genes for carb &/or lipid metabolism ↑↑ ***LPL activity!!!*** ↓↓VLDL lvls **esp ↑↑ TG's*** more pronounced than other drug**; to treat hypertriglyceridemias; side efx: more pronounced w/when used w/other drugs – GI sx, myopathy (myositis), cholesterol gallstones (b/c inhibits cholesterol 7-α hydroxylase ↓ bile becomes supersaturated w/cholesterol, +gallbladder hypomotility & mucus hypersecretion promote stone formation); Major DI's: can displace other albumin bound drugs like warfarin (thereby ↑anticoagulant effect of warfarin↓bleeding ↓tx'd w/vit K) & sulfonyl ureas (diabetic drug)

↑ **Bile Acid Binding Resins (Cholestyramine, Colestipol, Colesevelam)**: bind bile acids in intestine forming complex that's excreted in feces ↓ ↑oxidation of cholesterol to bile acids in liver ↓ ***↑LDL receptors, thus ↓↓serum LDL lvls, ↑bile acid synthesis (resp); +↑HDL; Side efx: Constipation, bloating, nausea, Bad tasting lead to compliance issues; Def fat soluble vit's: as resins bind bile acids interfering w/N fat digestion & absorption & so prevent ADEK absorption; DI's: may delay or ↓↓absorption of other concomitant oral meds (digitalis, warfarin) w/marked ↑PT time w/bleeding, interrupt Enterohepatic circulation of bile acids,

↓ **Ezetimibe**: prodrug ↓↓GI absorption of *ingested/oral* cholesterol; when used alone ↓↓LDL by 18% but combined w/statin, ↓↓LDL by 72% in clinical trials ↓ LOWERS ↓↓↓↓SERUM LDL & TG's!!! toxicity – well tolerated, MC'ly see diarrhea & abdominal pain

Drug	Mechanism	Effect on lipoproteins
Niacin	**↓ Synthesis of VLDL**	**↓TG's, ↓ LDL, ↑ HDL**
Statins	**↓Cholesterol synthesis** **↑LDL receptor**	**↓TG's** **↓ LDL**
Fibrates	**↑LPL (via PPARα), ↑triglyceride hydrolysis**	**↓ TG's, ↑ HDL (x APO-CIII)**
Ezetimibe	**↓ Intestinal absorption of cholesterol**	**↓ LDL, ↓Triglycerides**
Bile acid binding resins	**Interrupts enterohepatic circulation of bile acids** **↑Synthesis of bile acids, ↑Synthesis of LDL receptors**	**↓ LDL ↑ HDL**

Side efx:		
Bile acid-binding resins	**constipation, bloating, nausea, fat soluble Vit def**	**Bile acid-binding resin**
Niacin acid	**Flushing, diarrhea, hepatic dysfunc, nausea, pruritus, gout**	**Niacin acid**
HMG-CoA reductase inhibitors	**Hepatotoxicity (AST/ALT), myopathy**	**HMG-CoA reductase inhibitors**
Fibric acid derivatives	**Hepatotoxicity, nausea, myositis**	**Fibric acid derivatives**
Ezetimibe	**GI disturbance**	**Ezetimibe**

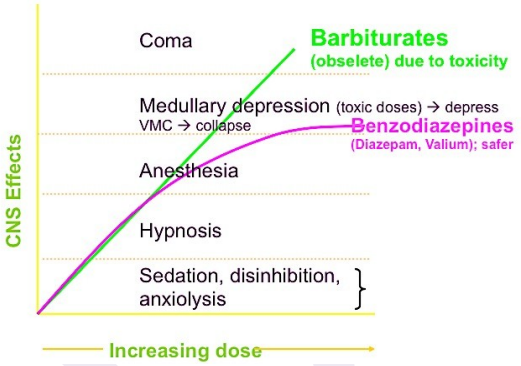
L6 Sedative Hypnotics*: Sedatives (used in anxiety), Hypnotics, Anxiolytic drugs (CNS)

FOR 2 MAJOR DISORDERS: *ANXIETY DISORDERS* (including phobias) ***&*** *SLEEP DISORDERS*

- **Sedative**: ability of these agents to calm or ↓anxiety, known as an anxiolytic effect
- **Hypnotic**: ability of these agents to induce drowsiness & encourage onset & maintenance of state of sleep; involve more pronounced depression of CNS than sedation

↓ Dose dependent CNS depression, majority these drugs have both efx depending on dose given (hence can't separate the 2 categories – get Sedative Hypnotics*)

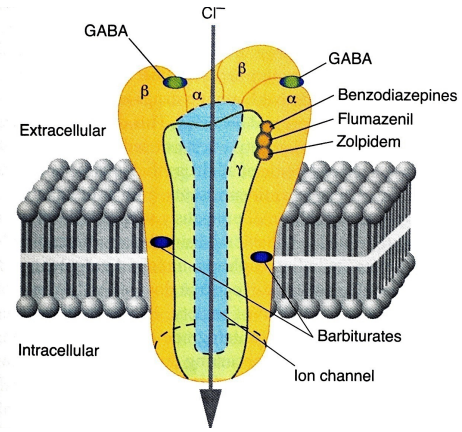
Dose dependent CNS depression



Except for buspirone, all these drugs have common axn ↓ ↑GABA (inhibitory NT in

Pharmacodynamics of sedative hypnotics

- **$GABA_A$ receptor:** Pentameric memb protein w/ion channel selectiv chloride ions ↓ once bound ↓ hyperpolarization*; has 2 α subunits, 2 β units & 1 γ subunit
- GABA binds btwn α/β interface (Benzos & newer drugs like zolpidem (Z-drugs for sleeping) also bind at α/γ interface) hence called BZ1 receptor on GABA A
- More hydrophobic Barbs bind in transmemb region of receptor



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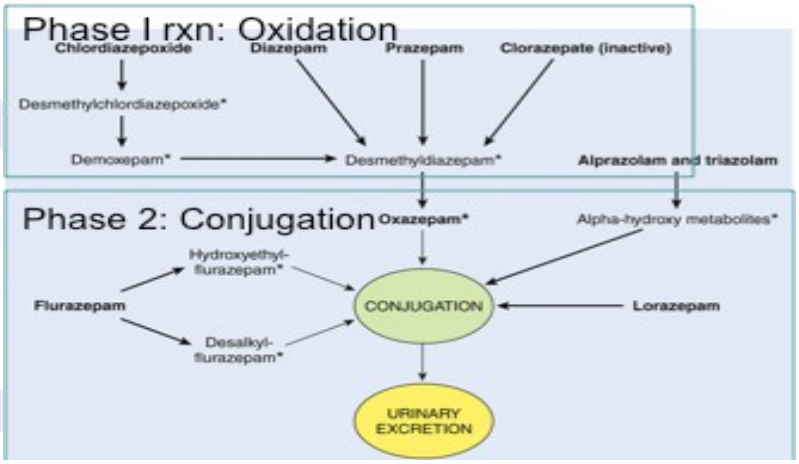
- *Absorption & distribution*: CNS entry depend on lipid solubility; *Ie. Highly lipid soluble = Triazolam, Thiopentone (barbiturate)- high lipid soluble; rapid onset of axn;
- *Metabolism*: when BZDs metabolized, metabolite can itself be active ⏤active metabolites responsible for their prolonged duration of axn; vs. Barbiturates are CYP inducers so drug interaxns
- *CNS Axns*:
  - 1. ***Sedation (smaller dose):*** Benzo's, barbiturates & most older sedative-hypnotic drugs exert calming efx w/concomitant ¬¬ anxiety at relatively low doses. In most, however, anxiolytic axns of sedative-hypnotics accompanied by some depressant efx on psychomotor & cognitive func's.
    - *Benzo's* also exert dose-dependent anterograde amnesic efx (inability to rmr events occurring during drug's duration of axn).
  - 2.***Effect on sleep pattern (hypnosis):*** promote sleep onset & ↑duration of sleep state & shortens time taken for onset of sleep, stage 2 NREM Sleep duration & ¬¬REM sleep duration
    - On discontinuation (barbiturates, triazolam benzo) rebound in REM sleep, hangover (irritability, dizziness, mood upset) less common w/Z drugs
  - 3. ***Anaesthesia high doses:*** benzo's, barbiturates but no others but ones mentioned under here; via depress CNS – general anaesthesia (requires LOC); depends on lipid solubility, which determines rapidity of onset & duration of efx
    - *Thiopental, methohexital*- inducing anaesthesia (don't maintain it, give another drug for that)
    - Thiopental is 1 of most lipid-soluble barbs, penetrating brain tissue rapidly after IV injection. Anesthetic effect terminated by redistribution
    - Midazolam (short $t_{1/2}$) & Diazepam (long $t_{1/2}$) used as adjuncts to other anesthetic agents.
    - Depressant axns of BZDs usually reversible w/flumazenil (ANSWER)
  - 4. ***Anticonvulsant***: clonazepam, nitrazepam, lorazepam, diazepam, Phenobarbital; High IV doses of Phenobarbital, Diazepam, or Lorazepam used in Status Epilepticus
  - 5. ***Skeletal m relaxation***: ONLY Benzo is Diazepam effective at sedative dose lvls for specific spasticity states; mechanisim: by inhibiting spinal reflexes
- ***Effect on RS*** ⏤High doses- respiratory depression
- ***Effect on CVS*** ⏤High doses- fall in BP
- ***Tolerance*** ⏤ Chronic use causes ¬¬responsiveness (tachyphylaxis), commonly occurs when sedative-hypnotics used continuously, need higher dosage to achieve same resp*; cross-tolerance occurs among diff sedative-hypnotics
- ***Psychologic dependence***: occurs frequently w/most sedative-hypnotics due their anti-anxiety, euphoric, disinhibitory & sleep-inducing efx
- ***Physical dependence***: altered state that requires continuous use of drug to prevent abstinence or w/drawal syndrome; w/drawal signs include anxiety, tremors, hyper-reflexia → to seizures; occurs more commonly w/shorter-acting drugs such as Pentobarbital & Secobarbital; unlikely to occur w/ Buspirone
  - Heroin: opioid w/half-life 30 min, to treat opioid w/drawal, give methadone (also opioid)
  - Diazepam DOC for alcohol w/drawal
- DOC for types of disorders:
  - *Acute Anxiety Disorders* – Propranolol (fast acting)
  - *Panic Disorder* – 1) Alprazolam / Clonazepam (immediate), 2) SSRI (long term)
  - *Phobic Disorders* (MC) – benzo (**Alprazolam)** or SSRI
  - *Obsessive-Compulsive Disorder* (OCD) – SSRI or TCA (clomipramine)
  - *Generalized Anxiety Disorder (GAD)* – BZD for immediate relief plus Buspirone or Venlafaxine (long term)
  - *Insomnia* – Zolpidem or Eszopiclone w/no efx on sleep architecture

- ***Drug Interaxns:** Drugs w/ efx on $GABA_A$ (BZDs, Barbs): Additive w/other CNS depressants such as general anesthetics, antihistaminics, alcohol, opiates (possible life threatening respiratory depression)
  - Barbiturates induce metabolism of drugs – oral contraceptives, phenytoin, warfarin, thus ↓↓their therapeutic effect

Benzodiazepines: bind to BZ_1 receptor (btwn α/β interface), on $GABA_A$ ↑↑frequency of chloride channel openings ↑CNS depression; but don't mimic GABA - this limits CNS depression (vs. barbiturates mimic GABA...thus more CNS depression); special b/c undergoes both phase 1 (oxidation; metabolized in liver by microsomal oxidation (N-dealkylation or aliphatic hydroxylation)) & phase 2 (gluconiridation; conjugation to form glucuronides (get excreted in urine)); overdose tx'd w/flumazenil (ANSWER) (see in pic above, binds in same place); imp feature of metabolism is forming active metabolites w/long half-lives; excreted via kidney; in low dose, sedative/anxiolytic (exert calming efx w/concomitant ↓↓of anxiety, esp for immediate anxious relief but most, accompanied by some depressant efx on psychomotor & cognitive func's), phobic disorders (MC), & GAD's w/buspirone; side efx: exert dose-dependent anterograde amnesic efx (can't rmr events during drug's duration of axn), drowsiness & lethargy (MC), impaired psychomotor performance [↓rxn times (slower resp's), motor incoordination & confusion]; W/drawal efx =...Rebound ↓REM sleep, Daytime sedation/depression; Cross tolerance w/alcohol (alcoholics need higher dose of BZD, physical & psych'al dependence– only on long time use; ↓sensitivity in elderly w/1 dose due to changes in brain func accompanying age (multiple due to liver)



- **Desmethyldiazepam** not a drug name* ($t_{1/2}$ = 40-140 h) active metabolite of Chlordiazepoxide, Diazepam, Prazepam, & Clorazepate. After several days of therapy these benzo's (e.g., Diazepam, +Flurazepam), accumulated active metabolites can → excessive sedation
- **Chlordiazepoxide**, Flurazepam** (long acting)
- **Midazolam:** Preanesthetic for IV General Anesthesia**; short $t_{1/2}$** used as adjuncts to other anesthetic agents
- ***Oxazepam, Temazepam & Lorazepam** ***don't form active metabolites***, undergo direct extrahepatic Phase II conjugation ↑b/c don't make long acting metabolites, prefer for elderly b/c age is factor which efx rate of metabolism (↓↓liver func)
- **Oxazepam & Lorazepam:** safer in old age pt's w/**insomnia** b/c don't form active metabolites
- **Clonazepam, Lorazepam as anticonvulsants** [High IV doses of ~~Phenobarbital (not in this class tho)~~, Diazepam, or Lorazepam used in Status Epilepticus]
- **Clonazepam:** for immediate panic attacks in panic disorders
- **Diazepam & Lorazepam DOC for status epilepticus, m spasms, tetanus, IV General Anesthesia, *febrile convulsions** (per rectal route) in infants & children**, chronic alcohol w/drawal**
- **Diazepam (2 ANSWERS)**: *only benzo effective* at sedative low dose lvls for specific spasticity states by inhibiting spinal reflexes for skeletal m relaxation; DOC for alcohol w/drawal & DOC as anticonvulsant at high IV dose in Status Epilepticus (sustained seizure activity for >20 mins where pt won't regain consciousness in btwn); **long $t_{1/2}$ used as adjuncts to other anesthetic agents**

- ****Triazolam:** barbiturate *Ie. Highly lipid soluble = rapid onset of axn & CNS entry; short elimination half-life, 2–3 hrs favored as hypnotic **for insomnia** rather than sedative but on discontinuation, rebound REM sleep, hangover (irritability, dizziness, mood upset)
- **Alprazolam & triazolam undergo** -hydroxylation, & resulting metabolites exert short-lived pharmacologic efx b/c they're rapidly conjugated to form inactive glucuronides
- **Alprazolam:** DOC for Panic disorders & some phobias (agoraphobias), for immediate panic attack
- **Flunitrazepam**: Used for DATE RAPE, not tx!!! Due to its anterograde amnestic efx

Barbiturates (acidic): hydrophobic & bind transmemb region of receptor; mimic GABA… thus more CNS depression; Act on $GABA_A$ receptor complex ↑ prolong duration of chloride channel openings (**HYPERPOLARIZATION**) ↑& CNS depression; inhibitory efx on glutamate receptors; low doses for sedation (exert calming efx w/concomitant ↓in anxiety, often accompanied by some depressant efx on psychomotor & cognitive func's), sleep/hypnosis (but On discontinuation, rebound REM sleep, hangover (irritability, dizziness, mood upset); CYP inducers (induce metabolism of drugs – OCT's, phenytoin, warfarin, thus ↓their therapeutic efx)***, w/drawal by anxiety & agitation, may precipitate acute intermittent porphyria; some pregnancy category X (temazepam) & contraindicated in pregnancy, most category D

- **Phenobarbital/Phenobarbitone:** long acting **used for seizures*;** sodium salt; excreted unchanged in urine to certain extent (20–30% in humans) & elimination rate ↓sig'ly by urine alkalinization–pt'ly due to ↓ionization at alkaline pH, since weak acid w/pKa of 7.4; TOXICITY tx'd w/charcoal (physical antagonism)
- **Secobarbital, Pentobarbital –** more commonly can develop *physical dependence* b/c short acting
- ****Thiopental/Thiopentone:** barbiturate **for lethal execution & inducing anesthesia** (further maintained by other drugs); w/**(1) ULTRA shortest duration of anesthesia** (b/c redistributes from brain to other peripheral tissues so its [brain]↓) barbiturate w/half life of few secs-mins; *Ie. Highly lipid soluble hence (2) **rapid onset** of axn & CNS entry; 1 of most lipid-soluble barbs, penetrating brain tissue rapidly after IV injection. Anesthetic efx terminated by redistribution

Barbiturates	**Benzodiazepines**
Both bind to $GABA_A$ receptor complex Both have potential for tolerance & physical dependence (need more for required efx) Both w/low doses for sedation (exert calming efx w/concomitant ↓in anxiety, often accompanied by some depressant efx on psychomotor & cognitive func's)	
Act on $GABA_A$ receptor complex (but transmemb region) ↓ Prolong duration of chloride channel openings ↓ CNS depression	Act on $GABA_A$ receptor complex/Bind to BZ_1 receptor, on $GABA_A$ ↓ ↓frequency of chloride channel openings ↓ CNS depression
In high doses, have more intense efx than benzo's b/c inhibit on glutamate receptors	
Sedation (smaller doses)	
RMR OBSOLETE & TOXIC	MORE preferred, less toxic
When metabolized ↑ active metabolite responsible for prolonged duration of axn of these drugs	Barbiturates are inducers of CYP.so drug interaxns
➢ **Pentobarbital, Phenobarbital, Secobarbital, Thiopental (highly lipid soluble)**	➢ **Alprazolam, Chlordiazepoxide, Clonazepam, Diazepam, Flurazepam, Lorazepam, Midazolam, Oxazepam, Temazepam, Triazolam (highly lipid soluble), etc.**
	All benzo's that don't convert to metabolites preferred for elderly (whose liver func's have

	)
High IV doses of Phenobarbital, Diazepam, or Lorazepam are used in Status Epilepticus.	
Toxicity: – CYP inducer****** (RBCGAP; careful about what other drugs being concurrently admin'd), ie. Warfarin efx – may need higher dose of it – W/drawl signs…anxiety, agitation – enzyme inducers – May precipitate acute intermittent porphyria – **Porphyria** - overproduction & accumulated porphyrins (or their chem'al precursors). Acute hepatic porphyrias primarily affect NS, resulting in abdominal pain, vomiting, acute neuropathy, seizures, & mental disturbances, including hallucinations, depression, anxiety, & paranoia. Cardiac arrhythmias & tachycardia may develop as ANS affected. Pain severe & can, in some, both acute & chronic. Constipation frequently, as NS of gut affected, but diarrhea can also occur.	**Toxicity:** - Drowsiness & lethargy— MC - Impaired psychomotor performance (rxn times (slower resp's), motor incoordination & confusion) - W/drawal efx of BZDs…Rebound in REM sleep, Daytime sedation/depression - Tolerance. Cross tolerance w/alcohol (alcoholics need a higher dose of BZD) - Anterograde amnesia - Additive CNS depression when used w/other CNS depressant drugs - narcotic analgesics, anticonvulsants, antihistamines, TCA's - **Interaxn w/ethanol is MC of drug interaxn involving sedative-hypnotics.**** (less likely w/Buspirone than w/other sedative-hypnotics)
Some BZDs & Barbs pregnancy category X (Temazepam) & contraindicated in pregnancy. Most category D. So instead outside these categories, use Z-drugs (eg zolpidem) are pregnancy category C & so safer during pregnancy & Buspirone is category B.	
OD tx'd by alkalinizing urine	OD tx'd w/**flumazenil**** – BZD antagonist – reverses depressant benzo axns; no beneficial efx in OD w/other sedative hypnotics, only for benzos; BUT contraindicated in BZD abuse pregnancy F as it risk for seizures in newborn

***Non-sedating Anxiolytic Drugs*:** unlike benzo's, don't cause drowsiness

- **Buspirone:** unlike benzo's, don't cause drowsiness; partial serotonin agonist on 5-HT1A serotonin receptors in median raphe nuc **for tx'ing GAD**** (generalized anxiety disorders; along w/benzo's for immediate) but less effective in panic disorders; takes 1-2 weeks for efx, no rebound anxiety or w/drawal on abrupt discontinuance, minimal abuse liability, causes less psychomotor impairment than benzo's & doesn't efx driving skills, NO SEDATIVE, HYPNOTIC, ANTICONVULSANT OR M RELAXANT PROPERTIES; category B in pregnant F
- **Propranolol (b-blocker HR for acute anxiety, ie. stage fear) b/c fast acting**

Newer hypnotics/Z drugs: for sleep disorders to induce sleep (sedation), but not anxiety; stimulate specific benzodiazepine (BZ1) receptors (GABA A); adv that less rebound in REM sleep, hangover (irritability, dizziness, mood upset) less common; for category C in pregnancy thus safer

- **Zolpidem:** rapidly metabolized to inactive metabolites via oxidation & hydroxylation by CYP3A4 isozyme; half-life 1.5-3.5 hrs, w/clearance in elderly; for insomnia
- **Zaleplon:** metabolized to inactive metabolites, by hepatic aldehyde oxidase & pt'ly by CYP3A4; half-life ~1 hr; dosage should be in pt's w/hepatic impairment & elderly
- **Both these** chemically NOT benzo's, exert their efx on CNS thru interaxn w/certain benzo's receptors; used in management of insomnia; their efx antagonized by flumazenil
- **EsZopiclone:** for insomnia

Melatonin receptor agonists: **Ramelteon (ANSWER) (new): at MT1 & MT2 melatonin receptors,** acts as melatonin (on melatonin receptors for maintaining circadian rhythms underlying sleep-wake cycle), used for managing insominia); adv's – not associated w/next morning hangover efx, No reduction in alertness, No w/drawal, no sleep rebound when discontinued, no respiratory depression, rept'd adverse sx mild (↓ testosterone; ↑PRL)

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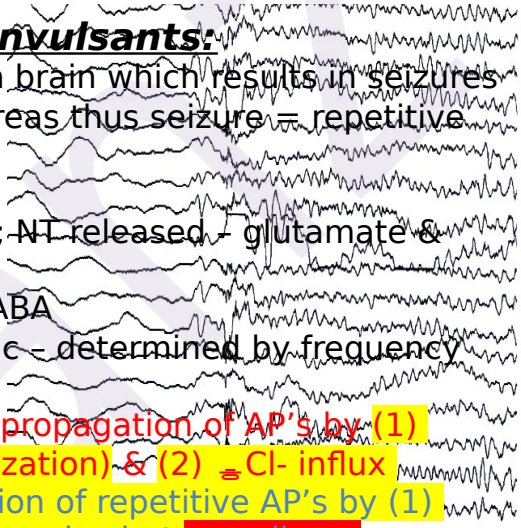
Special note about few drugs:

- Triazolam short duration action and rapid onset axn
- Drug w/shorter duration axn will produce more w/drawal sx. So Long acting drugs better for this.
- Zolpidem produces no w/drawal symptoms, day time sedation, & change in sleep pattern
- Alprazolam is DOC for Panic disorders & agoraphobia
- Buspirone is DOC for generalized anxiety
- Many BDZ Phase-I metabolites are still ACTIVE …so they have longer $\mathbf{t^{1/2}}$
- But some will not have active metabolites…so they're safer in old age pt's eg: Oxazepam & lorazepam

L7 Antiseizure/ Antiepileptics/Anticonvulsants:



- ***Epilepsy***: group of sx caused from abnormal elec'al activity in brain which results in seizures of varying magnitude; seizures caused by hyperactive brain areas thus seizure = repetitive generation of AP
- ***Cellular mechanisms of seizure generation***:
  - ***Excitation (too much)*** ↑ ionic-inward Na^+, Ca^{2+} currents; NT released – glutamate & aspartate
  - ***Inhibition (too little)*** ↓ ionic-inward Cl; NT released – GABA
- Rmr it's rate of AP propagation that determines neurologic func – determined by frequency of AP's
- Multiple chem'al classes of drugs, all have same approach - ↓↓propagation of AP's by (1) ↓↓Na^+, Ca^{2+} influx (delaying depolarization/ prolonging repolarization) & (2) ↑Cl- influx (hyperpolarizing memb); Antiepileptics MOA to inhibit generation of repetitive AP's by (1) block Na^+ channels, (2) block Ca^{2+} channels & (3) Open Cl- channels ; but rmr all are teratogenic – cleft lip, cleft palate

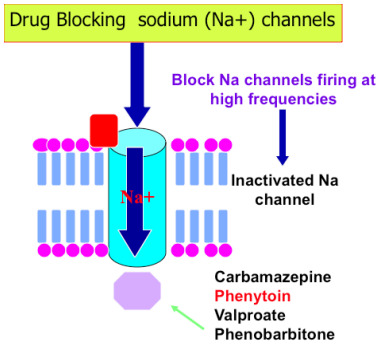
(1)***Na^+ channel blocking antiepileptics:*** block Na^+ channels firing at high frequencies ↓ inactivating Na^+ channel; phenytoin, Carbamazepine, valproic acid & Phenobarbitone (at high doses) block VG dependent sodium channels at high firing frequencies

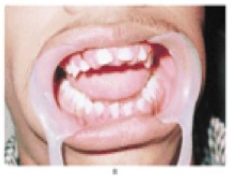
a. ***Carbamazepine, phenobarbitone & phenytoin** are CYP inducers ↓ DI's ↓↓efx of other drugs, ie. OCT's, & ↑their metabolism leading to therapeutic failure
b. **Carbamazepine (tegretol):** treats GTC seizures along w/newer drugs to ↓↓their side efx; & for complex partial seizures, ***trigeminal neuralgia***** & bipolar disorder; most potent CYP inducer, adverse efx: diploplia, ataxia, **hyponatremia (SIADH tx'd w/Demecocycline),** Stevens johnson syndrome, aplastic anemia, teratogenic in pregnant F's
c. **Phenobarbitone/Phenobarbital**: binds transmemb portion b/c lipid soluble as Barb; adverse efx of sedation, drowsiness, mood changes; as IV, given for maintenance in status epilepticus;
d. ***Phenytoin**: (1) High Protein binding*** & hence DI's& (2) Metabolism: enzymes responsible for degradation get saturated at [therapeutic], (3) in High doses – follows 0 order kinetics of elimination (like high dose aspirin & alcohol); [Plasma] not linearly rel'd to dose so need therapeutic drug monitoring; also interacts w/Warfarin (highly protein bound) & sulfonamide (treat UTI's); Css = 300 mg under day, but if pt doesn't respond to this amt, if was any other drug, could double the dose, but w/phenytoin you can't do that, can only ↑dose by 25-30 mg b/c kinetics change very quickly in this drug from 0 to 1st order (due to low to high dose change) – very dangerous b/c tend to accumulate drug, thus can only change phenytoin dose in minimal small increments; adverse efx: Nystagmus, diploplia, Ataxia, vertigo, Gingival Hyperplasia******, Hirsutism/Coarse facial features, Megaloblastic anemia, Osteomalacia (impedes vit D ↓), Teratogenic – fet**al hydantoin syndrome** (celft lip,

cleft palate, cardiac dfx) & Drowsiness,; treats GTC seizures along w/newer drugs to ↓↓their side efx; as IV, for maintenance in status epilepticus, also simple partial seizures, complex partial seizures

e. ***Phenytoin & Valproate highly plasma protein bound ↓ so NSAIDs, warfarin, sulfonamides can displace them from its protein binding sites, ↑in free drug lvl & toxicity

f. Valproate: only drug that's not enzyme inducer, but still has drug interaxns b/c highly plasma protein bound





g. **Zonisamide**: new; block high frequency firing via axn on Na^+ channels; treats **myoclonic seizures**

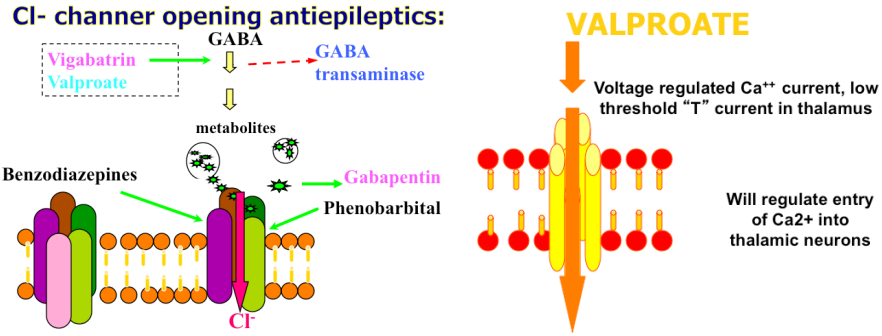
h. **Lamotrigine**: prolongs inactivation of Na channels, presynaptic voltage gated N type of Ca^2+channel - ↓synaptic release of glutamate

(2) ***Cl- channer opening antiepileptics***: ↑Cl- influx during seizure ↓ hyperpolarization ↓ ↓↓seizure activity

a. **Benzo's (focus on anti-seizure ones!)**: ↑frequency of GABA-mediated Cl- channel openings
   i. **Diazepam:** IV for *immediate* tx for **status epilepticus**, IV or rectal for **febrile convulsions**
   ii. **Clonazepam**
   iii. **Lorazepam:** IV for *immediate* tx for **status epilepticus**
   iv. **Nitrazepam**

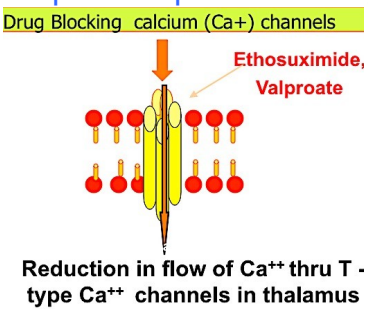
b. **Barbiturates: Phenobarbitol:** prolong duration of GABA-mediated Cl- channel openings; treats GTC seizures along w/newer drugs to ↓↓their side efx

c. **GABA transaminase inhibitors****
   i. ★**Valproate (valproic acid): special drug w/3 mechanisms –** opens Cl- channels (by enhancing GABA transmission), blocks VG Na^+ channels & T-type*** Ca^{2+} currents/channels (this counteracts mechanism of absence seizures – influx Ca^{2+}) & least sedative*; only anti-epileptic that's not enzyme inducer, but still DI's b/c highly plasma protein bound; adverse efx: ***category X in pregnancy (↑↑ spina bifida),*** N/V, weight gain, ***hepatotoxicity in kids***** ***(b/c produces 2-propyl-2-pentanoic acid) hence why prefer ethosuximide in kids, pancreatitis (abdominal pain, steatorrhea, ^amylase) & dose dependent alopecia, CYP INHIBITOR;*** treats GTC seizures along w/newer drugs to ↓↓their side efx; for GTC seizures, simple partial seizures, complex partial seizures & **absence seizures**, myoclonic seizures & bipolar disorder, prophylactically bipolar disorders & migraines
   ii. ***Vigabatrine**: new drug; **irreversibly** inhibits GABA transaminase (GTA); ~~↓GABA by irreversibly inhibiting GABA transaminase~~



(3) ***Ca^{2+} channel blocking antiepileptics***: ↓↓flow of Ca^{2+} thru T-type Ca^{2+} channels in thalamus; both drugs block slow, threshold, "transient" T-type Ca^{2+} channels in thalamic neurons

a. **Ethosuximide**: **treats absence seizures**; prefer in kids due to valproate's side efx; less side efx – fatigue, headache & nausea
b. ***Valproate/valproic acid: special drug w/ALL 3 MOA's–** opens Cl- channels (by enhancing GABA transmission), blocks VG Na^+ channels & T-type*** Ca^{2+} currents; (counteracts mechanism of absence seizures – influx of Ca^{2+})
c. **Lamotrigine**: prolongs inactivation of Na channels, presynaptic VG N type Ca^{2}+ channel - ↓synaptic glutamate release; SE: Stevens-Johnson syndrome
d. ***Gabapentin**/pregbalin: GABA analogue; bind to presynaptic VG N type of Ca^{2+} channel to ↓synaptic glutamate release; analgesic & antiepileptic for epilepsy, postherpetic neuralgia, neuropathic pain & RLS; no anti-inflammatory efx



▫ *Conventional or Old drugs* - Benzo's, Barbiturates ***Phenytoin,** Carbamazepine, Valproate, Ethosuximide

▫ *New drugs*: all these have inhibitory efx on excitatory NT's; **Gabapentin, Lamotrigine, Topiramate, Levetiracetam, Felbamate, Tiagabine, Vigabatrine, Zonisamide**

- **Topiramate**: blocks Na+ channels & glutamate receptors, enhances GABA activity, used in focal seizures in adults & kids >age 2; also used in migraine prophylaxis
- ***Levetiracetam**: **bind to synaptic vesicular protein (SV_2A) – ↓synaptic release of glutamate; can be used apart from phenobarbital, to treat seizures in pregnancy**
- **Felbamate**: **block NMDA (glutamate) receptors; treats Lennox-Gastant syndrome (infant w/seizures leaving to irreversible CNS damage)**
- **Tiagabine**: block GABA reuptake by blockade of GAT (GABA transporter)

- ***Status epilepticus***: **repeated attacks of GTC seizures in quick succession in brief period**, mostly by not regaining consciousness in btwn attacks; Eg: 25 yr woman w/LOC followed by urinary incontinence & tongue biting, m rigidity & jerky movements of her limbs. Episode lasted for 1 min & she had another similar episode w/in next 10 mins; ***DOC for immediate tx: IV Diazepam or IV Lorazepam; for maintenance, use IV Phenytoin or phenobarbital; or fosphenytoin***

- *Generalized seizures*: electrical abnormality thru out cerebral cortex
  - **Generalized Tonic Clonic (GTC)**: suddenly falls, rigid & unconscious, may begin to shake, or convulse w/vigorous & regular m contractions; ± w/fecal oral incontinence;

tx'd by **phenytoin**, **Carbamazepine, Valproate, phenobarbital**, along w/newer drugs to ¬¬their side efx

- **Absence seizures**: in kids, noticed by mother or teachers in nursery school; star gazing, looking at space constantly, or Dropping pencil; brief LOC; Typical EEG ….3Hz spike & wave pattern (see next slide); T current in thalamus is responsible for these, so can only be tx'd by drugs affecting this – **Valproate** (other ages, b/c hepatotoxicity) & **Ethosuximide** (*kids*)
- **Myoclonic seizures:** tx'd by **valproic acid & zonisamide**
- **Atonic**
- **Infantile**

➢ ***Febrile convulsions***: tx'd by **diazepam (IV or rectal)**

➢ ***Partial Seizures***: elec'al abnormality lmtd to 1 pt of cerebral cortex

- ***Simple partial*** *seizures*: consciousness preserved; convulsions confined to group of m's, or localized sensory disturbance; tx'd by **phenytoin**, **Carbamazepine, Valproate, phenobarbital**, along w/newer drugs to ¬¬their side efx

- ***Complex partial*** *seizures*: confused, repetitive & inappropriate behavior; unaware of surroundings or of what they're doing; involuntary activities like lip smacking, chewing; tx'd by **phenytoin, Carbamazepine, Valproate**

➢ **Trigeminal neuralgia***:** tx'd by **Carbamazepine**

➢ **Bipolar disorder**: tx'd by **valproic acid & Carbamazepine** (used to be lithium, but has many side efx)

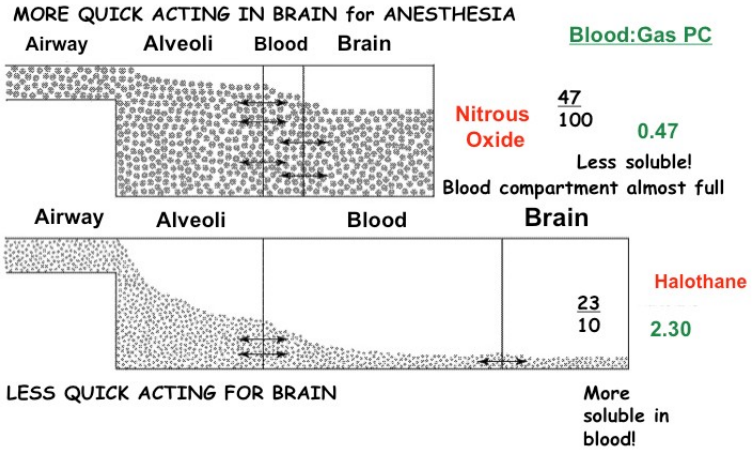
L8 General & Local Anesthetics: Interpret drug by onset of axn

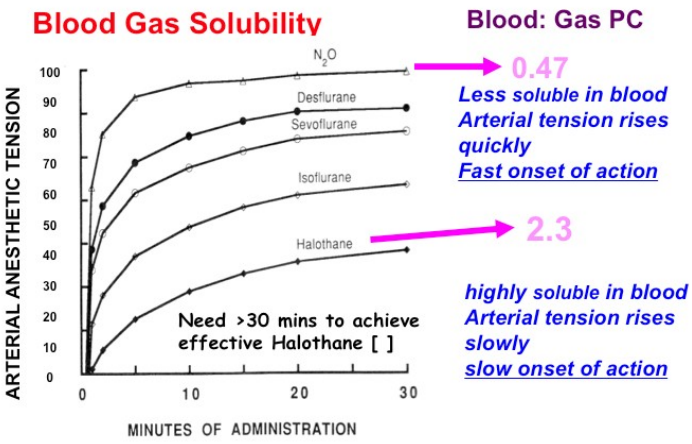
➢ **General Anesthesia***: state – analgesia, amnesia, LOC, inhibition of sensory & autonomic reflexes, & skeletal m's relaxation;* ALL **directly activate $GABA_A$ receptors** [Inhaled GA, barbiturates, BZDs], ONLY diff one is ketamine *-NMDA receptor antagonism – ketamine (NMDA – excitatory NT receptors)*;* inhibit nicotinic Ach receptors

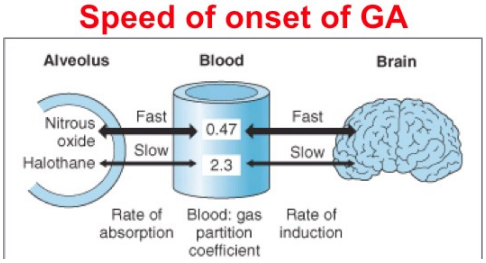
- ***Stage 1: Analgesia***: analgesia, amnesia
- ***Stage 2***: Disinhibition, delirious, excitement, amnesia, reflex enhanced
- ***Stage 3: Surgical anesthesia****** **what we need as quickly & smoothly as possible;** deep *unconsciousness*, no pain reflexes, regular respiration & m relaxation
- ***Stage 4:*** *Medullary paralysis, severe respiratory & cardiovascular depression*

Inhaled General Anesthetics: many steps involved btwn admin of anesthetic from vaporizer & its deposition in brain; onset depends on how fast drug will diffuse; uptake & distribution depends on (1) partial pressure or tension in inspired air as measure of [drug's] & (2) induction speed of anesthesia (depends on 5 factors below)

1. ****Blood Gas Solubility of anesthetic:** aka **Blood:Gas Partition coefficient** = ratio of [ ] in blood to [ ] in gas phase; more soluble anesthetic in blood = more of it which must dissolve to raise partial pressure; thus *soluble agents have larger blood reservoir whereas reservoir for insoluble agents is small & fills more quickly*; determines onset of anesthesia; more soluble = slower onset axn of inhalant & arterial tension rises slowly & lower in graph, wider blood compartment width; ALL VICE VERSA







- Solubility is first thing to determine onset.
- Can give graph or number.
- **Just know lower # is faster onset & faster recovery.**

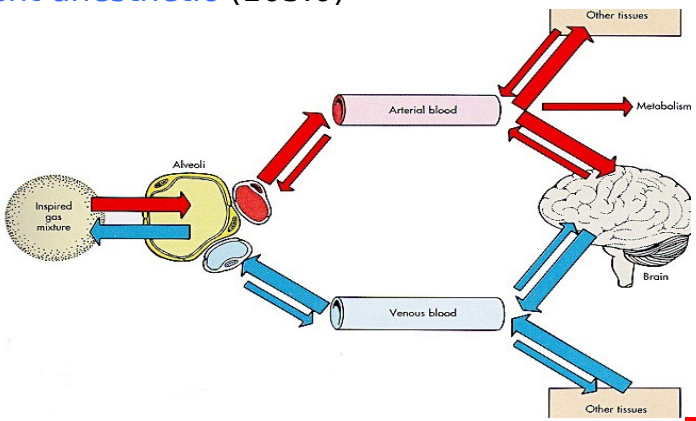
2. ***Inspired gas partial pressure***: [drug] in inspired air determined by pulm ventilation rate (BF & CO); Higher partial pressure of gas in lungs ␣ more rapid induction; achieved by giving [high]'s of gas initially
3. ***Pulm ventilation rate***: ⁷⁷ **ventilation rate = ⁷⁷ rapid onset** of anesthesia (difference btwn O_2 – CO_2)
4. ***Pulm BF (decided by CO):*** **⁷⁷ pulm BF = slower onset** of anesthesia; means same volume of gas from alveoli diffuses into larger volume of blood per unit time
5. ***Arteriovenous [ ] gradient***

␣ *Elimination of inhaled anesthetics*: Anesthesia terminated by redistribution of drug from brain to blood & elimination of gases thru lungs; N_2O least potent, never used alone b/c highest dose not enough to get to stage 3 anesthesia & no skeletal m relaxant property

␣ ***MAC (Minimal Alveolar concentration):*** measure of ***potency*** of Inhaled Anesthetics; Less the MAC, more the potency of drug; rmr, lower EC50 = more potency; minimal alveolar [anesthetic] at which 50% pt's do not respond to surgical stimulus, ie. ***Methoxyflurane*** is most potent (0.16) & ***N_2O*** is least potent anesthetic (105.0)

Properties of Inhalation Anesthetics

Drug	*Minimum Alveolar Concentration	*Blood: Gas Partition Coefficient	Rate of Induction	Amount of Skeletal Muscle Relaxation
Nitrous oxide	>100	0.47	Fast	None
Desflurane	6.0	0.42	Fast	Medium
Enflurane	1.7	1.9	Medium	Medium
Halothane	0.75	2.3	Slow	Low
Isoflurane	1.2	1.4	Medium	Medium
Sevoflurane	1.9	0.63	Fast	Medium



Quantal dose resp curve (quantal effect à when testing in large pop à can determine potency based on many exp'al animals)

␣ ***CNS efx***: ¬brain metabolic rate ␣ ¬vascular resistance ␣ ↑cerebral BF ␣ *↑ICP (careful when giving to pt who needs surgery for head trauma)*; *+Enflurane- changes in EEG- muscle twitching*

␣ ***CVS efx:*** (1) *hypotension* from multiple factors, direct myocardial depression – enflurane, halothane. ¬CO OR Vasodilatation by Isoflurane, (2) Nitrous oxide less likely to affect cardiac func & (3) Halothane arrythmogenic - sensitizes myocardium to catecholamines, bad in surgery

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↓ ***Respiratory efx:*** all agents depress min volume & tidal volume- leading to ↑*arterial CO_2 tension*

- *Nitrous oxide- less effect on respiration*
- Most inhaled agents are bronchodilators except *desflurane- bronchospasm*

↓ Toxicity:

- ***Malignant Hyperthermia** ↓ genetically determined abnormality in ryanodine receptors, can lead to tachycardia & respiratory/cadio collapse** (↑tone & core body temp); esp. when halogenated GA used w/ or w/out succinylcholine (ie. esp halothane); tx w/**IV Dantrolene** (immediately) blocks Ca^{2+} channels which prevents release of Ca^{2+} via directly inhibiting its release in skeletal m
- Halothane undergoes >40% hepatic metabolism, rare postop hepatitis; sensitize heart to catecholamines (arrhythmias)
- Nitrous oxide: Megaloblastic anemia may occur after prolonged exposure due to ↓↓methionine synthase activity (Vit B_{12} def)

➢ **Gas Nitrous Oxide (N2O): INHALED** & best for induction so in almost any anesthetic protocol; less soluble in blood (low blood:Gas PC; shorter width), more quickly absorbed, faster induction, arterial tension rises quickly, so fast onset of axn in brain; also has very quick recovery; least potent (MAC = 105.0), never used alone b/c highest dose not enough to get to stage 3 anesthesia & no skeletal m relaxant property; *less effect on respiration;* Toxicity = Megaloblastic anemia may occur after prolonged exposure due to ↓↓ in methionine synthase activity (Vit B_{12} def), b/c of hypoxia can cause spontaneous abortions

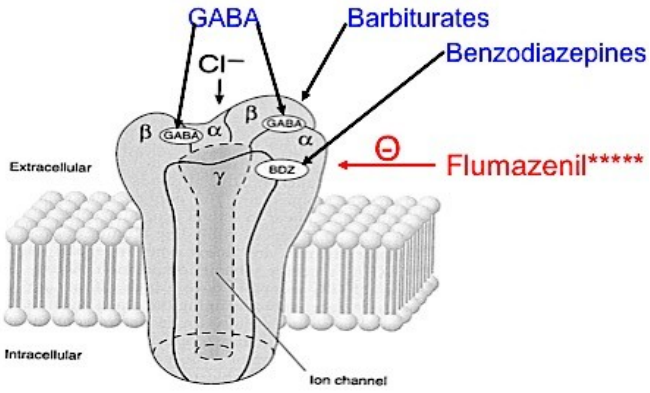
➢ **Volatile liquids: INHALED;** easily ***vaporized liquid*** halogenated HC's (hydrocarbons)

- **Halothane**: more soluble in blood (larger width compartment) so slow absorption in blood & less quick acting for brain aka **slower acting**, arterial tension rises slowly (lowest height on graph), need >30 mins to achieve effective dose; ↓↓CO ↓direct myocardial depression & hypotension; arrythmogenic - sensitizes myocardium to catecholamines, bad in surgery so no longer prefer; more side efx – undergoes >40% **hepatic metabolism**, Rare postop hepatitis; malignant hyperthermia esp in genetically disposed ind's
- **Enflurane:** *changes in EEG- muscle twitching as CNS efx so do not prefer for surgery in pt w/epileptic seizures (can induce seizures)*; ↓↓CO ↓direct myocardial depression & hypotension;
- **Methoxyflurane**: most potent (MAC = 0.16)
- **Sevoflurane**
- **Desflurane:** ONLY bronco constrictor ↓ bronchospasm so don't give in asthmatics
- **Isoflurane**: vasodilator ↓ hypotension

↓↓ ***IV General Anaesthetics:*** MC'ly used drugs to induce anaesthesia

- ***Benzo's & Barbs MOA – both*** bind to GABA A receptors at diff sites, both cause ↑Cl- influx in presence of GABA

↓↓ ***Barbiturates at high doses also GABA mimetic, block Na^+ channels & NMDA/glutamate receptors; both thiopental & methohexital highly lipid soluble*** & produce unconsciousness & surgical anesthesia in <1 min; for induction of anesthesia & short procedures; axns terminated by redistribution; w/single bolus – emergence from GA occurs w/in 10 mins; rmr OD tx'd by alkanization urine b/c barbs are acidic!!!!



- ***Thiopental:*** ultrashort acting barbiturate used to anesthetic induction & short procedures, don't use anymore; axns terminated by redistribution; produce unconsciousness & surgical anesthesia in <1 min
- ***Methohexital***: highly lipid soluble & fast+short acting barbiturate; axns terminated by redistribution; produce unconsciousness & surgical anesthesia in <1 min; to induce anesthesia & short procedures

- ***Diazepam:***
- ***Midazolam***: benzo for anxiolysis, amnesia & sedation prior to induction of GA w/another agent – inhaled anesthetics; good maintenance drug & good pre-anesthetic; ↓↓anxiety; short acting & used w/inducing drugs or can use for short procedures; efx reversed by flumazenil
  - ***If Benzo OD during surgery à use flumazenil***

- ***Propofol*:*** IV, for induction of anesthesia as rapid as IV barbs but **recovery more rapid so**, used in place of thiopental; antiemetic efx (stops vomiting); as anesthetic in out pt surgical procedures; cause marked hypotension (↓↓PVR), HSR rxns due to egg lipids in it
- ***Etomidate:*** used for **rapid induction of anesthesia**; short duration of axn, adv of little efx on CV & respiration; mainly **for those w/lmtd cardiac or respiratory reverse**; side efx: pain & myoclonus on injection, prolonged admin can cause adrenal suppression

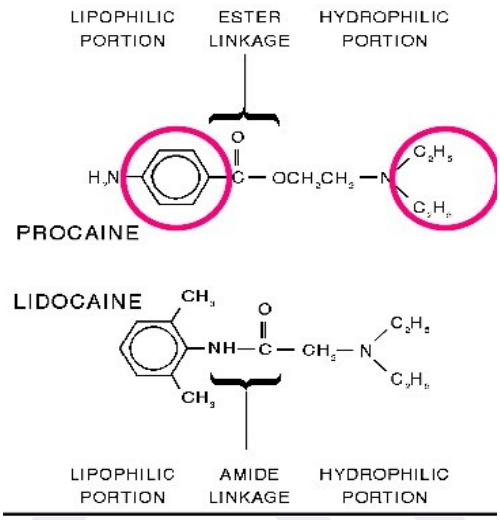
- ***Opioids (as pt of IV general anesthetics) for Neurolept anesthesia***
- ***Fentanyl***: IV, preferred over morphine; opioid derivative; via IV, used more b/c fast & short acting; produces **state of analgesia & amnesia** when used w/**droperidol & nitrous oxide**, called **neurolept anesthesia**; in **procedures w/short duration** (like endoscopies, or ↓↓of fractures); cause respiratory depression (via mu receptors), high doses cause chest wall rigidity & post-op respiratory depression reversed by naloxone (opioid antagonist)
- ***Morphine:*** opioid, don't prefer anymore; inhibits Ca2+ influx to inhibit substance P transmission of pain; in spine, bind to mu receptors on primary afferent neuron ↓ closing VG Ca2+ channels, ↓↓Ca2+ influx, & ↓↓excitatory NT release (ACh, NE, 5-HT, glutamate, substance P from presynaptic terminal); bind to mu receptors on postsynaptic memb to open K+ channels w/subsequent memb hyperpolarization due to K+ efflux; thus inhibits synaptic activity in CNS to attenuate pain transmission producing analgesia
- ***Newer opioids: Alfentanil & Remifentanil***: **for induction, w/rapid recovery** b/c metabolism by blood & tissue esterases; high doses cause chest wall rigidity & post-op respiratory depression reversed by naloxone

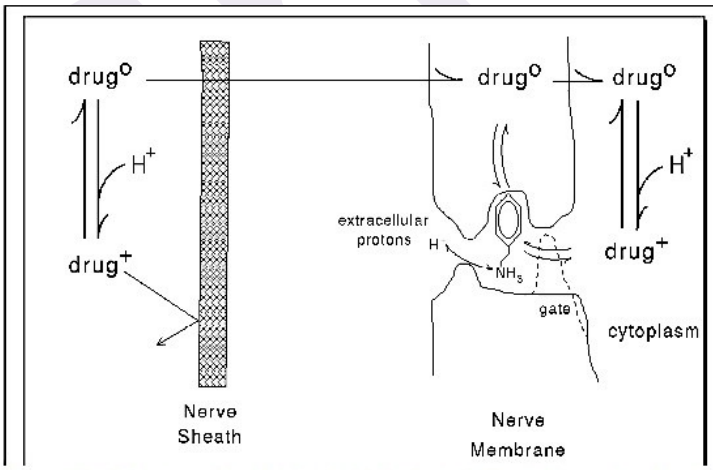
- ****Dissociative anesthetic: Ketamine:*** PCP analog (phencyclidine, angel dust hallucinogen, drug of abuse); only 1 which doesn't act on GABA receptors, rather **NMDA receptor antagonist (glutamate receptor blocker)**; disassociative = of person, place & time; produces cataleptic state of intense analgesia, amnesia, eyes open, unresponsive to commands/pain; ONLY IV anesthetic which cardiac stimulant ↓ ↓HR & BP; for **shock states**

(hypotensive) or risk for **bronchospasm**; & in **kids & young adults** for **short surgical procedures** where we don't need m relaxant or in vet's otherwise NOT USED; side efx: nystagmus, pupillary dilation, salivation, hallucinations

Preanesthetic meds: relieve anxiety (sedatives), analgesia (opioids, NSAIDS), ↓secretions (anticholinergics), antiemetic (D_2 receptor blockers), ↓gastric acidity (H_2 receptor blockers & PPI),

Local anesthetic: ***reversibly*** **block n conduction in local area**, so applied locally to block pain transmission; cause **loss of sensation w/out LOC**; lipophilic aromatic portion, intermediate chain & hydrophilic amine portion; *intermediate chain either posses ester linkage or amide linkage*, depending on which LAs – so classified as esters or amides**; MOA see 2nd pic – voltage & time dependent** blockade of Na channels in n's à ↓/prevent depolarization (n AP) ↓ blocking AP conduction (thus block Na^+ channels **in inactivated state**) [Note Na channel toxins/fish toxins – tetrodotoxin & saxitoxin block in same way]; all weak bases (pH ~6-8) & get more ionized in acidic pH à makes it more insoluble (more easily secreted) – can't be absorbed; either exist as ionized or unionized form depending on pH of body fluids [ie. ↓LA efx during inflammation b/c EC acidosis ↓ ↑more ionized form); using topically; ***Unionized*** **form penetrates n sheath** à once in n cell, becomes ***ionized*** ***this cation form*** **binds to Na channels & blocks n conduction**. If ionized à can't enter (must be unionized) [rmr Acidic: aspirin, barbs & Bases: local anesthetics (both amides & esters); co-admid'd w/ α1 agonists (epinephrine – works on all receptors, just not used w/cocaine b/c that already causes vaconstriction) ↓ ↓systemic absorption due to local vasoconstriction (↓systemic side efx ie. Lidocaine ↓ seizures & convulsions), ↑neuronal uptake (higher local [ ]), ↓systemic toxicity & Prolong duration of local anesthesia





LA act in their cationic(ionic) form but most reach their site of axn by penetrating n sheath & axonal memb as unionized form

Side note: VG Na+ channel toxins:

Tetrodotoxin (Japanese puffer fish)	Bind Na+ channels, inhibiting Na+ influx & preventing AP conduction in n & cardiac tissue (tetrodotoxin)
Saxitoxin (dinoflagellates in red tide)	
Ciguatoxin (exotic fish, Moray eel)	Bind Na+ channel, keeping it open & causing persistent depolarization
Batrachotoxin (SA frogs)	

LA Esters: -caines; hydrolyzed by pseudocholinesterases (is in **plasma** à succinylcholine (m relaxant) also hydrolyzed by pseudocholinesterase, whereas ACh-ase is in n synapse) to PABA (*Paraaminobenzoic acid* derivatives) ↓ cause allergic rxns

- ***Cocaine***: blocks reuptake of NE (or DA, 5-HT); ester LA which causes **vasoconstriction by blocking NE uptake (NET transporter)… used locally in nasal surgeries to control bleeding in surgery**; only LA not co-admin'd w/Epinephrine; topical drug; In cocaine abusers- HTN, cerebral haemorrhage, cardiac arrythmias, ulcers in mucus memb, damage to nasal septum when snorted; affects all transporters for reuptake (NET – NE reuptake transporter) (DAT – Dopamine transporter) (SERT – serotonin reuptake transporter) but has more affect on NET & DAT (more pleasure seeking effect)
- ***Tetracaine***: only used locally to control bleeding while doing surgery
- ***Procaine***: short plasma half life (< 1 min)
- ***Benzocaine***: **surface anesthetic, topical application to skin & mucus memb's – nasal mucosa & wounds**

LA Amides: "i" before "caine"; metabolized by hepatic CYP so longer activity b/c must reach liver 1st; careful in pt's w/Liver dis's –toxicity of amide LA; allergy is rare & seizures (lidocaine or inadvertent IV admin of large dose** most imp efx))

- **Lidocaine**: surface anesthetic, topical application to skin & mucus memb's – nasal mucosa & wounds; rmr 1B antiarrhythmic ⊏ Na channel but only at ACTIVATED OR INACTIVATED STATE, NOT RESTING (not answer choice) (here it's n's but b4 it was cardiac); for tooth extraction but if pt has infection (thus inflammation) ⊏ ¬its absorption; can cause seizure & convulsions so co-admin'd w/α1 agonists (epinephrine) for vasoconstriction to localize anesthetic at desired site & ¬systemic toxicity (ANSWER); for ***Epidural anaesthesia*** where LA Injected to spinal dural space, used **in obstetrics & pregnancy; seizures tx'd by diazepam**
  - **Pt was given epidural anesthesia.** This drug has what mechanism?
    - **Blocks Na+ channels at resting state**
    - **Given with a vasoconstrictor to ↑ its localizing efx & prolong its axn (ANSWER)**
- **Bupivacaine**: most cardiotoxic, blocks Na^+ channels in heart ⊏ depressing cardiac pacemaker activity, conduction ⊏ **arrhythmias & CV collapse** (¬BP) Levobupivacaine & Ropivacaine less cardiotoxic)
  - ***Ropivacine for Epidural anaesthesia***: LA Injected to spinal dural space **in obstetrics & pregnancy**
- Mepivacaine:
- Etidocaine:
- **Prilocaine**: methaemoglobinemia – due to accumulated 0-toluidine. Tx'd by ascorbic acid;

⊏ ***Differential blockage***: peripheral n func's not affected equally by local anaesthetics; efx depend on fiber dm & myelination*; ***smaller* & unmyelinated fibers more sensitive** & block 1st to local anesthetic block, then large & unmyelinated; but rmr *fiber dm most imp*! Pain more affected by LA than temp, touch, last thing affected is m ⊏ Smaller & myelinated > smaller & UM > large myelinated > large UM; ie. Type B & type C similar dm. But B myelinated so they are blocked before unmyelinated C fibers.

Type	Func	Dm	Myelination	Sensitivity to block
Type A				
Alpha	Motor	12-20	Heavy	+
Beta	Touch pressure	5-12	Heavy	++
Gamma	Muscle	3-6	Heavy	++
Delta* affected 1st	Pain, temp	2-5	Heavy	+++
Type B	Preganglionic autonomic	< 3	Light	++++
Type C				

Dorsal root	Pain	0.4-1.2	None	++++
Symp	Post ganglionic	0.3-1.3	None	++++

Order of sensitivity is Type B &C > Type A $_{\delta}$ > Type A $_{\beta}$> Type A $_{\gamma}$ > Type A$_{\alpha}$

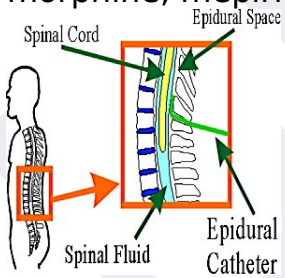
LA toxicity

Warning signs

- ***CNS efx:*** **Circumoral paresthesia,** tongue numbness **& metallic taste (earliest sig** Nystagmus, m twitching, Seizures, Depression / LOC; **Tx w/diazepam (for seizures)**
- ***CVS efx***: All LA vasodilators ⇨ hypotension except Cocaine – inhibit NE reuptake (NET transporter)- vasoconstriction
  - In cocaine abusers- HTN, cerebral haemorrhage, cardiac arrythmias, ulcers in mucus memb, damage to nasal septum when snorted
  - *Bupivacaine* is most cardiotoxic…don't use anymore
  - block of Na channels in heart- depress cardiac pacemaker activity, conduction- Arrhythmias, CV collapse
  - Instead use …Levobupivacaine, Ropivacaine - less cardiotoxic (but still carries risk of cardiotoxicity)
- ***Other efx***:
  - Prilocaine- methaemoglobinemia – due to accumulation of 0-toluidine. Tx'd by ascorbic acid
  - Ester type LAs are metabolised to PABA (*Paraaminobenzoic acid)* derivatives (by pseudocholinesterase): cause allergic rxns aka HSR's
  - Amides- allergy is rare

Types of LA

1. ***Surface anaesthesia***: topical application to skin & mucus memb- nasal mucosa, wounds
   a. ***Benzocaine, lidocaine***- surface anaesthestic
2. ***Infiltration anaesthesia***: infiltrated under skin- blocks sensory n endings. Ex: incisions, excisions
3. ***Conduction block***: injected around n trunk
4. ***Spinal anaesthesia***: injected into subarachnoid space L2-3 or L3-4 **used in surgeries of lower limbs & abdomen**; most popular form; *Adv's:* safer, produces good analgesia & m relaxation w/out LOC, less problematic in dis'd; *complications:* Hypotension, Headache, N/V, Neuro'al damage, Septic meningitis
5. ***Epidural anaesthesia***: LA Injected to spinal dural space used **in obstetrics & pregnancy**- ⇩susceptibility to LAs; commonly used drugs: **lidocaine, ropivacaine, opiods** (not LA; morphine, mepiridine but can cause fetal respiratory depression so use w/caution)

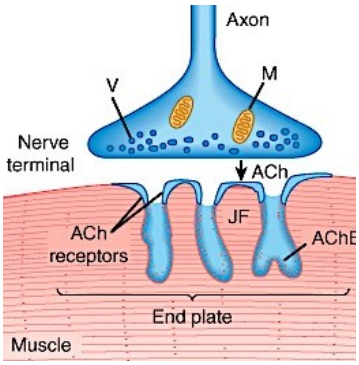


L9 Skeletal Muscle Relaxants:

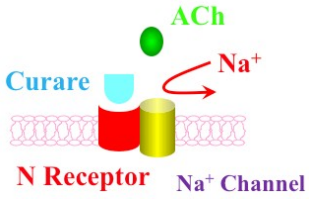
- ***Skeletal Muscle Relaxants***: drugs used to ⇩m tone &/or cause paralysis; **usesd** as (1) adjuncts in General Anesthesia, also in (2) certain CNS disorders (Convulsions, malignant hyperthermia) & (3) Day to day MSK rel'd pains (m sore following vigorous tennis play/football play); affect Nm receptors!

➢ ***2 categories*** – Neuromuscular blockers work on Nm receptors & Spasmolytics work on CNS

- ***Neuromuscular blockers***: used during general anesthesia; act on Neuromuscular junc; all quaternary nitrogens- poorly lipid soluble, do not enter CNS



- ***Competitive blockers***: **competitive antagonists of Nm receptor on skeletal m**, toxic blockade overcome by anticholinesterase admin (cholinesterase inhibitor – ***Neostigmine*** **** **rather than ACh b/c short-acting!)**; **like Physostigmine for Atropine toxicity**



- **DTC (D-tubocurarine)**: curare derivate that competitively blocks Nm nicotinic receptors; adverse efx: **blocks ganglia–hypotension, tachycardia w/H release, dry mouth, ANTIDUMBELLS, anaphylaxis type I HSR**
- **Vecuronium**: **Adverse efx:** intermediate onset of axn (2-4 mins) & duration of axn (25-40 mins).
- **Pancuronium**: **Adverse efx:** no histamine release, but **blocks muscarinic receptors**. Similar onset of axn & duration as DTC; moderate blocking agent causes tachycardia
- **Doxacurium**:
- **Rocunronium**: **alternative for SCh in emergencies where rapid-induction anesthesia needed; Adverse efx:** rapid onset 1-2 mins & intermediate duration 30-60 mins;
- Adverse efx
  - **Tubocurarine blocks ganglia–hypotension, tachycardia & Histamine release-hypotension, bronchospasm, anaphylaxis**
  - **Pancuronium:** no histamine release, but blocks muscarinic receptors. Similar onset axn & duration as DTC
  - **Rocuronium:** rapid onset 1-2 mins & intermediate duration 30-60 mins; alternative for SCh in emergencies where rapid-induction of anesthesia needed
  - **Vecuronium:** intermediate onset axn 2-4 mins & duration axn 25-40 mins

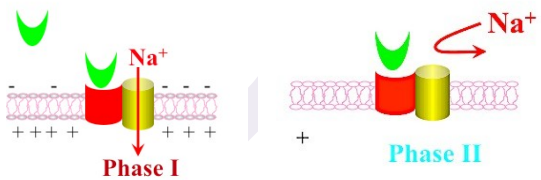
olarizing blocker (succinylcholine).

		Succinylcholine	
	Tubocurarine	**Phase I**	**Phase II**
tion of tubocurarine	Additive	Antagonistic	Augmented[a]
tion of succinylcholine	Antagonistic	Additive	Augmented[a]
ostigmine	Antagonistic	Augmented[a]	Antagonistic
atory effect on skeletal muscle	None	Fasciculations	None
o tetanic stimulus	Unsustained ("fade")	Sustained[b]	Unsustained
c facilitation	Yes	No	Yes

⊟ *Depolarizing blockers*

- **SCh (Succinylcholine) (ANSWER):** **nicotinic agonist** depolarizing blocker at neuromuscular end plate w/**more rapid onset axn (1 min)** & **short duration axn** 3-5 mins vs most nondepolarizing neuromuscular blockers, making it **DOC for emergencies where rapid endotracheal intubation necessary;** rapidly hydrolysed by plasma pseudocholinesterase BUT Genetic abnormality: pt's w/congenitally def plasma cholinesterase exp long lasting block (this also metabolizes INH) ▭ develop **pSCh apnea** & don't recover from m relaxation (pt remained paralytic aka delayed paralysis & didn't wake up after general anesthesia surgical procedure); **Indications as Adjunct to general anesthesia to facilitate endotracheal intubation & relax skeletal m during surgery or mechanical ventilation**; initial depolarization often accompanied by twitching fasciculations (prevented by pre-tx w/small doses of nondepolarizing blocker); when given by continuous infusion, efx change from continuous depolarization (phase I) to gradual repolarization w/resistance to depolarization (phase II, ie. curare like block); in phase I, paralysis ⏚by cholinesterase inhibitors BUT during phase II, block by SCh made reversibly by cholinesterase inhibitors; Other efx (1) axn at autonomic ganglia ▭ DTC blocks, SCh may stimulate cardiac muscarinic receptors – causing cardiac arrhythmia; (2) **Histamine Release: but** d-DTC causes *most* histamine release by direct efx on mast cells, causing bronchospasm, hypotension, salivary secretions (type I HSR)
  - **Contraindications:** Genetic def plasma pseudocholinesterase, hx of malignant hyperthermia, ⁊⁊ **risk for potentially fatal malignant hyperthermia (m rigidity, hyperthermia, hyperkalemia, tx w/dantrolene)**, recent burns/trauma, myopathies w/ ⏚CPK lvls, & acute narrow-angle glaucoma or penetrating eye injuries; ***can cause **hyperkalemia**; don't give 24–72 hrs after major burns or trauma b/c may cause acute hyperkalemia, hyperkalemic rhabdomyolysis & cardiac arrest; also produced acute hyperkalemia & cardiac arrest in otherwise healthy boys w/unrecog'd muscular dystrophy so FDA issued warning about use in kids (dont use in kids except for emergency airway control); Heavily m'd can suffer from m pain due to m fasiculations (rhabdomyolysis) & ⏚risk for regurg & aspiration of gastric contents caused by ⏚intragastric pressure; rapid ⏚IOP b/c efx ocular blood vessels & myofibrils; cardiac arrhythmias (⏚or ¬¬HR) b/c efx muscarinic & nicotinic-ganglionic receptors
  - **Phase I blocker**, agonist at N_M receptor ▭ ion channel opens, but for longer time vs ACh ▭ Initial depolarization à contraction = small ***fasciculations*****;** depolarized post-junc'al memb ▭inactivating Na channels ▭ postjunc'al memb becomes unresponsive to ACh released by motor neurons **=Phase I block** & produces charac ᶜᶜ **contractile resp (w/no fade) during train of 4 stimuli; augmented by neostigmine****
  - **Phase II block:** in <1 min after IV admin, get **flaccid paralysis** due to dev'd desensitized state where memb becomes repolarized, but insensitive to ACh (due to receptor desensitization) = **Phase II block** & responds to train of 4 stimuli w/fade pattern similar to that produced by non-depolarizing neuromuscular blockers; reversed by neostigmine

Succinylcholine **Succinylcholine**



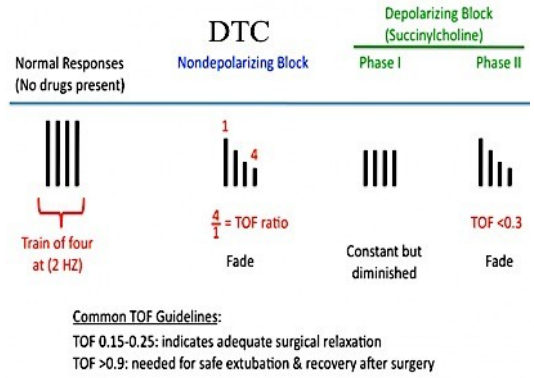
augmented by neostigmine

reversed by neostigmine

▭**Non depolarising blockers**: cause "fade" in contractile resp's during "train of four" (TOF) stimuli

▭**SCh "Phase I block"** produces charac ¬¬contractile resp (w/no fade) during TOF Stimuli
▭**SCh "Phase II block"** responds to TOF stimuli w/fade pattern similar to that produced by non-depolarizing neuromuscular blockers

- **Train-of-four stimulation:** clinical tool to assess neuromuscular block in anaesthetized pt; stimulate ulnar n w/TOF supramaximal twitch stimuli, w/frequency of 2 Hz, *TOF ratio* calculated from strength of 4th twitch divided by 1st; only way you can assess extent of skeletal m relaxation & so recovery from anesthesia very quick; know how to differentiate curare derivative & SCh
  - **DTC –** fade in resp
  - **SCh–** diminished but somewhat resp; have to have both phase I & phase 2 depicted to conclude its SCh; if you just see phase 2 lines – then it could be neostigmine
  - **Phase 2 –** fade



TOF 0.15-0.25 = adequate surgical relaxation
TOF >0.9 = needed for safe extubation & recovery after surgery

▭ ***Spasmolytics***: for conditions w/acute or severe m spasms; ¬¬m tone w/out causing paralysis, via centrally acting (BZDs, tizanidine, baclofen) – depress spinal & supraspinal reflexes in spinal cord- ¬¬m tone OR Peripheral acting (bolutinum toxin, dantrolene)– either at cholinergic n terminal or SR of skeletal m); for Acute m spasm, Sprain, ligament tear, Backache, torticollis, Tetanus, Spastic neurological dis's (cerebral palsy, MS, stroke)

- ***Centrally acting spasmolytics:*** BZDs/Diazepam, tizanidine, baclofen; ¬¬spinal & supraspinal reflexes in spinal cord, ¬¬m tone; for Acute m spasms, backache, Neuralgias, Anxiety & tension induced ⏚m tone, Spastic Neurological dis's, Tetanus, Orthopedic manipulations

- **Diazepam**: centrally acting benzo, facilitates GABA inhibition
- **Baclofen**: only $GABA_B$ agonist aka G protein coupled receptors to treat spasticity – ie. in ALS, MS, tardive dyskinesia, trigeminal neuralgia; centrally acting, **$GABA_B$ agonist** - ⏚K^+ flow – hyperpolarization- ¬¬release of excitatory NT's;
- ***Tizanidine**: like clonidine, α_2; ¬¬spasticity; centrally acting α_2 agonist in CNS ¬¬excitatory NT release (¬¬NE)

- ***Peripheral/Directly acting spasmolytics:*** bolutinum toxin, dantrolene; either at cholinergic n terminal or SR of skeletal m

- **Dantrolene (ANSWER)**: **ONLY for malignant hyperthermia**; directly acting SMR **inhibits Ca^{2+} release from SR** during excitation-contraction coupling & suppresses uncontrolled Ca^{2+} release; underlies skeletal m pharmacogenetic disorder ***malignant hyperthermia (*DOC & life saving!!) b/c acts by inhibiting ryanodine receptor & Ca^{2+} channel in skeletal m
  - **Malignant hyperthermia**: rare inherited, triggered by inhaled GA's (those w/halothane ie. –thane at end) w/ or w/out SCh✦; causes persistent Ca^{++} release from SR leads to m rigidity & fever; tx'd w/Dantrolene✦
- **Botulinum toxin**: neuromuscular transmission blocker acts at vesicles in cholinergic n's (prevent fusion of motor neuron secretory vesicles w/in memb) aka **prevents ACh release;** intramuscular toxin made by Cl. Botulinum; thereby ¬¬local skeletal m activity; diff subtypes cleave diff SNARE proteins (synaptobrevin, syntax, SNAP-25; N essential to docking & release of ACh from vesicles in n endings) — m may atrophy, axonal sprouting may occur & extra junc'al ACh receptors may be expressed; treats moderate-severe glabellar & lateral canthal lines & overactive bladder, migraine HA prophylaxis for **chronic migraine** (>15

episodes/month), upper limb spasticity & cervical dystonia, **used in c**erebral palsy (¬¬spasticity), blepharospasm (involuntary tight closure of eyelids), strabismus, cosmetic use, diffuse esophageal spasm

- **Gabapentin**: anti-seizure drug also used as m relaxant

Summary uses of SMR's

- N_M blockers used only along w/general anesthetic agents to achieve skeletal m relaxation in surgeries
- Dantrolene used only in malignant hyperthermia
- Botulinum used in Cerebral palsy (to ¬¬spasticity), Blepharospasm, Strabismus, cosmetics
- Centrally acting drugs: Acute m spasms, backache, Neuralgias, Anxiety & tension induced ⏚m tone, Spastic Neurological dis's, Tetanus, Orthopedic manipulations

L10 Opioids

Opiate: opium poppy derivative; Prototype: morphine; Opioid = natural, synthetic & semisynthetic drugs w/morphine- like axns

Opioid receptors & Endogenous Opioid Peptides: Opioids produce analgesia thru axns at receptors in CNS that respond to certain endogenous peptides w/opioid-like pharmacologic properties – these are **endogenous opioid peptides** & **Opiod receptors are G protein coupled receptors**

Opioids: used for (1) Analgesia: tx of relatively constant moderate-to-severe pain. Morphine is DOC for relief of pain due to MI **(2) Anesthesia:** as preoperative meds & intraoperative adjuncts in balanced anesthesia protocols. High dose IV (ie. morphine, fentanyl) often major component of anesthesia for cardiac surgery & **(3) Acute Pulm Edema**: produces remarkable relief due to combo ¬¬anxiety, ¬¬PL due to venodilation & ¬¬AL due to ¬¬peripheral resistance) **(4) Cough suppression**: at doses lower than those for analgesia; Antitussives – Codeine & Dextromethorphan. **(5) Control Diarrhea** due to almost any cause; Selective antidiarrheal opioids ***Diphenoxylate & Loperamide (little or no CNS activity).*** **(6) Opioid Dependence tx'd by Methadone, buprenorphine** to manage opioid w/drawal states & in maintenance programs for addicts. In w/drawal states, methadone permits slow tapering of opioid effect, which diminishes intensity of abstinence sx. Rmr shorter half life of drug = more intense w/drawal efx; so these drugs longer acting **(7) Tolerance** ****seen w/nausea, analgesia, sedation, respiratory depression, cardiovascular, euphoric (except: miosis & constipation not signs of tolerance****); may be minimized by admin'ing opiates in small doses w/long time intervals btwn doses; once drug stopped, tolerance is reversible via receptor uncoupling **(8) Dependence:** euphoria & easing of pain during drug use can lead to uncontrollable need to continue taking it; physical dependence revealed on abrupt discontinuance of drug causes *w/drawal sx including*: **Chills, lacrimation, rhinorrhea, gooseflesh, mydriasis, hyperventilation, diarrhea, anxiety & hostility; tx w/ *Methadone/buprenorphine***; Duration & severity depends on opiate's half life, short $T_{1/2}$ like in case of heroin (.5hrs) leads to severe w/drawal sx, while methadone w/long half life has milder w/drawal sx **(9) Acute opiate toxicity**: **OPIATE TRIAD: coma, miosis,** Marked respiratory depression, **Biliary spasms, G.I. smooth m spasm, m twitches, peripheral vasodilation, hypotension shock**; Overdosage confirmed if antagonist tx w/**Naloxone** given IV, w/very short duration of axn (1-4 hrs)→ prompt signs of recovery; death due to opioid poisoning nearly always due to respiratory arrest **!! also tx w/**Support respiration w/oxygen, monitoring critical b/c its short duration of axn; or give **Naltrexone** (oral opiate antagonist which has relatively long duration of axn of 24 hrs) so given in pt physically dependent on opioids (b/c use of antagonists, may precipitate w/drawal – 'Antagonist precipitated w/drawal'; Supportive therapy & monitoring must be continued **(10) Most imp interaxns** in opioid analgesics are additive CNS depression w/Ethanol/alcohol, Sedative-hypnotics, Anesthetics, Antipsychotics, TCA's &

Antihistamines; concomitant use of certain opioids (Meperidine) w/MAO inhibitors ↑incidence of **serotonin syndrome**

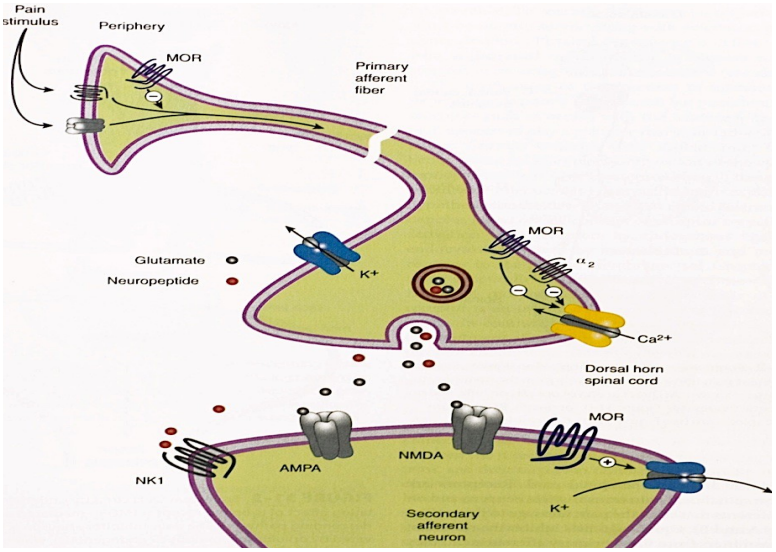
Opioid Receptor Subtypes, Their Func's, & Their Endogenous Peptide Affinities		
Receptor type	Func's	Endogenous Opioid Peptide Affinity
(mu)	Supraspinal & spinal analgesia; sedation; inhibit respiration; slow GI transit; modulate hormone & NT release	Endorphins > enkephalins > dynorphins
(delta)	Supraspinal & spinal analgesia; modulate hormone & NT release	Enkephalins > endorphins & dynorphins
(kappa)	Supraspinal & spinal analgesia; psychotomimetic efx; slow GI transit	Dynorphins > > endorphins & enkephalins

↔ Opioid selectively: +++, ++, +, strong agonist, ± partial agonist, --- antagonist; note primary efx on mew receptors ↔ responsible for most axns

	Receptor Efx		
Generic Name	μ	δ	κ
Morphine	+++		+
Hydromorphone	+++		
Oxymorphone	+++		
Methadone	+++		
Meperidine	+++		
Fentanyl	+++		
Sufentanil	+++	+	+
Alfentanil	+++		
Remifentanil	+++		
Levorphanol	+++		
Codeine	±		
Hydrocodone	±		
Oxycodone	++		
Pentazocine	±		+
Nalbuphine	--		++
Buprenorphine	±	--	--
Butorphanol	±		+++

⊟ Opioids: Biochem'al mechanisms of analgesic axns:** act on G-proteins by pre- & post-synaptic mechanism

- **Pre synaptic (spinal lvl): (1) Inhibit adenylate cyclase ⊟ ⊏ ⊏ cAMP ⊟ ⊏ ⊏ kinase activity & inhibit release of NT** ACh, NE, 5-HT, glutamate & substance P & (2) **Calcium modulation: ⊏ in neuronal Ca^{2+} entry ⊟ preventing NT release**
- **Postsynaptic:** ↑K^+ currents → to hyperpolarization & ↓firing of post synaptic impulses



G protein ↓, ↓cAMP, ↓glutamate & substance P NT's of pain****

- **Opioids *CNS efx*: Analgesia (↑pain tolerance, ↓perception & rxn to pain), Euphoria & Sedation**
  - ***Respiratory depression*- ↑Pco_2 leads to cerebral vasodilation → ↑ cerebral BF→ ↑ ICP** – Hence Contraindicated in head injury!!!
  - **Suppression of cough**
  - **Miosis –** Pupillary constriction charac effect via direct axn on oculomotor n (Edinger Westphal Nucleus)– no tolerance; 1 sign of opioid toxicity – pinpoint pupil* (also seen in organophosphates)
  - **Nausea vomiting: via stimulation of mu receptors**
  - **Trunkal rigidity: ↑ tone of these m's in OD**
- **Opioid *Peripheral efx*:**
  - ***GIT***: Constipation due to ↑m tone & ↓intestinal peristalsis via stimulating mu receptors; thus can use where too much GI motility but not ALL preferred due to abuse potential
  - ***CVS***: most w/no direct efx on heart except Meperidine- tachycardia b/c its antimuscarinic axn
  - ***Biliary tract***: ↑biliary sphincter tone & intrabiliary pressure (>10X), which may cause biliary colic (except meperidine) & ↑rupture of gall bladder, thus opioids contraindicated in biliary colic!

→ Thus opioids contraindicated in head injury & biliary colic

- **Opioid Agonists**

- *Strong Opioid Agonists:*

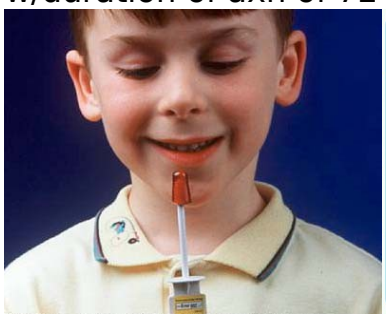
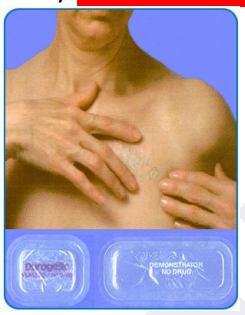
➢ ***Morphine***: also ↑kappa, better than codeine b/c this isn't partial agonist; **DOC for relief of pain due to MI (**relatively constant moderate-to-severe pain); High dose IV (ie, morphine, fentanyl) often major **component of anesthesia for cardiac surgery**; ****tolerance seen w/nausea, analgesia, sedation, respiratory depression (bronchoconstriction), cardiovascular, euphoric (except: miosis & constipation not signs of tolerance****); tolerance minimized by admin'ing opiates in small doses w/long time intervals btwn doses; once drug stopped, tolerance reversible; Mechanism: Receptor uncoupling; give docusate for chronic use pt's for constipation

➢ ***Heroin* (Diacetylmorphine):** banned in US; 2-5x potent as morphine as analgesic; more lipid soluble & crosses BBB faster than morphine → causes extreme euphoria when admin IV; short $T_{1/2}$ (.5hrs) leads to severe w/drawal sx

➢ ***Methadone**: manages opioid w/drawal states & maintenance programs in addicts; permits slow tapering of opioid efx, which **diminishes intensity of abstinence sx**; Rmr shorter half life = more intense w/drawal efx; so this drug longer acting; duration of axn for analgesia longer than morphine ($t_{1/2}$ 15-55 hrs) long half life SO milder w/drawal sx; for (1) **Severe pain** (pain of terminal cancer) & (2) **Detox & maintenance of narcotic**

dependence (less sedation, euphoria & emesis than morphine; w/drawal milder, slower in onset & more prolonged than w/heroin or morphine)

- ***Meperidine*****: ONLY opioid agonist that blocks muscarinic receptors in <3 thus antimuscarinic; & anticholinergic weak SERT inhibitor (serotonin reuptake transporter thus ↑risk serotonin syndrome); ***in CVS*** only opioid that afx <3 ↓ tachycardia b/c antimuscarinic; & Only opioid w/no effect on biliary tract (↓↓risk biliary colic) so DOC to treat biliary colic!* all other opioids contraindicated! Side efx: Mydriasis (vs pinpoint pupils for other opioids), visual disturbances & tachycardia b/c anticholinergic, ****Seizures*** at higher doses or in pt's w/renal failure (due to accumulated metabolite normeperidine)
  - **Serotonin syndrome**: similar to malignant hyperthermia – extreme m rigidity & fever, ↑CPK (m injury)
- **Fentanyl**: neuroleptic (antipsychotic) used in combo w/others for **anesthesia**, used w/N2O or dropyridol as **neurolept; major component of anesthesia for cardiac surgery; along w/alfentanil & sufentanil** - Synthetic opioid, More potent than morphine, Rapid onset & short duration, for **balanced anesthesia**, transdermal patch & lollipop that dissolves slowly for transmucosal absorption; **patches used for chronic malignant pain**, w/duration of axn of 72 hrs; risk cutaneous rxns

- **Oxymorphone**:
- **Hydromorphone**:

- *Mild to Moderate Opioid Agonists:*

- ***Codeine**: partial agonist at opioid receptors; most effective & ONLY opioid analgesic for cough suppressant (+dextromethorphan); **converted to active form morphine by CYP2D6**** (if genetic variability ↓can cause failure to respond to codeine); taken **orally, Low doses** (tablets or syrup) sufficient to relieve cough
- **Dextromethorphan**: most effective & also ONLY opioid for **cough suppressant**; *interrupts transmission of cough impulses by depressing medullary cough center thru sigma receptor stimulation*; Side efx: reported to be free of addictive potential, produces less constipation compared to codeine
- **Hydrocodone**: opioid analgesic partial agonist at mu receptors; for tx of moderate-severe pain & cough suppression; no anti inflammatory efx
- **Oxycodone**:

- **Opioid Mixed agonist-antagonist:** act as agonist on 1 receptor & antagonist on other
- ***Buprenorphine**: mixed agonist-antagonist; **partial agonist at mew; block kappa & delta receptors**; manages opioid w/drawal & maintenance programs in addicts; Rmr shorter half life = more intense w/drawal efx; so its longer acting; Potent, Partial m agonist, weak k antagonist, d antagonist; **used for opioid dependence;** less efficacy than morphine at mu receptors for pain management b/c its partial agonist whereas morphine full agonist. When mu receptors occupied by partial agonist prior to admin of full agonist —> full agonist can't exert its full efx, +long duration of axn b/c its slow dissociation from mu receptor; more potent but less efficacious* - so less of it needed to produce analgesia

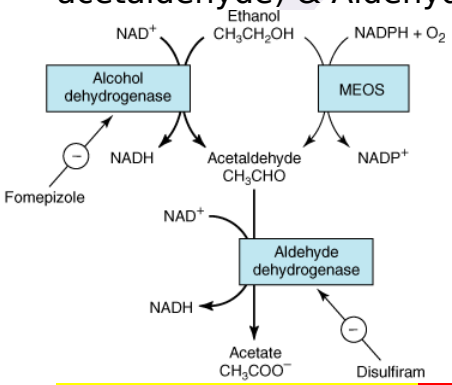
- **Nalbuphine**: **mew antagonist & kappa agonist**; Strong k agonist, m antagonist (can precipitate w/drawal); semi-synthetic opioid used commercially as analgesic, given IM'ly thru large m's like buttocks
- **Pentazocine**: **partial mew agonist** (submaximal efx, less affective than agonist) but behaves as antagonist in presence of natural agonist, kappa agonist ↓ hence mixed agonist-antagonist; *1/3 potent as morphine as analgesic,* **k agonist, mew partial agonist** (can precipitate w/drawal); effective orally; shorter duration & faster onset axn than morphine

Opioid Antagonists

- **Naloxone**: for **Acute opiate toxicity**: **OPIATE TRIAD: coma, miosis,** Marked respiratory depression, **Biliary spasms, GI smooth m spasm**, **m twitches, peripheral vasodilation, hypotension shock**; OD confirmed & tx'd by this antagonist given IV, w/very short duration of axn (1-4 hrs)→ prompt recovery signs
- **Naltrexone**: approved for alcohol deaddiction (↓craving); oral opiate antagonist w/relatively long duration of axn of 24 hrs) so given in physically dependent on opioids (b/c use of antagonists, may precipitate w/drawal – 'Antagonist precipitated w/drawal'; Supportive therapy & monitoring must be continued
- **Nalmefene**: pure opioid receptor antagonist

L11 Alcohol – Ethanol, Methanol, & Ethylene Glycol

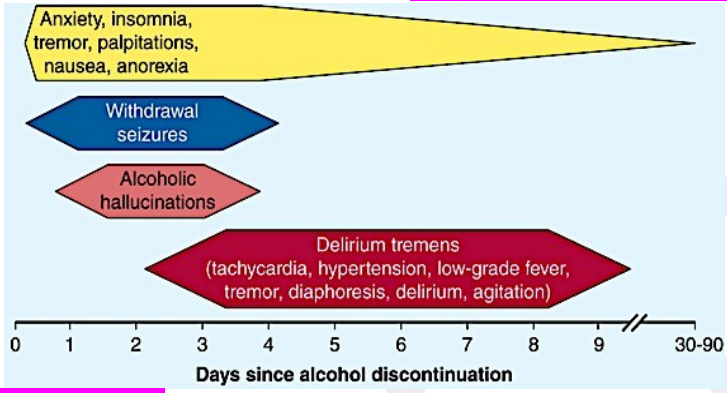
- KNOW METABOLIC PATHWAYS***
- **Ethanol**: rapid & complete absorption after ingestion; MOA Poorly understood but facilitates **GABA at $GABA_A$ receptors & inhibits glutamate so it can't activate NMDA receptors**; acute efx – sedation, loss of inhibition, impaired judgment & slurred speech & ataxia; Tolerance & Dependence seen as Both psycho'al & Physical; abrupt discontinuation demonstrated by abstinence syndrome; on liver ↓gluconeogensis ↓ hypoglycemia & progresses on to fatty liver, hepatitis, cirrhosis & liver failure; in GIT ↓ inflammation, scarring & bleeding of gut wall, gastritis, hematemesis, +↑risk pancreatitis**; CNS w/peripheral neuropathies, ***thiamine def (Wernicke-Korsakoff syndrome) so admin of thiamine imp to prevent it;*** Endocrine efx: Gynecomastia, testicular atrophy; Cardiovascular system w/↑incidence HTN, anemia & dilated cardiomyopathy;
  - Ingestion of moderate quantities (10-15 g/day) ↑serum HDL (only in certain observational studies)
  - 2 enzyme systems metabolize ethanol to acetaldehyde – Alcohol DH (ethanol ↓ acetaldehyde) & Aldehyde DH (acetaldehyde to acetate)



BAC (mg/dL)[1]	Clinical Effect
50–100	Sedation, subjective "high," increased reaction times
100–200	Impaired motor function, slurred speech, ataxia
200–300	Emesis, stupor
300–400	Coma
> 500	Respiratory depression, death

  - **Wernicke-Korsakoff syndrome**: relatively uncommon charac'd by paral**ysis of external eye m's, ataxia, & confused state**; can progress to coma & death; associated w/thiamin def; pt's suspected should receive thiamine therapy; often, ocular signs, ataxia & confusion improve upon prompt admin of thiamine, but, most left w/ chronic disabling memory disorder as Korsakoff's psychosis

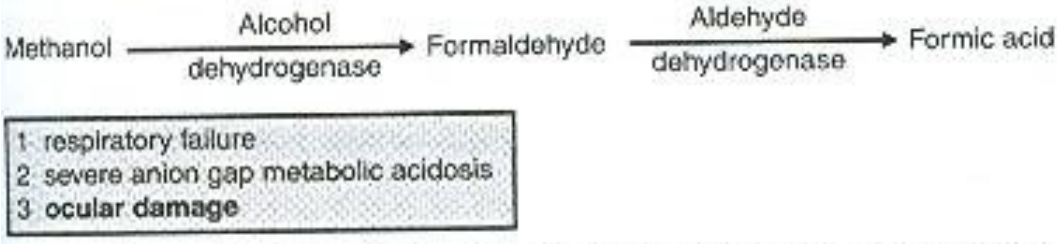
- **FAS (fetal alcohol syndrome)**: intrauterine growth retardation, microcephaly, poor motor coordination, underdev't of midfacial region (appearing as flattened face), & Minor jt anomalies.
- Tx of ***ACUTE*** alcohol intoxication
  - **Supportive measure:** prevent respiratory depression & aspiration pneumonia, give fluids & electrolytes
  - **Pharm'al measure:** glucose to treat hypoglycemia & ketosis, Thiamin (100 mg) to protect against Wernike-Korsakoff; Prevent seizures, delirium, & arrhythmia; & Restore K, Mg, & Phosphate ions
- Management of alcohol w/drawal syndrome w/CF's (opp of CNS depression): insomnia, tremor, anxiety, life threatening seizures, visual hallucinations, delirium tremens
  - Managed by thiamine, restoration of fluid electrolyte balance
  - ***long acting sedative-hypnotic drug (BZDs-diazepam, chlordiazepoxide) – DOC****
  - In alcoholic pt's w/liver dis, prefer Lorazepam or oxazepam (Why?) – b/c doesn't produce long acting metabolites (rmr also preferred in elderly w/ ↓↓liver func)
  - Intensity of w/drawal efx ↓↓by *clonidine (α-2 agonist) or propranolol



↓ Tx of alcoholism: sociomedical problem (complex approach) w/high relapse rate; 3 drugs FDA approved – **disulfiram, naltrexone, acamprosate**

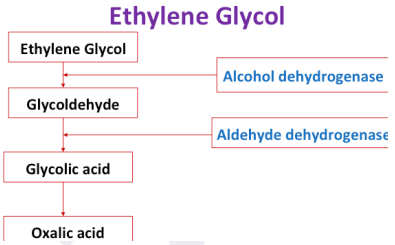
- **Disulfiram**: aldehyde DH inhibitor; if pt on disulfiram consumes ethanol then acetaldehyde accumulates ↓this leads to nausea, vomiting, intense headache, sweating, flushing & hypotension
- **Naltrexone** (opioid antagonist)
- **Acamprosate** (NMDA antagonist): stabilize chemical balance in brain that would otherwise be disrupted by alcohol w/drawal
- **Fomepizole**: inhibitor of alcohol DH
- *****Other drugs w/disulfiram like efx: **Metronidazole**, **Cephalosporins** (not all, only those w/charac chem'al nature), **Sulfonylurea hypoglycemic** drugs (anti-diabetic drugs – clorprormomide?), & Griseofulvin (anti-fungal drug); ALSO IMP FOR BLOCK 3***

- **Methanol**: constituent of windshield cleaners & "canned heat"; intoxication includes **visual dysfunc, GI distress, SOB & LOC**; metabolized to (formaldehyde ↓) formic acid, which may cause severe metabolic acidosis (just like the other 2 – alcohol & ethylene glycol) & ***RETINAL DAMAGE/BLINDNESS****



- Tx of methanol poisoning:

- **Gastric lavage**
- **Ethanol:** given IV as preferred substrate for alcohol DH so methanol not metabolized to formaldehyde
- **Fomepizole**: inhibitor of alcohol DH;
- Rx w/**bicarbonate** (to manage profound metabolic acidosis)
- **Hemodialysis** done in high alcohol lvls



➢ **Ethylene glycol**: used as heat exchangers, in antifreeze formulations, & as industrial solvents; Glycolic acid = oxalic acid – can precipitate stones in your kidney; toxic efx of toxicity: young kids sometimes attracted by sweet taste; Signs of excitation followed by CNS depression; after delay of 4–12 hrs, severe metabolic acidosis from accumulated acid metabolites & lactate; & then finally delayed renal insufficiency follows deposition of oxalate in renal tubules; Tx w/

- **Ethanol**: IV as preferred substrate for alcohol DH so drug not metabolized to glycolic/oxalic acid
- **Fomepizole**: inhibits alcohol DH ▭ prevents accumulation of acid metabolites (glycolic/oxalic acid)
- Supportive measures

▭ Summary: know metabolic pathway of all 3 alcohols, drugs acting specifically in this pathway; Management of ethanol: toxicity, addiction; & Management of methanol & ethylene glycol poisoning

L12 Drug w/imp axns on SMOOTH M's: Eicosanoids, H, 5-HT, N2O, Ergot Alkaloids

- **Histamine**: **Histidine-decarboxylase catalyzes formation of histamine from L-histidine; in** Mast cells, basophils, cells of epidermis, cells in gastric mucosa, neurons, cells of rapidly growing tissues (esp certain tumors); **Major types of Histamine receptors- H_1, H_2 (G-protein coupled)**
  - enterochromaffin cells: predominantly produce 5-HT, but also produce histamine
  - H1 activation ▭ ⇂capillary dilation (via NO) ▭ ⇂BP; ⇂capillary permeability ▭ ⇂edema; ⇂bronchiolar SM contraction (via IP3 & DAG release), ⇂activation peripheral nociceptive receptors ▭ ⇂pain & pruritus; ⇂AV nodal conduction
  - H2 activation ▭ ⇂gastric acid secretion ▭ ⇂GI ulcers; ⇂SA nodal rate, +ve inotropism & automaticity

Type of receptor	Predominant organ of Distribution	Histamine –mediated response
***H1- Gq- IP3 and DAG (BLOCK 2)	Blood vessel*	Vasodilation - ↓ BP (by releasing NO) Bronchoconstriction (Features of Anaphylaxis)
***H2 Gs- cAMP (IMP FOR LATER)	Stomach*	↑gastric secretion
H3- Gi - ↓ cAMP	Presynaptic: brain, myenteric plexus, other neurons	
H4- Gi - ↓ cAMP	Eosinophils, neutrophils, CD4 T cells	

▭Histamine inhibitors & Antagonists:

➢ **Physiologic antagonists: Epinephrine (hence used in anaphylactic shock) –**

- **ie. p. 240 first AID – 1st graph, R ward shift in dose resp curve, change in potency – decreases, = COMPETITIVE ANTAGONIST – could be atropine (ANTI-DUMBBELL)**

- **2nd graph, Consider ACh, efficacy decreases – NONCOMPETITITVE ANTAGONISTS**
- **ie. child who consumes wild berries – comes w/excessive sweating, dry mouth, dry eyes, palpitations dilated pupils – Atropa beladona/Atropine toxicity (Anti-dumbbell efx)**
- **1st graph, imagine NE as agonist, looking at α resp on y axis more specifically, what causes shift to line A? still competitive antagonist but for α receptors – ie. prazosin**
- **2nd graph, imagine NE as agonist, looking at α resp on y axis, what causes shift to line B? phenoxybenzamine – NONCOMPETITIVE ANTAGONISTS**** - tx for pheochromocytoma**
- **1st graph, but looking at b resp, what causes shift to line A? beta blockers**
- **Now comparing 2nd & 3rd graph,**
  - **2nd – drug A is agonist, drug A + B – means you've added noncompetitive antagonists – ↓↓ efficacy rather than potency**
  - **3rd graph – drug A agonist, drug A + B – means you've added partial agonist – ie. in beta blockers – Pindolol***, imp for adrenergic & cholinergic drugs; others – morphine, buprenorphine**

➢ **Histamine degranulation inhibitors: Cromolyn sodium/sodium cromoglycate or Nedocromil: inhibit degranulation by stabilizing mast cells during various stimuli (ie. inflammation, allergy);** inhibits both Ag- & exercise-induced asthma & chronic use slightly ↓↓overall bronchial reactivity; cellular mechanism **alteration in func of delayed chloride channels** in cell memb that inhibits cellular activation in eosinophils & specific mast cells subtypes in lung; **for Prophylaxis of asthma caused by allergens or exercise;** only formulation of these 2 "cromoglycates" available to treat asthma are sol'ns for nebulization; rarely used

➢ **Receptor antagonists/Histamine blockers**

- **H1-receptor antagonists/antihistamines:** unless specified, always H1 blockers; all require hepatic metabolism & cross placental barrier
  - **1st GEN Antihistamines**: sedating, anti-muscarinic & adreno-receptor α-blockers; peripheral antimuscarinic axns ?? (dry mouth) Central antimuscarinic axns (use in tx'ing drug induced EPS) & Adreno receptor blocking axns (some compounds); **Competitive H1 receptor antagonist**; **Antihistaminic** (allergic conjunctivitis allergic skin manifestations of urticaria & angioedema), **Motion sickness** (block muscarinic receptors in vestibular & vomiting centers – Scopalamine too), **Antiparkinsonism** (for antipsychotic drug induced EPS), **Sedation** (mild sedative in Tylenol PM®, Advil PM®); Adverse efx: marked sedation & motor incoordination, **Antimuscarinic side efx: dry mouth, blurring vision, urinary hesitancy, & **Postural hypotension – b/c α-receptor blocking axn; Major DI's: additive efx w/alcohol & other CNS depressants (hypnotics, sedatives, tranquilizers)
    - **Diphenhydramine** (benadryl): also adjunct in Parkinson's, & EPS (but trihexphenadryl & …more effective), widely used OTC as cold med & sleep aid; more effective in tx'ing motion sickness than fexofenadine (b/c 2nd GEN)
    - **Chlorpheniramine** (Nyquil): possible CNS stimulation
    - **Promethazine** (Phenargan): pre-op & post-op sedation; SE hangover after sedation, at least 24 hrs, & α-block risk of vasodilation & reflex tachy, +blocks Na+ channels ⎓ local anesthetic efx
    - ~~**Hydroxyzine: strong anticholinergic efx**~~
    - **Meclizine**
  - **Second GEN**: ***Nonsedating***; *w/*Negligible additional efx; antihistamine w/**selective peripheral H1-receptor antagonist activity**; used for seasonal allergic rhinitis in adults & children 6 yrs+, **chronic idiopathic urticaria** in adults & kids 6 yrs+.

- **Side efx:** less lipid soluble, & hence have little or no sedative & far fewer autonomic efx; no efx on muscarinic receptors & adrenergic α- receptors
- **DI's: Tachycardia, arrhythmias (after high doses)-**
- ***Terfenadine (ANSWER) & astemizole cause polymorphic ventricular tachycardia (torsades de pointes arrhythmia/long QT syndrome) when given at high doses or w/CYP inhibitors (erythromycin macrolide & antifungal azoles); B/c this these 2 no longer in US]***
- **Loratidine** (claritin)
- **Fexofenadine** (allegra): no sedation adv! metabolite of terfenadine; does not have same effect on heart – doesn't produce Torsades des pointes;
- **Cetirizine** (zyrtec)
- **Azelastin** (intranasal spray)

- **H2-receptor antagonists:** competitively blocks H2 receptors in parietal cells which supresses basal & meal-stimulated acid secretion in dose-dependent manner; for duodenal & gastric ulcer (90% success), Drug- or stress-induced ulcer, GERD, Hypersecretory conditions (Zollinger-Ellison syndrome);
  - **Cimetidine**: **Adverse efx:** inhibits binding of DHT to androgen receptors & inhibits estradiol metabolism, both can alter androgen/estrogen balance in men & ↑PRL, W/chronic use may cause gynecomastia/impotence in men & galactorrhea in women; these efx not w/other H2 blockers; **DI's:** inhibits multiple forms of CYP P450 (CYP1A2, CYP2C9, CYP2D6 & CYP3A4). Hence half-lives of drugs metabolized by these pathways prolonged. Ex's: warfarin, theophylline, phenytoin, lidocaine, quinidine
  - Ranitidine
  - Famotidine
  - Nizatidine: antagonizes H2 receptors, for GERD, gastric & duodenal ulcers

Serotonin (5-Hydroxytryptamine-5HT): made from Tryptophan & stored in vesicles of enterochromaffin cells of gut, CNS neurons, & platelets; Metabolized by MAO- to form *5-hydroxyindoleacetic acid (5HIAA – indicator of serotonin rather than catecholamines –VMA)*; excess produced 5-HT in carcinoid syndrome so Marker of carcinoid syndrome is 5HIAA; CF's of carcinoid syndrome: flushing, wheezing, diarrhea ~~w/cardiac fibrosis (results in <3 w/normal rhythm & CT, but ↓PL & EDV; TIPS, pellagra – outflow of serotonin can cause depletion of tryptophan leading to Niacin def~~;

Serotonin Receptor subtypes

Subtype	Distribution (main sites)	Post-receptor mechanism
5HT1*	**Buspirone (anxiolytic), Sumatriptan/Triptans (migraines)**	
A	**Hippocampus, raphe nuclei**	**Gi- ↓ cAMP**
B	**Striatum, substantia nigra**	
D	**Cranial blood vessels (SM)**	
E	**Cortex, striatum**	
F	**CNS, periphery**	

~~5HT2~~ ~~A~~ ~~B~~ ~~C~~	**Platelets, smooth m, CNS** **Stomach fundus** **Choroid, substantia nigra**	**Gq - IP3/DAG**
5HT3	**Area postrema, sensory & enteric nerves**	**Na+/K+ ion channels**
5HT4	**CNS & myenteric neurons, SMC**	**Gs cAMP**
***5HT1C receptor has now been officially declared nonexistent (it has been reclassified as 5HT2C)**		

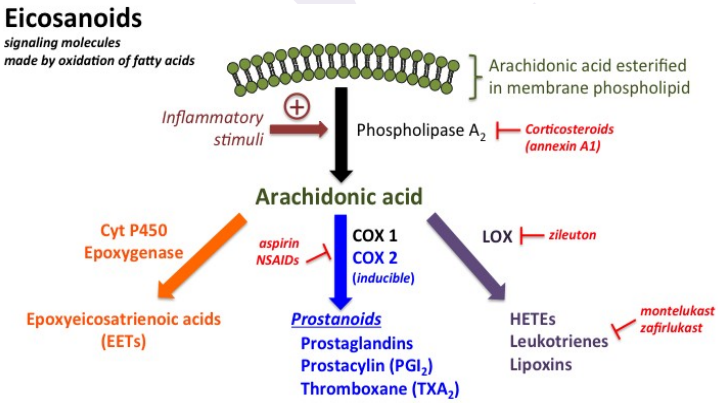
Migraine, vomiting & anxiety!!! 3 imp conditions 5-HT plays imp role in!

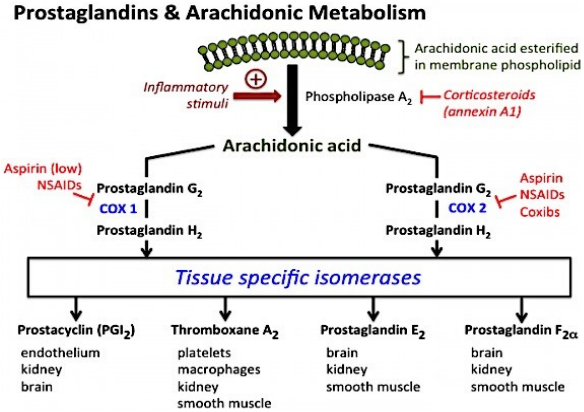
- **5HT1 receptor agonists:**
  - **Sumatriptan** /Triptans: 5 $HT_{1B/D}$ agonist *******, **for acute migraine attack (w/ or w/out aura) & cluster headaches**; SE: possible asthenia, chest or throat pressure or pain; contraindicated in Prinzmetal angina/Coronary a vasospasm; this drug can cause coronary a spasm, partial 5-HT1D agonist for acute migraines; but — >MI, vtach/fib, severe HTN, hypertensive crises & serotonin syndrome
  - **Buspirone** – non sedating anxiolytic drug – ***$5HT_{1A}$ agonist*** ******** - refer to previous ppt's
- **5HT4 Receptor agonists:**
  - **Tegaserod**: for IBS associated w/constipation – $5HT_4$ agonist
- **5HT2 Receptor antagonists**
  - **Olanzapine**: +other atypical antipsychotics ↓↓psychosis sx
  - **Ketanserine** – 5 HT2 antagonist & adrenoceptor α-blocker
  - **Cyproheptadine**- old, for carcinoid tumors, ↑appetite [Carcinoid tumour neoplasm secretes serotonin w/*CF's:* diarrhea, flushing vasodilatation & bronchoconsticts]; +H1 blocking axn for seasonal allergies
- **5 HT3 Receptor antagonists***:** central antiemetic axn; Ondansetron, Granisetron & dolasetron, Alosetron
  - ***Ondansetron- DOC to control of vomiting associated w/chemo**** & hyperemesis in pregnancy
  - Alosetron used in irritable bowel syndrome w/diarrhea

↓ **Ergot Alkaloids**: produced by *claviceps purpurae* (fungus found in wet or spoiled grain); used **for Post partum haemorrhage** (Ergonovine & Ergotamine), **Hyperprolactinemia** (Bromocriptine, pergolide), **Parkinson's dis** (Bromocriptine), **Acute attack of migraine** (Ergotamine)

- Ergot alkaloids *acting in CNS*: LSD & **Bromocriptine, pergolide**: **both for Hyperprolactinemia**
  - **Bromocriptine**: used for Parkinson's/ Parkinsonism
- Ergot alkaloids *acting on uterus* – **Ergonovine & Ergotamine /Ergometrine: for Post partum hemorrhage**
- Ergot alkaloids *acting on blood vessels* – **Ergotamine: for acute attack of migraine & PPH**

- **Migraine**: subtype of headache afflicting ~10-20% pop; recurrent attack of throbbing (usually unilateral) headache w/ or w/out visual & GI disturbances; pathophysio'al basis unknown. 1 commonly held view that its due to vascular changes, & that their triggered by 5HT release & activation of 5HT receptors; tx w/–
  - **Drugs for acute attack = NTE**
    - **NSAIDs & Analgesic: Acetaminophen, Aspirin & Caffeine**
    - **Triptans (Sumatriptan, Rizatriptan, Eletriptan, Almotriptan):** selective **5-HT1B/1D** agonists; activate 5HT1B or 5-HT1D receptors **inhibits activation of trigeminal n & this effect inhibits meningeal vasodilation (double –ve)**. By this mechanism, produce meningeal vasoconstriction; used **for Acute migraines**; Contraindicated in pt's w/cardiac ischemia, if risk factors for CAD, stress test is indicated prior to prescribing these drugs, **+cerebrovascular, or peripheral vascular dis; Side efx: Coronary a vasospasm, hypertensive episodes*****;
    - **Ergot derivatives (Ergotamine, Dihydroergotamine): used for acute migraine headaches**; contraindicated in pregnancy, vascular dis (ie. CAD, HTN) & psychosis; side efx - OD produces charac poisoning **ergotism/"St. Anthony's fire"**: prolonged vasospasm resulting in *GANGRENE* & amputations; hallucinations & dementia; & abortions & *CONVULSIONS*
      - **Ergotamine**: **partial agonists at α-adrenergic receptors** in blood vessels ⊟vasoconstriction
      - **Dihydroergotamine**: ergotamine derivate; **5-HT1D agonist vasoconstrics intracranial blood vessels**; ↑5-HT1D receptors on sensory n endings in trigeminal system ⊟**inhibiting pro-inflammatory neuropeptides release; treats acute migraine headaches but may induce vasospastic angina as constricts vascular SM via ↑both α-adrenergic (partial agonist) & 5-HT receptors (other triggers: cig smoking, cocaine/amphetamines & triptans)**
  - **Drugs for recurrences (prophylaxis)**
    - **Beta Blockers (Propranolol):** β-1 receptor blockers w/out intrinsic sympathomimetic activity (propranolol) ⊟⊟frequency & severity of attacks; ↓↓**neuronal firing rate of noradrenergic neurons of locus coeruleus**; **regulate firing rate of PAG (periaqueductal grey) matter neurons via GABA-mediated axn**; some β-blockers may also block some 5-HT2C & 5-HT2B receptors in brain
    - **Tricyclic antidepressants: Amitriptyline**
    - **CCB: Verapamil (& Flunarizine in Europe)**
    - **Antiseizure drugs: Valproate, Topiramate**

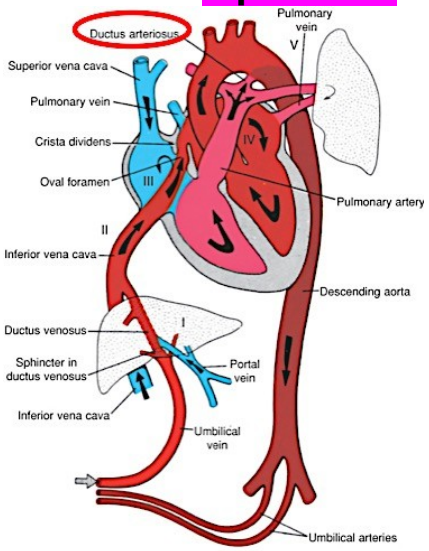




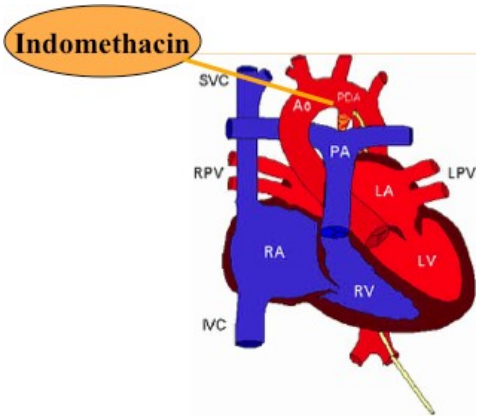
- **Eicosanoids**: members of fam of FA's derived from FA precursor arachidonic acid.
  - **PG's/Prostanoids** (PGs): PGD2, PGF2α, PGI2
    - **PGE_2** keep Ductus arteriosus (DA) open in fetus; In fetus DA carries blood from Pulm A to aorta (lungs collapsed in fetus → pulm pressure > aorta); After birth → ↓PGE_2 → DA closes

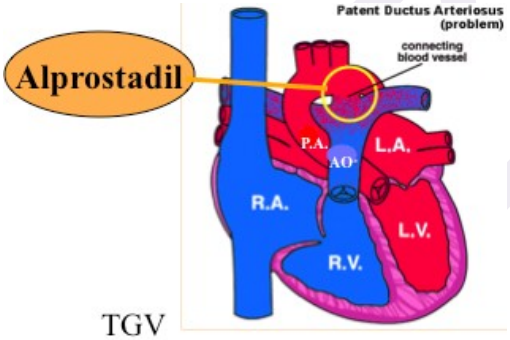
Dis States:

- **PDA (Patent Ductus Arteriosus):** DA not closed; Tx w/**Indomethacin**
- In some cyanotic heart dis's (**TOF**, TGV) **ductus must be kept OPEN** where **PGE_1 alprostadil** maintains patency of DA



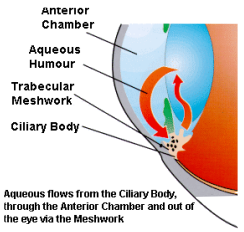
Fetal Circulation





TGV

- **Peptic ulcers:** COX-1 enzyme expressed in stomach → synthesizes PGE_1 → – stomach mucus secretion; Mucus has cytoprotective axn (protects mucosa from damage by gastric acid); chronic NSAIDs or corticosteroids→ ↓COX-1 → ↓local PGE → mucosal damage by acid→ peptic ulcer
  - **PGE_1 agonist misoprostol** for tx of NSAID–induced peptic ulcers & ↓↓acid production
- Use in Abortion/labour; all 3 tend to be used
  - **Misoprostol (PGE_1)** w/**mifepristone (antiprogestin)**: to induce abortions by inhibiting gestation
  - **Dinoprostone (PGE_2)** used in 'cervical ripening'/priming & abortifacient
  - **Carboprost ($PGF_{2\alpha}$)** used in 'cervical ripening' & abortifacient
- Use in **impotence**: Synthetic PGE_1 **Alprostadil**, into corpus cavernousum as suppository induces erection in dysfunc'al males by vasodilation
- Use in **Glaucoma**: **PGF2α (Latanoprost)** → out flow from ant chamber→ ↓IOP
- Use in Pulm HTN: **PGI2 (epoprostenol):** platelet stabilizer & vasodilator

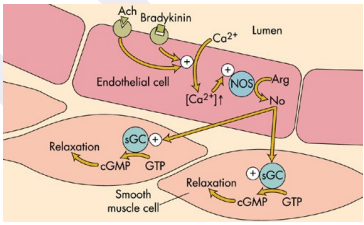


PG DRUG	PG CLASS	EFFECT	USE
Alprostadil	PGE_1	Vasodilation	Erectile dysfunc; patency of ductus arteriosus
Carboprost	$PGF_{2\alpha}$	Contraction of uterine m	Abortifacient; post partum bleeding
Dinoprostone	PGE_2	Contraction of uterine m	Abortifacient; cervical ripening/priming
Epoprostenol	PGI_2	Vasodilation	Pulm HTN
Latanoprost	$PGF_{2\alpha}$	↓↓AH outflow	Glaucoma
Misoprostol	PGE_1	Gastric cytoprotection	NSAID induced gastric & duodenal ulcers

- **Thromboxanes** (**TX**): TX_{A2}
- **Leukotrienes** (**LTs**): LTC_4, LTD_4, LTE_4; form via hydroperoxides from LOX on arachidonic acid
  - **LTB4**: inflamatory mediator→neutrophil chemoattractant
  - **LTC4**, **LTD4**, **LTE4**: ↑anaphylaxis & bronchoconstriction (role in asthma)

Eicosanoid Antagonists:

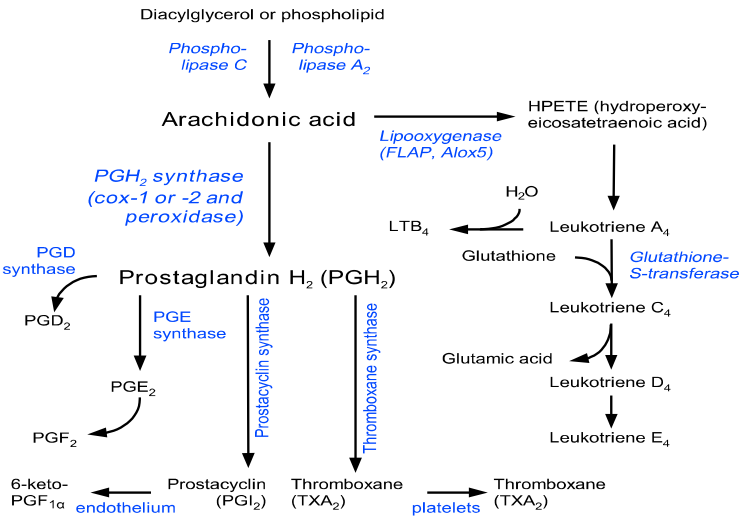
- **Dysmenorrhea**: ↑endometrial synthesis of PGE2 & PGF2α during menstruation leading to dysmenorrhea; NSAIDs (ibuprofen) inhibit synthesis of these PGs → relieve pain
- **Corticosteroids**: inhibit Arachidonic acid production by **inhibiting phospholipase A_2; also inhibit COX-2** –for its anti inflammatory axn
- **NSAIDS:**
  - **Aspirin irreversibly** inhibits platelet COX I & II- inhibit production of thromboxane, PG & prostacyclins; also for primary & secondary prevention of MI & stroke
  - **Celecoxib**, **rofecoxib**- selective COX II inhibitors
  - **Ibuprofen**, **indomethacin** - closure of PDA; closes open duct which should be closed
- **Anti-LT drugs**: all **for bronchial asthma**
  - **5-LOX enzyme inhibitors**: **Zileuton**
  - **LT receptor antagonists**: **Zafirlukast, monteleukast**
  - **Phospholipase A2 inhibitors**: **Corticosteroids** (both anti inflammatory & immunosuppressant axn)
- **NO (Nitric Oxide):** released by **Nitrates, sodium nitroprusside, ACh, H, Bradykinin; imp & powerful vasodilator (SM relaxation) via ↑cGMP**; made by NOS's (nitric oxide synthases) via Arginine metabolism converted to citruline & NO; for pulm a HTN & neonatal ARDS/HMD – via inhalation; +dietary supplements w/arginine: slows process of AS

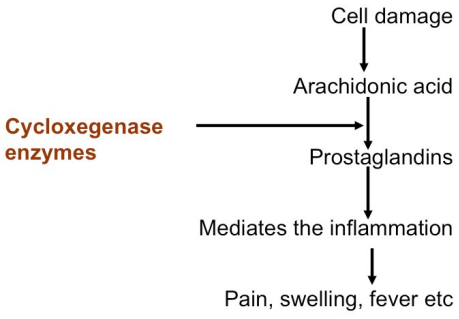


- **Sildenafil (Viagra): selectively inhibit predominant PDE-5 expressed in male corpus cavernosum which breaks down cGMP;** facilitates erection in resp to sexual stimulation by enhancing NO-induced relaxation of corpus cavernosal SM; similarly, ↑cGMP w/in pulm vascular SM ↓ relaxation; for tx of Erectile Dysfunc & Pulm Arterial HTN; contraindicated w/**coadmin of nitrate w/in 24 hrs likely to produce exagerated hypotensive resp**
- **Tadalafil**: PDE-5 inhibitor indicated for both BPH & erectile dysfunc

L13 Drugs Used in Inflammatory Dis's

- Inflammation: Pain, Fever & Swelling common manifestations; PGs, LTs, Ifs, ILs, Histamine, NO, TNF-α& various other cytokines considered as mediators; ***PGs are imp mediators of inflammation***

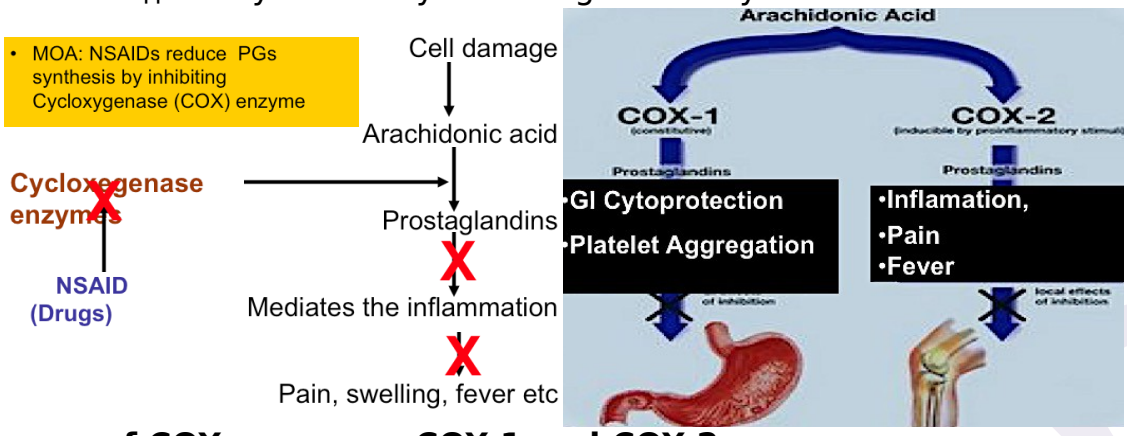




- ***PG's*** cause constriction or dilation in vascular SMC's, cause aggregation or disaggregation of platelets, sensitize spinal neurons to pain, induce labor, acts on parietal cells in stomach wall

to inhibit acid secretion, ↓↓IOP, regulate inflammation, acts on thermoregulatory center of hypothalamus to produce fever, & acts on mesangial cells in glomerulus of kidney to ↓GFR

- Drugs that can <u>inhibit PG synthesis</u> will ↓↓inflammation & its manifestations (pain, fever & swelling)
- NSAIDs ↓↓PGs synthesis by inhibiting COX enzyme



2 types of COX enzymes: COX-1 and COX-2

- **<u>COX-1</u>**: Constitutive, house keeping enzyme, & considered as good COX, not responsible for inflammation. So inhibiting COX-1 won't ↓↓inflammation. Rather produces harmful efx like Gastric ulcers
- **COX-2**: induced by inflammation, mainly at sites of inflammation, Bad COX. Inhibition of cox-2 leads to beneficial efx like suppression of inflammation, swelling, pain & fever
- Very few NSAIDs to some extent act in this way. These few NSAIDs belong "Highly selective COX-2 inhibitors"
- Based on **which cox they're inhibiting** NSAIDs split into 2 groups. **N**on **S**teroidal **A**nti **I**nflammatory **D**rugs (**NSAIDs)…** B/c they're not steroids. Other names: **Non opioid analgesics** B/c ↓↓**Pain. Antipyretics**… B/c they ↓↓**Fever**; Some powerful analgesics, some powerful anti-inflammatory & some only antipyretic but not good anti-inflammatory; most acidic; all inhibit COX reversibly except Aspirin; common adverse efx – Gastric & duodenal ulcers (Upper GI bleeding & heamatemesis; b/c ↓↓mucus secretion (PGs required for mucus) & ↑↑acid production cause gastritis. This adverse effect due to cox-1 inhibition but not cox-2 inhibition – not seen or rarely seen w/selective cox-2 inhibitors); & Renal toxicity (papillary necrosis & tubulo-interstitial inflammation of kidney), hepatic toxicity, Iron def anemia, & Precipitate Bronchial asthma by ↑↑LT's (since cox inhibited, all arachidonic acid now diverted to produce more LT's ↑↑mediates asthamatic inflammation)

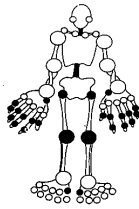
- (1) **<u>Highly selective Cox-2 inhibitors</u>**: for any inflammatory condition; esp those suffering from inflammatory **condition w/co existing gastritis or peptic ulcer**; avoid in pt's allergic to sulfonamides (as both drugs chemically rel'd, exerts cross allergy); except gastric irritation, rest all other side efx of NSAIDs seen w/these. Eg: ***<u>Celecoxib (avoid in MI & strokes b/c prothrombotic)</u>***, ***<u>Rofecoxib</u>*** (discontinued), ***<u>Valdecoxib</u>***, ***<u>eterocoxib</u>***
- (2) **<u>Nonselective inhibitors of both cox-1 & cox-2: Aspirin, Naproxen, Indomethacin, Ketorolac, Ibuprofen, Diclofenac sodium</u>**
  - **<u>Aspirin/Acetyl salicylic acid</u>**: powerful anti-inflammatory drug; in addition very good antiplatelet axn (**No other NSAIDs do this**); **by acetylation of enzymes, irreversibly inhibit** both COX-1&2 [vs all other NSAIDs (even highly selective COX-2 inhibitors)]; Antiplatelet due to Irreversibly inhibiting/ **<u>Acetylating</u>** Cox-1. Since other NSAIDs can't inhibit cox irreversibly (**<u>acetylate</u>**), none them clinically sig antiplatelet axn so DOC in: MI & TIA, as antiplatelets to prevent thrombus in **Very low dose 81-325 mg;** for all other conditions, use very high dose; in ARF, as anti-inflammatory (very high dose 4-8 g/day)

- Aspirin poisoning OD: Accidental, MC in kids w/CF's: Vomiting, dehydration, metabolic acidosis, respiratory acidosis, hypokalemia, hypoglycemia, delirium, hyperthermia, confusion, convulsions, coma & death due to respiratory failure.; MCCOD: pulm edema; Tx w/External cooling by tepid sponging, IV fluids, $NaHCO_3$, gastric lavage, forced alkaline diuresis, antacids ranitidine & haemodialysis; why hyperthermia? Even if salicylates antipyretic, cause hyperthermia in *high doses* due to uncoupling ox phos in skeletal m (ox proceeds w/out phos so producing heat)
- Adverse efx: (not w/other NSAIDS); Reyes syndrome in kids w/viral fever; Salicylism: occurs w/higher dose (as acute & chronic) charac'd by Vomiting, Tinnitus, Vertigo, loss hearing (resembles quinidine poisoning); reverse by sodium bicarbonate

- **Indomethacin**: most potent, powerful, anti-inflammatory axn than other NSAIDS; preferred over other NSAIDs in RA (unless have peptic ulcer), **Gout, Ankylosing spondylitis & PDA; GRAP**
- **Ketorolac**: poor antinflammatory property but very good analgesic axn; best in mild-moderate post op pain (opiods for severe pain), in parenteral formulation that can be injected IM'ly or IV'ly; not good for fever or inflammatory conditions
- **Ibuprofen**, **Diclofenac sodium**, **Ketorolac**: very good anti-inflammatory, widely used, better tolerated, safer; for **Chronic or acute MSK pain, General Inflammatory swellings & Fever**; also for (as alternative to Indomethacin) – RA, Gout, Ankylosing spondylitis & PDA
- **Analgesia:** ketorolac >ibuprofen/naproxen > ASA
- **GI irritation:** <ASA, but still occurs

➢ **Acetaminophen** (**Paracetamol in UK**): like NSAIDs w/has similar MOA – inhibits COX better in non inflammatory area; thus not good anti-inflammatory but **very good antipyretic & analgesic**; combined w/other NSAIDs to achieve synergistic efx; **for** any fever & non inflammatory pain (Headache, Toothache); safest, no gastric intolerance or ulcers but OD causes hepatic cell necrosis (imp ques) or alcohol-acetaminophen syndrome

- **Acetaminophen poisoning:** Normally metabolized by glucouronidation. **N-acetyl benzoquinone is minor metabolite** detoxified by glutathione conjugation. In poisoning, more **minor*** metabolite formed. Not enough glutathione in body to detoxify minor metabolite ⇒ accumulates ⇒ liver cell necrosis. Tx'd w/specific antidote **N-acetyl cysteine** (also for CF) replenishes glutathione stores of liver & provides –SH group. So minor toxic metabolite metabolised; also used for haemorrhagic cystitis



➢ **RA (Rheumatoid arthritis):** chronic progressive crippling autoimmune w/waxing & waning course charac'd by jt destruction that mediated by IC's, inflammatory cells & lysosymes

⇒ Drugs used for RA: help by either ¬¬inflammation or suppressing immune system; R. arthritis usually 1st tx'd w/NSAIDs relieve pain & swelling in **acute RA but don't prevent dis progression**

- Chronic RA pt if don't respond to NSAIDs, add DMARDs. DMARDs not useful in acute RA.
- Unlike NSAIDs, don't give immediate relief, but arrest dis progression & benefit in long run.
- Generally they're combined w/NSAIDs in chronic management of RA
- **Goal of tx:** relief in sx, ¬¬inflammation. & Modify progression of dis

⇒ **2 major group of drugs for RA:**

➢ (1) Anti-inflammatory drugs: NSAIDs & Corticosteroids

- **NSAIDs**: relieve pain & swelling, anti-inflammatory used in acute & chronic conditions; do not alter dis course. Any NSAIDs can be used. But Indomethacin more preferred over other NSAIDs
- **Corticosteroids**: for acute conditions for short period Or used chronically in low dose when NSAIDs ineffective; doesn't modify dis course; anti-inflammatory &

immunosuppressant property; used in ~70% RA pt's, rapidly relieve sx & slow appearing new bone erosions; as bridging therapy (while classic DMARDS taking efx), at continuous low dose therapy & in short term high dose bursts to control flare

- ***Prednisone*** is steroid of choice for RA;

➢ (2) **DMARDs** (Dis Modifying Anti Rheumatoid Drugs)/**SAARDs** (Slow Acting Anti Rheumatoid Drugs)

- **DMARDs** modify dis course, given for long time; beneficial efx only after some weeks; slow acting & more toxic than NSAIDs; any used – Chloroquine, D-pencillamine, Gold, Sulfasalazine but now prefer **Mtx, infliximab, etanarecept & anakinra**
- **Infliximab**: TNF-α blocker anti-TNF Ab's imp chimeric monoclonal Ab for RA; adverse efx: Infections, reactivation Tb & heptatitis, DLE
  - **Adalimumab**: TNFα antagonist, similar to infliximab; most TNF antagonists also useful in tx'ing Psoriasis, CD, UC
- **Mtx**: immunosuppressant/anticancer drugs used in very low dose in RA (in cancer high dose)
- **Anakinara**: recombinant **IL-1 receptor antagonist**
- **Leflunomide**: inhibits mitochondrial dihydroorotate DH (involved in de novo pyrimidine synthesis)
- Most TNF antagonists also useful in **tx'ing Psoriasis, crohn's dis, ulcerative colitis**
  - **Receptors** those found embedded in WBC's that respond to TNF by releasing other cytokines
  - **Soluble TNF receptors:** used to deactivate TNF & blunt immune resp
  - **Etanarcept:** mimics inhibitory efx of naturally occurring soluble TNF receptors & deactivates TNF by competitive binding & preventing its interaxn w/cell surface receptors ↓inhibiting inflammation, diff b/c it's fusion protein rather than simple TNF receptor, greatly extended half-life in bloodstream & more profound & long-lasting biologic efx than naturally occurring soluble TNF receptor; anti-inflammatory so used in RA, psoriasis & psoriatic arthritis

➢ **Gout**: metabolic disorder charac'd by hyperurecemia (N plasma urate 1-4 mg/dl); in Acute & chronic forms; inflammatory/painful swelling of GREATER TOE … mostly GOUT (at least until you pass step-1 exam)

Tx of Acute Gout	Tx of Chronic Gout
Should start Immediately to ↓↓Inflammation & sx & not to treat route cause of dis or to ↓↓uric acid lvl • **NSAIDs** (COX inhibitors – Naproxen, Indomethacin) & • **Colchicine**: 2nd line antinflammatory **ONLY In acute gout;** has neither analgesic nor anti-inflammatory axns in any other dis's but specifically suppresses gouty inflammation; often used in pt's w/mild-moderate renal failure, peptic ulcers or other contraindications to NSAIDs; binds to IC protein tubulin preventing tubulin polymerization into MT's ↓impairing leukocyte migration, ↓↓neutrophil chemotaxis & emigration to sites inflamed by MSU crystals, & ↓phagocytosis, ↓↓inflammation; also disrupts MT formation in GI mucosal cells ↓ diarrhea & less often, nausea, vomiting & abdominal pain • **GC's**: anti-inflammatory efx by inhibiting PLA2	Aim to ↓↓blood uric acid by-- 1. Promoting Excretion of uric acid (Probenecid) 2. Inhibiting synthesis of uric acid (Allopurinol) • Probenecid & Allopurinol • Tx started only – 2-3 weeks after 5- 6 acute attacks – if "tophi" present & uric acid lvl high OTHERWISE can exacerbate acute arthritis

➢ **Probenecid**: inhibits tubular reabsorption of uric acid, promotes excretion of uric acid ↓↓blood uric acid; **used for** Chronic Gout, 2ndary Hyperurecemia & prolongs duration of axn of Penicillins & METHOTREXATE; **↓↓ efx of diuretics!!!!!!!**

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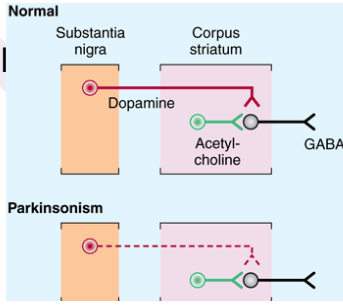
- **Allopurinol**: pro drug; produces active metabolite Alloxanthine; ↓↓uric acid production by preventing conversion of Hypoxanthine to uric acid by inhibiting *Xanthine oxidase*; **for** Chronic Gout, 2ndary Hyperurecemia, to potentiate axn of anticancer 6-mercaptopurine & Azathioprine; **Note: Not for acute gout**

L1 Pharmacotherapy for Parkinsonism & other Movement Disorders

- **Parkinson's Dis**: degenerative CNS disorder* often impairs motor skills & speech; aka EPS (extrapyramidal sx) –resting tremors (^ACh), cogwheel rigidity, rigidity, bradykinesia (slow shuffling gait)/akinesia: respectively, slowness or absence of movement, postural instability, gait abnormalities, fatigue & soft speech /drooling
  - * **MSA: Multiple System Atrophy** may be confused w/PD. Also called Parkinsons + dis; much less common & doesn't respond to drugs used in PD.
  - In parkinsonism –↓↓[N high DA] in basal ganglia & pharmacologic attempts to restore DA'ergic activity w/levodopa & DA agonists alleviate many motor sx of disorder. Alternate, but complementary approach to restore N balance of cholinergic & DA'ergic influences on basal ganglia w/antimuscarinics; basis for therapies that in idiopathic parkinsonism, have loss DA'ergic neurons in SN that normally inhibit output of GABAergic cells in corpus striatum

↓Drugs that induce parkinsonian syndromes are –
- **D2 receptor antagonists** eg, **antipsychotic agents** – ie. Haloperidol
- **MPTP**- (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine): chem'al which destructs DA'ergic neurons ⇒ irreversible parkinsonism



↓DA'ergic neurons (red) originating in SN inhibit GABAergic output from striatum, whereas cholinergic neurons (green) exert excitatory effect. In parkinsonism, have selective loss of DA'ergic neurons (dashed, red).

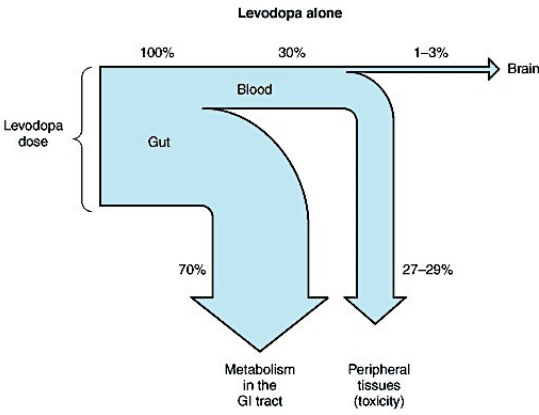
Drug tx: 2 strategies - ↑↑ DA lvls or ↓↓ (ACh) cholinergic lvls

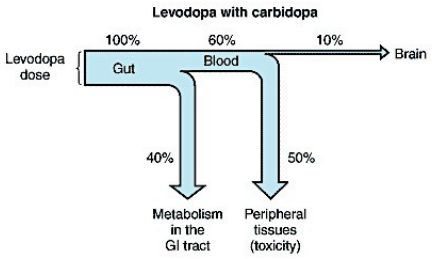
↑↑ DA lvls (dopaminergic activity in brain)

A. Give DA precursors (converted to DA in body)

1. ***L-Dopa (Levodopa)**: most effective drug for parkinsonian sx; immediate DA precursor enters brain; converted to DA by DOPA-decarboxylase (in most body tissues both central & periphery); b/c DA doesn't cross BBB & if given in peripheral circulation has no therapeutic efx hence why peripheral conversion of L-dopa, ↓↓amt L-dopa reaching brain & ↑↑peripheral DA side efx– *face & distal extremities MC; ADR – GI Efx: When given w/out peripheral decarboxylase inhibitor ↑↑anorexia, nausea & vomiting so given in combo w/carbidopa to ↓↓adverse GI efx; & CVS arrhythmias – tachycardia, ventricular extrasystoles & rarely atrial fib

2. **Carbidopa**: inhibis peripheral DOPA-Decarboxylase/AAAD (**Aromatic L-AA Decarboxylase)**
3. ***Sinemet**: L-dopa + Carbidopa dopa prep in fixed proportion (1:10 or 1:4). ****Adv's: ↓↓L-dopa available brain, so lower doses of L-dopa can be used & less periphe efx***, ↓↓GI efx*; ameliorates signs of parkinsonism, esp bradykinesia, BUT Not cure to dis & as dis progresses, resp ↓↓↓↓=(





4. ADR: arrhythmias (↓peripheral catecholamines), long term dyskinesias (after admin, as on-off rxns), & akinesia btwn # Motor Fluctuations describe 3 phenomena, wearing off, o fluctuations & dyskinesias);
    1. ***Dyskinesias** 80% pt's receiving levodopa for long periods (chorea, ballism) – constant blinking, pouting; +Choreoathetosis of face & distal extremities; muscarinic recept prevent this; >commonly w/levodopa in combo w/carbidopa & w receptor agonists; involuntary m jerks that afx proximal m's of li
        1. **Choreoathetosis**: involuntary movements in combo of chore athetosis; afx hands, feet, trunk, neck & face. In face often w/ wrinkling, continual flitting eye movements & mouth/tongue movements
        2. **Athetosis**: continuous stream slow, sinuous, writhing movements of hands & feet. Movements typical to athetosis sometimes called *athetoid* movements; due to damaged corpus striatum
        3. **Chorea:** Greek word *khoreia* (kind of dance), quick movements of feet or hands comparable to dancing or piano playing
        4. **Ballism:** When chorea serious, slight movements become thrashing motions, form of severe chorea
    2. Behavioral efx: many adverse mental efx – depression, anxiety, hallucinations & other mood/personality changes; More w/L-dopa & carbidopa combo
    3. *Fluctuations In Resp: to levodopa occur w/↓↓frequency as tx continues. In some, fluctuations relate to timing of levodopa intake as **wearing-off rxns**. OR fluctuations unrel'd to timing (**on-off phenomenon** – off-periods of marked akinesia alternate over few hrs w/on-periods of improved mobility. Mechanism not well known)
        1. Apomorphine, via subcutaneous injection used for temporary relief of off periods of akinesia ("rescue") in parkinsonian pt's on DA'ergic drug therapy; pre-tx w/antiemetic triemthobenzamide for 3 days essential to prevent severe nausea
    4. Pharmacologic doses of **pyridoxine (vit B_6)** enhance extracerebral metabolism of levodopa & may thus prevent levodopa's therapeutic efx
    5. Contraindicated in psychotic pt's (exacerbate mental disturbance) & **angle-closure** glaucoma, but those w/chronic open-angle glaucoma can take levodopa if IOP well controlled
    6. L-dopa precursor of skin melanin & may activate malignant melanoma; rare

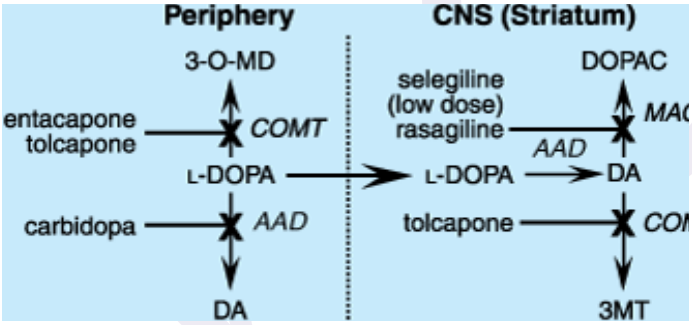
B. *Drugs that stimulate DA receptors:* most often given along w/L-dopa to prolong its effectiveness; ADR: nausea vomiting, postural hypotension, dyskinesia; **Bromocriptine***, **Pergolide, Pramipexole, Ropinirole & rotigotine** (antioxidants)

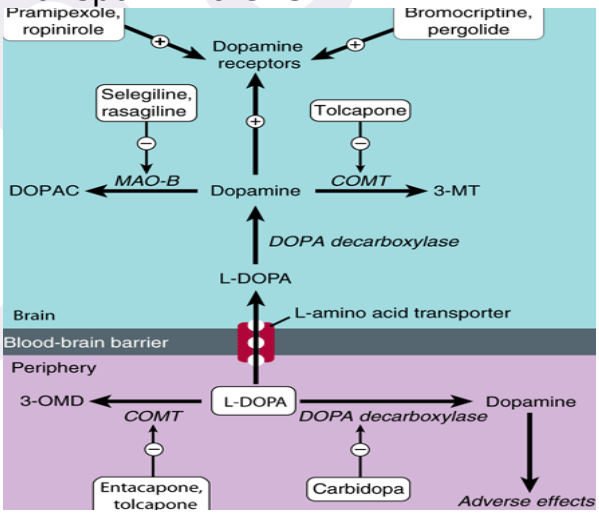
1. **Bromocriptine***: partial agonist at D_2 receptors in brain; also for hyperprolactinemia (b/c DA inhibits PRL release, can treats in women w/galactorrhea, infertility, pituitary adenoma or induced by haloperidol) & acromegaly (infertility, gynecomastia); contraindicated in pt's w/psychotic illness
2. **Pergolide**: D_2 receptor agonist
3. **Pramipexole**: D_3 receptor agonist, now considered 1st line drugs, less ADR
4. **Ropinirole**: non-ergot stronger D2 receptor activator but also D3 receptor antagonist, doesn't need bioactivation; confusions, delusions & hallucinations more frequently w/DA receptor activators than w/levodopa; use of DA'ergic agents w/antimuscarinics common in tx'ing parkinsonism; metabolized by hepatic CYP1A2 & its plasma lvls ↓by other substrates for this enzyme ie. caffeine & warfarin; effective as

monotherapy in mild parkinsonism; sometimes value in pt's who've become refractory to levodopa; adverse efx – dyskinsias, postural hypotension & somnolence

C. *Drugs that inhibit enzymatic DA degradation* ▭ ***Pharm'al preservation of L-DOPA & striatal DA***

1. **MAO-B-inhibitors- Low dose Selegiline & Rasagiline**: selective MAO-B inhibitors; as adjunct to Levodopa; tried alone in newly dx'd pt's; act w/in CNS to ↓↓oxidative deamination of DA, thus enhancing vesicular stores; ADR: insomnia (b/c metabolized to amphetamine), mood changes, GI distress & hypotension; DI w/*meperidine* – agitation, delirium & death, alone doesn't do this but extreme caution w/TCA & SSRI b/c causes serotonin syndrome ▭ hypertensive crises, ↓BP 160/110, tachycardia) + cheese rxn
    1. 2 isoforms of MAO (A & B) – MAO-B: isoform that metabolizes DA in preference to NE & 5-HT
2. **COMT-inhibitors: entacapone (prefer), tolcapone**: mainly block COMT peripheral *O*-methylation of levodopa (L-Dopa) & ↓L-dopa fraction to deliver to brain; as adjunct to Sinemet/Levodopa – prolong its axn by diminishing its peripheral metabolism; ADR: dyskinesias & postural hypotension
    1. **Tolcapone:** also CNS efx – inhibits central & peripheral COMT+; side efx – hepatic damage so prefer entacapone
    2. **Entacapone:** only peripheral inhibitor of COMT**;** prefer over Tolcapone
    3. COMT converts Levodopa to 3-0-MD. ↓plasma 3-0-MD indicates poor resp to Levodopa. AAD, aromatic L-AA decarboxylase; DOPAC, 3,4-dihydroxyphenylacetic acid; 3MT, 3-methoxyltyramine; 3-O-MD, 3-*O*-methyl DOPA which can act as partial agonist so both compete for active transport into CNS, or competes w/it in CNS; AAD in pic = dopa decarboxylase. Both compete for active transport into CNS





▭ **Drugs ↓↓ cholinergic activity –to treat drug induced Parkinsonism ie. Benzotropine**

D. ***Anticholinergic/Anti muscarinics*** (should cross BBB): **Benztropine, biperiden, procyclidine & trihexyphenidyl;** improve tremor & rigidity; little efx on bradykinesia; imp use: reverse EPS efx of antipsychotics & treat drug induced parkinsonism/EPS; diff types based on time of onset; ADR: Anti-DUMBELLS: Dry mouth, urinary retention (so don't give to BPH pt's!), constipation, sedation, mydriasis, ↑↑HR, delirium, confusion, hallucinations, dry flushed skin tx'd w/physostigmine; 3 C's: cardiotoxicity, coma, convulsions

E. ***Dyphenhydramine: antihistamine H1 1st GEN*** w/antimuscarinic efx –treats EPS caused by psychotics

F. ***Amantadine***: doesn't exactly stimulate DA receptor but antiviral enhances DA'ergic neurotransmission; ↓synthesis, release & inhibition of DA reuptake; & blocks muscarinic receptors; less efficacious than levodopa & benefits short-lived, often disappearing after only few weeks of tx; ADR: restlessness, depression, irritability, insomnia, agitation, excitement, hallucinations & confusion, levido reticularis (skin looks very pale & vessels underneath dilate, netlike reddish to bluish discoloration of skin)

Therapy of Other Movement Disorders

- **Tremors** tx'd by Propranolol b-blocker (metaprolol preferred if pt w/pulm dis) or topiramate (anti-epileptics)
- ***Huntington's Chorea:*** choreoathetosis w/ ↓↓mental abilities & psychosis (paranoia); tx'd w/Tetrabenazine (depletes DA), reserpine (depletes cerebral DA) & Haloperidol (block DA'ergic receptors)
  - **Reserpine**: drugs depleting NE stores in adrenergic n terminal; blocks vesicular uptake & storage of biogenic amines by interfering w/uptake (VMAT: vesicular memb associated transporter) causing NE, serotonin & DA depletion; readily crosses BBB, so toxicities: depleting cerebral amines stores causing sedation, mental depression & Parkinsonism sx; don't use anymore but will be tested on, clinical sig ↓ 1 of earliest models understood depression thru; caused depression via side efx
- ***Tourette's Syndrome*** – multiple tics; tx'd w/Haloperidol (blocks central D_2 R), carbamazepine, clonazepam & clonidine (a_2 agonist), or **Pimozide** but w/very unfavorable side efx similar to or even worse than haloperidol & +appears to cause breast & liver cancer
- ***Wilson's Dis*** – accumulated copper ion (inherited) leads to chronic hepatitis, cirrhosis & neuro'al damage ↓movement, psychiatric disorders, Kayser-Fleischer rings & sunflower cataracts; MC'ly in 10-40 yrs age, dec ceruloplasmic, ^copper excretion, tx'd & reversed by copper chelator penicillamine w/pyridoxine to prevent neurologic complications & improve tx success; +potassium disulfide, zinc sulfate or trientine. Copper in urine >100 µg/24h can confirm, but low in serum
  - ***Penicillamine***: also used to ↓↓cysteine excretion in cystinuria & tx severe, active RA unresponsive to conventional therapy; also adjunctive therapy in lead, gold & arsenic poisoning; can cause HSR, bone marrow suppression, proteinuria, fever, lymphadenopathy, lupus-like syndrome (not associated w/hypocomplementenemia, +/- nephropathy vs SLE), some w/hypogeusia (diminished taste perception)
  - ***Trientene (triethylenetetramine dihydrochloride)***: effective in tx'ing penicillamine-intolerant pt's but less potent; SE: bone marrow suppression & proteinuria; iron & other minerals may dec its efx
  - ***Zinc sulfate/Zinc salts***: takes weeks to work! Never immediate tx; stimulate synthesis of endogenous chelators (metallothionein in liver & intestine) ↓ this binds copper w/high affinity, preventing its serosal transfer into blood ↓ lost in stool following desquamation of intestinal cells ↓ forces body to use its copper stones to restore normal balance
- ***Restless legs syndrome*** tx'd w/DA agonist – ropinirole or pramipexole
- Diazepam & other BZDs also helpful in Huntington's. But, efficacy ↓↓sig'ly w/dis progression. Chorea associated w/thyrotoxicosis, PV, SLE, hypocalcemia & hepatic cirrhosis, managed by tx'ing underlying cause. Drug-induced chorea managed by w/drawing offending drug levodopa, antimuscarinic, amphetamine, lithium, phenytoin or OCT

L2 Antipsychotics

- **Psychosis**: variety of mental disorders – presence of delusions (false beliefs), various types of hallucinations, usually auditory or visual, but sometimes tactile or olfactory & grossly disorg'd thinking in clear sensorium
- **Schizophrenia** - psychosis charac'd by clear sensorium but marked thought disturbance; mesolimbic system & mesocortical responsible for sx w/ ↓↓DA'ergic activity ↓ psychosis; tx'd w/Haloperidol – DA antagonist – but can cause hyperprolactinemia; **Positive & negative sx of schizophrenia –**
  - **+ve sx of schizophrenia**: hallucination (visual or auditory), delusions (false beliefs), thought dysfunc, rel'd to ↓DA lvls in meso***limbic*** pathway; give typical antipsychotics
  - **–ve sx of schizophrenia** – def in emo'al responsiveness, spontaneous speech & volition, flattening of affect, poverty of speech & drive, loss of feeling/depression, social w/drawal

& ↓↓spontaneous movement - due to ↓↓DA'ergic activity in meso***cortical*** pathway; give atypical antipsychotics

- Pathophysiology of Schizophrenia:
  - *DA hypothesis*: proposes disorder is caused by excess of DA in mesolimbic-mesocortical pathway causing most +ve sx; typical antipsychotics act on DA; ie. **Haloperidol** (D2 antagonist à controls psychosis), but Cocaine stops reuptake of DA à see psychosis
  - *5-HT hypothesis:* new hypothesis suggests serotonin also involved in pathophysiology (5-HT_2); Drugs LSD & mescaline (powerful hallucinogen; serotonin agonists) cause hallucinations; so 5-HT 2 blockade is principal mechanism of atypical drugs clozapine; believe 5-HT afx –ve & some +ve sx; esp 5-HT2 receptors; atypical drugs act on 5-HT
- 5 DA receptors (D_1-D_5)
  - **D1 Class (↑ cAMP) – D1, D5**
    - **D1**: in basal ganglia
    - **D5**:
  - **D2 class (↓ cAMP) – D2, D3, D4**
    - **D2**: in basal ganglia, pituitary lactotrophes, VTA, CTZ, presynaptic (autoreceptors); blocked by antipsychotics; cause nausea & vomiting; blocking them ↓ antiemetic efx; Lot lmtd to brain à if you block D2 in basal ganglia = Parkinsonism, or EPS
    - **D3**: in limbic system (nucleus accumbens)
    - **D4**: in prefrontal cortex, brain stem
  - Diff affinity for receptors w/drugs à some target D2 (most mostly block D2 w/strong affinity) ie. Haloperidol
- **Antipsychotics**: therapeutic efx in schizo are result of axns on mesolimbic & mesocortical areas in CNS; As result of their "dirty pharmacology" or relative non-selectivity, all have side efx ie. sedation (antihistamine), dry mouth (anti-muscarinic), hypotension (α block); for schizophrenia by causing immediate quieting axns, ↓↓ +ve sx (apathy, blunted affect) whereas atypicals – greater efx on –ve sx; also for manic episode in bipolar disorder (olanzapine, aripiprazole), Tourette's syndrome (haloperidol), emesis (prochlorperazine – DA receptor blockade at chemoreceptor trigger zone) & neurolept anesthesia (Droperidol +fentanyl); adverse efx: EPS syndrome due to DA receptor blockage of nigro-striatal pathway; diff types of EPS –
  - **Acute dystonia**: spastic retrocolis or torticollis; spasm of m's (esp neck) **w/in few mins-hrs** of drug
  - **Akathisias**: motor restlessness, can't stay in pos for very long, always restless; few days-weeks
  - **Parkinson**-like sx: tremors, bradykinesia, rigidity; few days-weeks
  - **EPS Tx'd by benztropine, biperiden, trihexphenyl, diphenhydramine (H1 first GEN blocker)**
  - **Tardive dyskinesia**: involuntary movements of tongue, lips, face, trunk & extremities in pt's tx'd w/long term DA'ergic antagonists; late occurring syndrome, Oral/facial dyskinesias, m jerks, writhing of lip m's caused by relative cholinergic def secondary to supersensitivity of DA receptors; 20-30% pt's; early recog imp, since advanced cases may be difficult to reverse. Any pt w/TD tx'd w/typical antipsychotic should be switched to **quetiapine** or **clozapine** (atypical agents least likely to cause TD); **http://www.youtube.com/watch?v=WAg2iLEWVh0**; Choreoathetoid movement of face & oral cavity. (blinking or pouting); be able to **ID**: manifestation à abnormal choreathetoid movement of upper extremity & face, & occurs months or yrs after starting. (rare but imp)
  - **NMS (Neuroleptic malignant syndrome): rare but life-threatening; pt's highly sensitive to extrapyramidal drug efx; seen at high dose 'typicals' & w/parenteral admin; initial sx w/marked m rigidity, alterations in BP & HR, hyperthermia** ↑ m-type CK ↑↑; Cause: excessively rapid blockade of postsynaptic DA R;

tx by Stopping drug, dantrolene, diazepam (if seizures); [so If hyperthermia, m rigidity & ↑CK à look at situation. (if someone on anesthesia à malignant hyperthermia. If on antipsychotics à think NMS. Or could be serotonin syndrome]

- Adrenoreceptor blockage ▭ Orthostatic hypotension, reflex tachycardia, impotence & inhibit ejaculation
- Muscarinic receptor blockade ▭ ANTI DUMBBELLS – Dry mouth, constipation, blurred vision, tachycardia, urine retention
- Endocrine & metabolic side efx of antipsychotics as DA is inhibitory regulator of PRL secretion so D_2 antagonists (conventional antipsychotics & risperidone atypical agent) cause ****_hyperprolactinemia_ – seen w/amenorrhea & galactorrhea in women; or w/gynaecomastia & impotence – in men
- Weight gain: very common w/clozapine & olanzapine due to H1 receptor blockade & seen w/all conventional & atypical drugs *Except* aripiprazole & ziprasidone

TABLE 29–2 Adverse pharmacologic effects of antipsychotic drugs.

Type	Manifestations	Mechanism
Autonomic nervous system	Loss of accommodation, dry mouth, difficulty urinating, constipation	Muscarinic cholinoceptor blockade
	Orthostatic hypotension, impotence, failure to ejaculate	α-Adrenoceptor blockade
Central nervous system	Parkinson's syndrome, akathisia, dystonias	Dopamine-receptor blockade
	Tardive dyskinesia	Supersensitivity of dopamine receptors
	Toxic-confusional state	Muscarinic blockade
Endocrine system	Amenorrhea-galactorrhea, infertility, impotence	Dopamine-receptor blockade resulting in hyperprolactinemia
Other	Weight gain	Possibly combined H_1 and 5-HT_2 blockade

last 3 columns explain side efx –
- If something block H1 à sedation & weight gain (↑appetite)
- 1st GEN Histamine blockers à make drowsy, antimuscarinic (tachycardia, constipation, mydriasis, dry eye, dry mouth)
- Antimuscarinic: atropine & atropine rel'd drugs: mepiridine, Disopyramide, **anti-psychotics**, 1st GEN H1 anti-histamines
- If you block α-1 à hypotension & ↓ejaculation

Link mechanism of action to side effect

	D2	D4	5-HT	H1	M	α-1
Typical Antipsychotics – block D2; focus on 1st 3 columns; for +ve sx anti-THC						
Chlorpromazine	++	0	+	+++	+++	+++
Haloperidol	+++	0	+	0	0	+
Thioridazine	++	0	+	+++	+++ (brain muscarinic receptors, so prefer over Haloperidol	+++
Atypical Antipsychotics – mainly block serotonin 5-HT_2, some D2 & D4; exception: Aripiprazole; treat –ve sx; anti CRAZO						
Clozapine (ALL)	+	++	+++	++	+++	++
Risperidone	++	0	+++	++	+	+++
Aripiprazole	+++	++	+++	0	0	+
Olanzapine	++	0	+++	+	++	++
Ziprasidone	++	0	+++	0	+	+

➢ ***Typical antipsychotics: D2 receptor antagonist block D_2 receptors & their binding affinity very strongly correl'd w/clinical antipsychotic & extrapyramidal potency; efficacy achieved at least 60% occupancy of striatal D_2 receptors. EPS seen when occupancy of D_2 receptors reaches 80% or+, reversible by lowering dose or anti-muscarinics

- ***Phenothiazines**: most have anti-emetic axns, esp prochlorperazine*
  - **Chlorpromazine**: 1st drug discovered in 1950's w/antipsychotic axns; beneficial efx lead to synthesis of other phenothiazines & chemically rel'd "non-phenothiazines" like haloperidol & newer atypical antipsychotics; can cause weight gain & more pronounced ANTI-DUMBELLS
  - **Prochlorperazine**: solely promoted as anti-emetic for diabetic gastroparesis; due to DA receptor blockage at chemoreceptor trigger zone; H1-receptor blockade, most often

present in short side-chain phenothiazines, provide basis for their use as antipruritics & sedatives & contributes to their anti-emetic efx

- **Fluphenazine**: more common side efx of EPS
- **Thioridazine**: only non-anti-emetic; retinal deposit – browning of vision, prolong QT interval/torsade des pointes ventricular arrhythmias just like ziprasidone; fatal OD (^risk death in elderly w/dementia); has strongest autonomic efx so more pronounced ANTI-DUMBELLS
- **Trifluoperazine**: more common side efx of EPS

- ***Haloperidol/Butyrophenone***: relatively safe; *to treat schizo +ve sx blocks DA in mesolimbic pathway; also treats Tourette's syndrome; But side efx by also blocking nigrostriatal pathway; +When you Block DA à PRL (hyperprolactinemia) à Tuberoinfundibular pathway (ant pituitary) tx'd w/bromocryptine*

➢ ***Atypical Drugs ($5HT_2$ & D_4 receptor antagonist; weak D2 affinity): block 5 HT2 receptors & D_2 or D_4 receptors; lower affinity for D_2 receptors & higher for blocking other subtypes, esp but not lmtd to 5HT2 subtype; effective at lower occupancy lvls of 30–50%, b/c their concurrent high occupancy of 5-HT_{2A} R; Weight gain very common w/clozapine & olanzapine due to H1 receptor blockade seen w/all conventional & atypical drugs *Except* aripiprazole & ziprasidone [Clozapine, asenapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone, zotepine, & aripiprazole]

- Any pt w/TD tx'd w/typical antipsychotic should be switched to quetiapine or clozapine (atypical agents least likely to cause TD).
- **Clozapine (ANSWER)**: atypical antipsychotic $5HT_2$ & D_4 receptor antagonist; weak D2 affinity; used w/pt illicits TD from typical antipsychotics; side efx – weight gain very common due to H1 receptor blockade, also causes agranulocytosis***, so weekly blood counts required, neuroleptic malignant syndrome, seizures, TD, dystonia, PE/DVT, severe hyperglycemia, profound hypotension & cardiac arrest
- **Asenapine**: atypical antipsychotic $5HT_2$ & D_4 receptor antagonist; weak D_2 affinity
- **Olanzapine**: atypical antipsychotic $5HT_2$ & D_4 receptor antagonist; weak D_2 affinity; for manic episodes in bipolar disorder; side efx – weight gain very common due to H1 receptor blockade
- **Quetiapine**: atypical antipsychotic $5HT_2$ & D_4 receptor antagonist; weak D_2 affinity; used w/pt illicits TD from typical antipsychotics
- **Risperidone**: atypical antipsychotic $5HT_2$ & D_4 receptor antagonist; weak D_2 affinity; prominent efx on serotonin
- **Sertindole**: atypical antipsychotic $5HT_2$ & D_4 receptor antagonist; weak D_2 affinity;
- **Ziprasidone**: atypical antipsychotic $5HT_2$ & D_4 receptor antagonist; weak D_2 affinity; very little side efx – no weight gain nor PRL-nemia, prolong QT interval/torsade des pointes ventricular arrhythmias just like thioridazine
- **Zotepine**: atypical antipsychotic $5HT_2$ & D_4 receptor antagonist; weak D_2 affinity;
- ***Aripiprazole; partial agonist at D2; 5-HT_2 antagonist & But also afx D2 & D4; for manic episodes in bipolar disorder; better than other atypicals (esp –ve sx), very few side efx – no weight gain nor PRL-nemia

DA'ergic pathways

➢ **Mesolimbic System**: from VTA (ventral tegmental area) to amyggdala, nucleus accumbens…involved in emotions, memory, motivational behavior; *Too much activity here may contribute to +ve sx of schizophrenia*

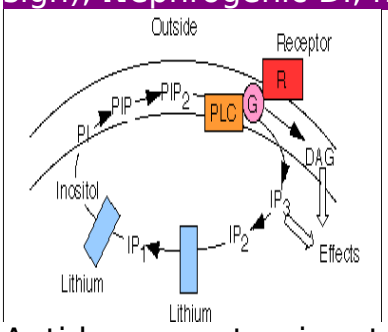
➢ **Mesocortical system**: from VTA to prefrontal cortex, frontal cortex…involved in cognition, comm, social func; *Hypofunc'ing here may contribute to –ve sx of schizophrenia*

➢ **Nigrostriatal Pathway**: from SN to striatum, which modulates extrapyramidal motor system (posture, movement); *insufficient activity here causes Parkinsonism; where typical antipsychotics cause more EPS*

➢ **Tuberoinfundibular Pathway (ANSWER)**: from hypothalamus to pituitary, modulates PRL release; *DA'ergic drugs produce some side efx by acting here; ie.* DA & PRL inversely rel'd.

DA antagonists inhibit this pathway à cause hyperprolactinemia (Galactorrhea, amenorrhea, infertility in women, gynecomastia & impotence in men à treat w/bromocryptine)

- ***Lithium bicarbonate (ANSWER): most imp for bipolar disorder (BPD)/acute mania w/onset of efx taking 2-3 weeks as mood stabilizer (others – Carbamazepine & valproate), for depressive phase of BPD give Lithium w/TCA; inhibits recycling of memb phospholipids by blocking IP2 to IP1 conversion thus blocks PIP2-depletion of 2nd msngr- DAG & IP3; eliminated entirely by kidney, 80% reabsorbed in proximal tubule (same reabsorption as sodium); narrow/low therapeutic index (0.8-1.2 mEq/L), plasma lvls must be monitored; Beyond 1.2 à develop toxicity; Adverse efx common at therapeutic range 0.5-1.4 mmol/l – severe tremors (imp 1st sign of toxicity) drowsiness, ataxia, causes **Nephrogenic** DI (not ~~neurogenic ADH lack~~; polyuria & polydipsia, as CD become unresponsive to ADH) tx'd w/Amiloride; Benign reversible thyroid enlargement, rarely hypothyroidism; & Contraindicated in Pregnancy – causes ebstein's anomaly (tricuspid valve defect); **LMNOP** à **L**ithium (toxicity), **M** Tremor (1st sign), **N**ephrogenic DI, hyp**O**thyroidism, contraindicated in **P**regnancy.



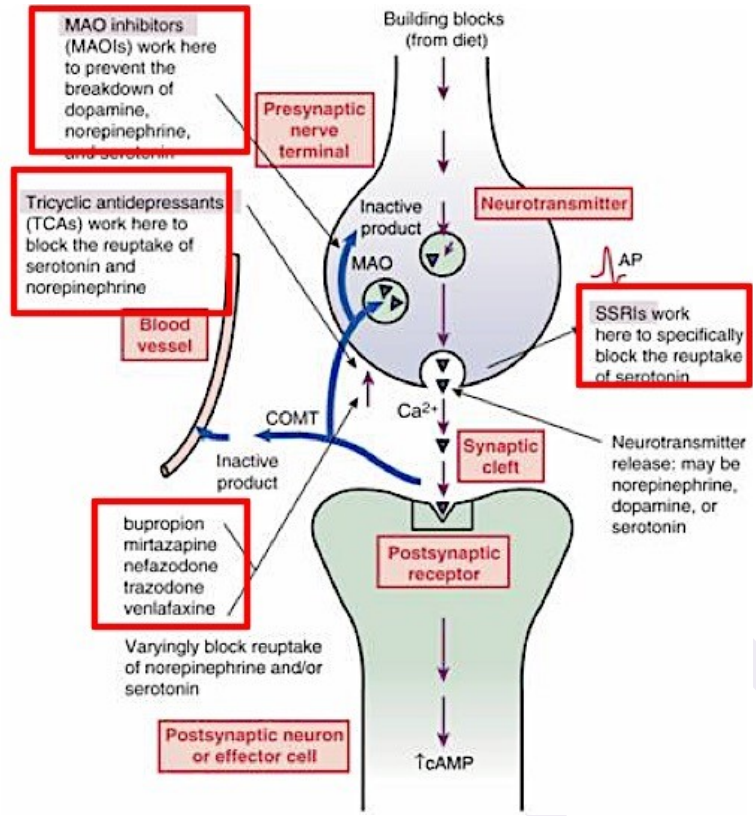
L3 Antidepressants – imp to know any drugs interacting w/SSRIs, cheese rxn & serotonin syndrome

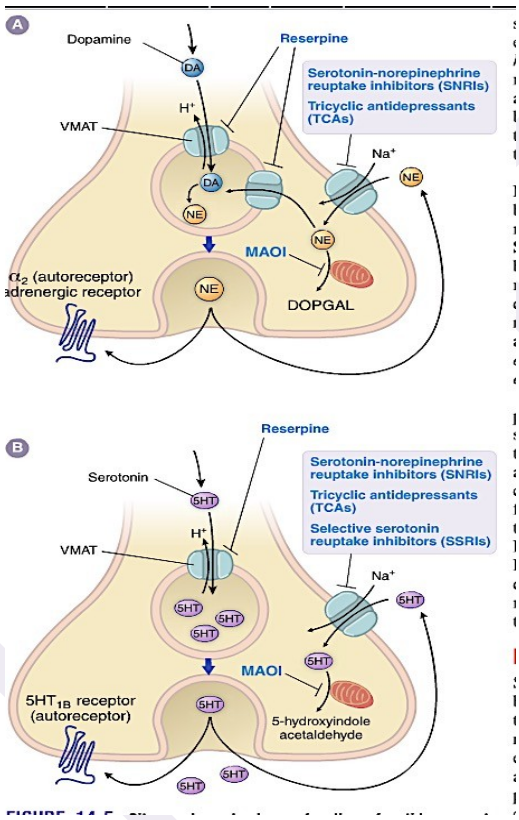
- **MDD (Major depressive disorder):** depressed mood most of time for at least 2 weeks &/or loss of interest or pleasure in most activities. In addition, depression charac'd by disturbances in sleep & appetite +deficits in cognition & energy. Thoughts of guilt, worthlessness, & suicide common; sx & signs – low energy lvl, sleep disturbances, lack of appetite, lmtd libido, inability to perform activities of daily living & overwhelming feelings of sadness, despair, hopelessness & disorg
- Pathophysiology of depression
  - ***Mono-Amine Hypothesis:** depression results from def in amt/func of cortical & limbic 5-HT, NE & DA
  - **Neurotrophic hypothesis:** BDNF (brain derived neurotropic factor) critical for reg of neural plasticisty & neurogenesis. In depression there is loss of BDNF in hippocampus
- ***Antidepressants drug usage:*** MC'ly prescribed meds in US; primary for tx of MDD; +received FDA approvals for tx of panic disorder, GAD, PTSD & OCD, +commonly used to treat pain disorders ie. neuropathic pain & pain w/fibromyalgia. Thus, broad spectrum of use but primary use as tx for MDD ⇒ Therapeutic use –
  - **Major depressive disorder: SSRIs, SNRIs, 5-HT antagonists, preferred over TCAs b/c better tolerability**
  - **Bipolar disorder (for depressive phase) SSRI /TCAs in combo w/Lithium (for maniac phase)**
  - **Panic disorder- SSRIs, venlafaxine**
  - **Obsessive compulsive disorder- SERT inhibitors – clomipramine, SSRI (esp fluvoxamine)**
  - **Enuresis (bedwetting in kids) – Imipramine**
  - **ADHD tx'd w/TCAs & Atomoxetine**
  - **Pt's who want to w/draw from nicotine dependence (to quit smoking)- Bupropion (ANSWER)**
  - **Neuropathic pain & fibromyalgia- Duloxetine, TCA**

- **GAD, panic attacks, social phobias, PTSD, bulimia, & premenstrual dysphoric disorder – SSRI**

Clinical issues: pt must understand importance of continuing drugs despite minimal initial resp b/c lag time of 1-4 weeks btwn initiation of therapy & resp must be emphasized

- Suicide precautions should be maintained until assessment indicates that suicidal ideation does not exist





5 Classes of Antidepressants:

1. **SSRIs (Selective serotonin reuptake inhibitors):** for MDD, bipolar disorder for depressive phase in combo w/Lithium (for maniac phase), panic disorders & panic attacks, OCD (esp fluvoxamine), GAD, social phobias, PTSD, bulimia & PMDD (premenstrual dysphoric disorder); inhibit SERT (serotonin transporter), block only 5-HT (not NE) reuptake 5-HT; CYP450 I's!!! so be watchful of DI's & adverse efx: **Sexual Dysfunc (↓libido)- upto 40% pt's - reason for non compliance, Nausea, diarrhea, Weight gain-paroxetine, Fluoxetine, paroxetine- CYP2D6 I's- possible DI's & Fluvoxamine CYP3A4 I's, (vs sertraline, citalopram & escitalopram no DI), & Serotonin Syndrome (w/MAOIs; flushing, diarrhea, wheezing) due to more 5-HT in synaptic cleft
   A. ***Fluoxetine (ANSWER)/Prozac***: treats depression or OCD in adults; metabolized to active norfluoxetine w/long elimination half life, thus must be discontinued 4weeks or longer b4 MAOI can be admin'd to risk serotonin syndrome; ie. pt w/anxiety for some time, paranoid of contracting germs…; CYP2D6 I;
   B. ***Fluvoxamine/Luvox***: esp for OCD; CYP3A4 inhibitor
   C. ***Sertraline***: modest CYP interax'ns so no DI's
   D. ***Paroxetine***: side efx: weight gain; CYP2D6 I;
   E. ***Citalopram***: modest CYP interax'ns so no DI's
   F. ***Escitalopram***: modest CYP interax'ns so no DI's
2. **Serotonin & NE reuptake inhibitors**: inhibit SERT & NET; SNRIs & TCA differ by side efx; both bind SERT & NET & inhibit reuptake of 5-HT & NE
   A. **SNRIs (Selective Serotonin & NE reuptake inhibitors)**: VDD for MDD! +; differ from TCAs b/c LACK potent antihistamine, α adrenergic blocking, & antimuscarinic efx of TCAs & so, SNRIs favored over TCAs in MDD tx & pain syndromes b/c better tolerability; side

efx: serotonergic A/E (diarrhea, vomiting) & noradrenergic efx – BP & HR, & CNS activation, such as insomnia, anxiety & agitation

1. **Venlafaxine:** SNRI for MDD & panic disorder;
2. **Desvenlafaxine/Pristiq**: SNRI for MDD
3. **Duloxetine**: SNRI for MDD & neuropathic pain & fibromyalgia;

B. **TCA (Tricyclic antidepressants):** 5-HT & NE reuptake inhibition w/efx on multiple receptor system & sodium conductance); for MDD (but not so preferred), bipolar disorder for depressive phase in combo w/Lithium (for maniac phase), ADHD, neuropathic pain & fibromyalgia; (**affect H1, Muscarinic & α1) side efx**: α-1 Blockade [orthostatic hypotension, sexual dysfunc, cardiac conduction delays (QT prolongation)], Histamine Blockade weight gain, sedation & Anti cholinergic (Dry mouth, Blurred vision, constipation, urinary hesitancy & lowers seizure threshold ↓ seizures, esp in OD ↓– 3 C's = Coma, Convulsions, Cardiac arrhythmias (b/c bind to Na^+ channels in heart) "TRI-C's) (OD tx w/****IV $NaHCO_3$)

1. ***Clomipramine***: antidepressant TCA; exception has more efx/affinity to bind SERT (like SSRI) thus DOC for OCD* (b/c primary mechanism to inhibit SERT)
2. ***Imipramine***: antidepressant TCA also for enuresis (bedwetting);
3. ***Trimipramine***: antidepressant TCA
4. ***Desipramine***: antidepressant TCA
5. ***Amitriptyline***: antidepressant TCA
6. ***Nortriptyline***: antidepressant TCA
7. ***Protriptyline***: antidepressant TCA
8. ***Doxepin***: antidepressant TCA

3. **5-HT 2 antagonists**: new class block 5-HT2 receptors & weak SERT inhibitors* (actual antidepressant efx for MDD) thus inhibiting reuptake of serotonin used in low doses b/c then behave as agonists (but in high dose, block receptor), act on post synaptic receptors; both trazodone & nefazodone rapidly absorbed & undergo extensive hepatic metabolism; both block 5-HT_{2A} receptor

A. ***Trazodone**: 5-HT2 antagonist & weak SERT inhibitors* (actual antidepressant efx for MDD) used in low doses, rapidly absorbed & undergo extensive hepatic metabolism; forms metabolite (m-cpp) that blocks $5\text{-HT}_{2A,2C}$ receptors, Modest - & H_1-receptor blockade; side efx – sedation via H1 block & priapism* (persistent & painful erection)

B. **Nefazodone**: 5-HT2 antagonist & weak SERT inhibitors* (actual antidepressant efx for MDD) used in low doses, rapidly absorbed & undergo extensive hepatic metabolism; potent CYP3A4 inhibitor thus DI's

4. **Tetracyclic & unicyclic antidepressants**: atypical antidepressants; buproprion, mirtazapine, trazodone, varenicline

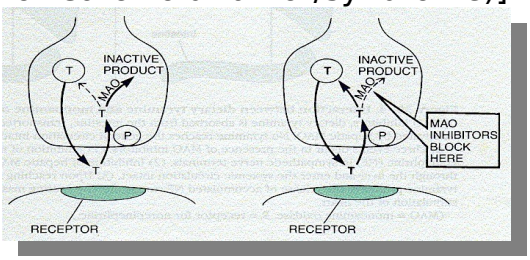
A. ***Bupropion (ANSWER)**: atypical antidepressant ↓↓**NE** & **DA** (blocks NET & DAT but ***no efx on SERT for 5-HT*** so No sexual dysfunc; ***for smoking cessation & MDD***; **A/E:** lowers seizure threshold (contraindicated in epilepsy, anorexia/bulimic pt's??). No sexual dysfunc (unlike SSRI)

B. **Amoxapine, maprotiline** – atypical antidepressant, afx NET > SERT inhibition thus ↓↓NE > ↓5-HT

C. **Mirtazapine** –presynaptic α_2-receptor antagonist NE & 5-HT release. Also antagonist of 5-HT_2 & 5-HT_3 & potent H_1 antagonist (sedation); side efx – sedation & weight gain

5. **MAOIs (Monamine oxidase inhibitors)**: inhibit MAO (for NT metabolism) thus ↓vesicular storage of NE & 5-HT; thus brain lvls of these NT's; DI's w/food high in tyramine ↓ cheese rxn Hypertensive Crisis (cheese, beer, wines, pickled meat, St. Johns wort, yeast extract w/large quantities of tyramine – Indirect sympathomimetic) ↓Tyramine escapes metabolism in MAO inhibited pt's ↓↓NE release ↓ *hypertensive crisis*; Tx'd w/IV Phentolamine; +Serotonin syndrome (potential life threatening due to combo of MAOI w/SERT inhibitors ↓ hyperthermia, mental status changes, seizures, muscular rigidity, tremor, myoclonus***, hyperreflexia, ↓m CK [↓ Adverse efx of any MAOI's, TCAs, SSRI, meperidine opioid, MDMA

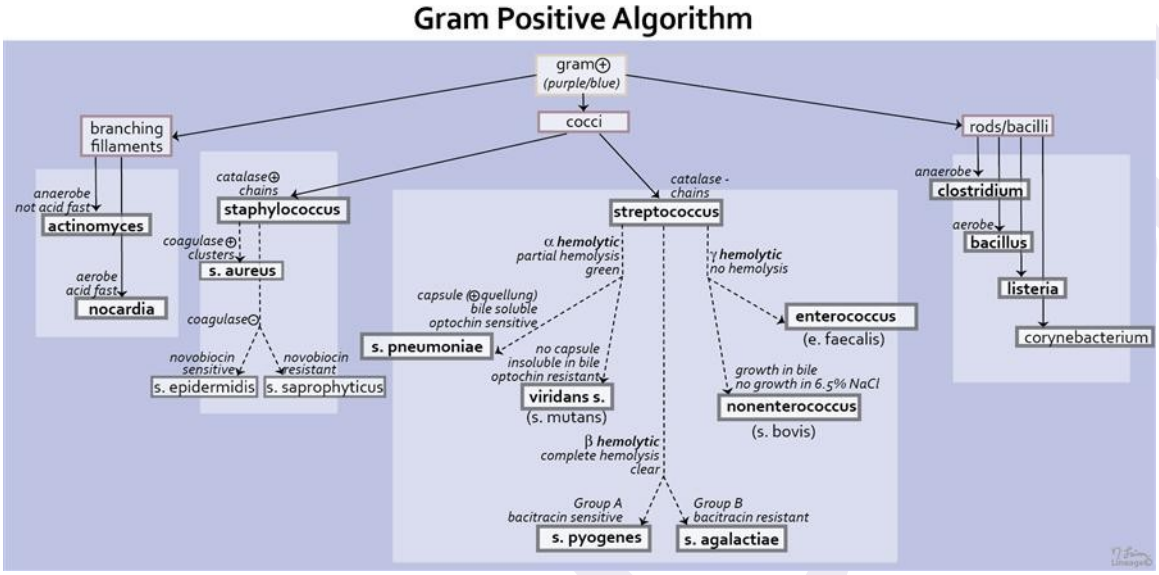
"ecstacy", tx w/antiseizure drugs, m relaxants (dantrolene) & cyproheptadine (also 2nd line for Carcinoid tumor/syndrome)]



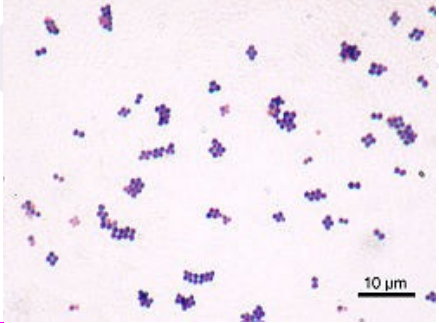
A. ***Nonselective MAO inhibitors***: block both MAO-A & B isoforms; contraindicated in pt's tx'd for Parkinson'
   1. **Phenelzine**:
   2. **Tranylcypromine**:

B. ***Selective MAO –B inhibitors***: **Selegiline**: not for depression, but for Parkinson's dis

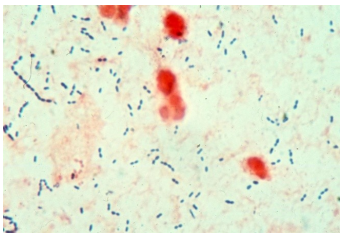
L4 Micro-Pharm Review

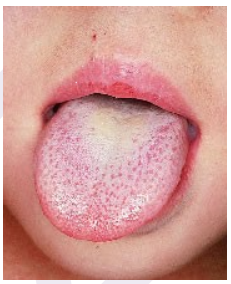


- **S. Aureus: GP cocci in clusters**; predisposed in surgical wounds, foreign body (tampons, surgical packing or sutures), severe neutropenia, IVDA, CGD, CF (in scalded skin syndrome); causes Gastroenteritis, IE (acute), Abscesses & mastitis, Toxic shock syndrome, Impetigo, Scalded skin syndrome, typical CA Pneumonia, Surgical infections, Osteomyelitis; can be MRSA (methicillin-resistant *S. aureus*) infection, imp cause of serious nosocomial & community-acquired infections & resistant to β-lactams due to altered PBPs; **Lab** Coagulase+, β-hemolytic, Small yellow colonies on blood agar; **tx w/**Nafcillin/oxacillin, but if MRSA use Vancomycin & if VRSA use Linezolid, quinupristin/dalfopristin

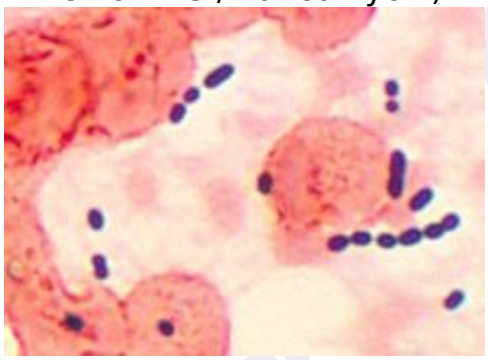


- **S. Pneumoniae/pneumococcus**: Lancet shaped, GP cocci causes "MOPS" - Meningitis (MCC in adults w/↑ PMNs, ↓ glucose, ↑ protein in CSF), Otitis media (children), Pneumonia (MCC of typical pneumonia w/rusty sputum & lobar pneumonia) & Sinusitis (children); DOC penicillin, alternatively **Erythromycin, doxycycline quinolones**

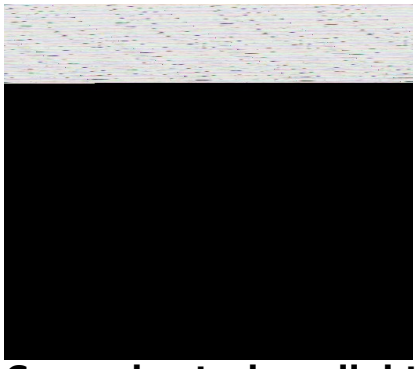




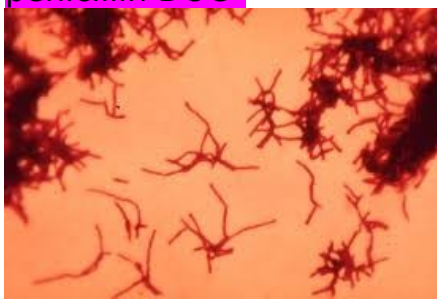
- **GAS Streptococcus pyogenes (group A streptococci)**: pyogenic, toxigenic & immunogenic causes pyogenic pharyngitis (acute onset sore throat, fever, malaise, headache), "exudative tonsillitis“, Toxigenic- scarlet fever- sandpaper rash sparing palms & soles, strawberry tongue, toxic shock syndrome, Immunogenic - rheumatic fever (subcutaneous plaques, polyarthritis, erythema marginatum, chorea, pancarditis) occurs following pharyngitis; & post-streptococcal glomerulonephritis (PSGN); "*PHaryngitis can result in rheumatic PHever & nePHritis“;* Dx by ASO (anti-streptolysin O) titer detects recent infection, >200 indicates rheumatic fever; DOC penicillin, alternatively **Erythromycin, doxycycline quinolones**
- **S. viridans group streptococci:** α-hemolytic, normal flora of oropharynx; causes dental caries (via biofilms forming plaque), subacute bacterial endocarditis (damaged or prosthetic heart valve + dental work) that’s prevented w/prophylactic antibiotics & proper oral hygiene, vancomycin for endocarditis
- **Enterococci (group D streptococci):** GP cocci, lancefield grouping based on differences in C carb on bacterial cell wall; transmitted endogenously, reservoir in normal flora of colon, urethra, female genital tract; GI or GU tract damage during surgery leads to bacteremia; presence of previously damaged heart valves leads to endocarditis thus can cause subacute Endocarditis in damaged heart valves predispose to infection, esp in elderly, UTI’s, & Biliary tract infections; tx/penicillin + gentamicin; alternative vancomycin for endocarditis; aka AG + PenicillinG / vancomycin)



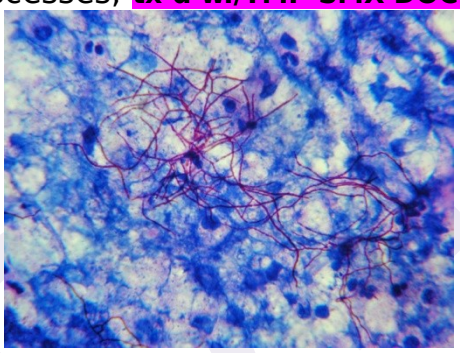
- **Bacillus anthracis:** GP bacilli, spore-forming (1) cutaneous contact causes → black eschar (painless ulcer) surrounded by edematous ring caused by lethal factor & edema factor, can progress to bacteremia & death; & (2) pulm inhalation of spores → flu-like sx w/rapid progression to fever, pulm hemorrhage, mediastinitis, shock & death w/near 100% mortality aka woolsorters' dis, spores inhaled from contaminated sheep or goat skin/wool; tx w/cipro, penicillin, alternatively, erythromycin
- **C. difficile:** GP bacilli, spore-forming causes diarrhea & colitis; lab w/toxin in stool, culture cant be used to dx or organism is pt of normal flora, GP spore-forming rods, anaerobic; drugs causing – ampicillin, cephalosporins, clindamycin/lincosamides, tetracyclines; tx w/metronidazole, or vancomycin



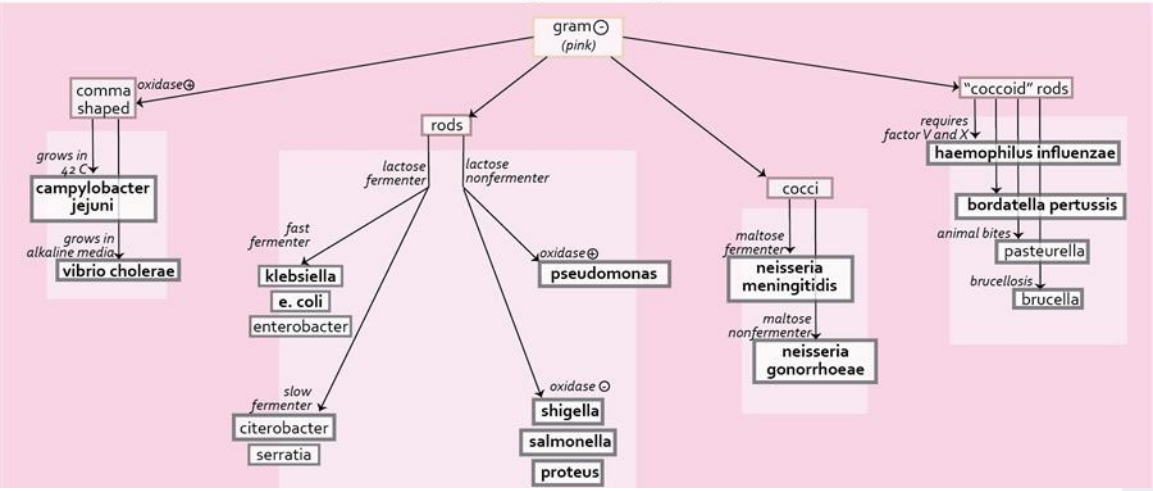
- **<u>Corynebacterium diphtheriae</u>**: Bacteria (aerobic), GP bacilli- non-spore forming; AB exotoxin encoded by β-prophage, inhibits protein synthesis via ADP ribosylation of Elongation Factor-2; Transmitted via respiratory droplets transmit bacterium or phage; Reservoir: In Throat, nasopharynx; Lab w/Growth on tellurite agar, GP rods, club-shaped rods arranged in V or L shape, granules stain metachromatically (blue & red); Elek test detects toxin production; Causes pseudomembranous pharyngitis: grayish-white memb, can extend into larynx & cause obstruction; lymphadenopathy, "bull neck", recurrent laryngeal n palsy, myocarditis & cardiomyopathy b/c toxin inhibits β-oxidation of FA's in myocardium; neuropathy & paralysis; Tx w/erythromycin, alternatively penicillin
- **<u>Actinomyces israelii</u>**: GP br'ing rods, anaerobic, non-acid fast; causes eroding abscesses of oral/face drain thru sinus tract in skin, drainage from abscess contain "sulfur granules", tx penicillin DOC*



- ***<u>Nocardia</u>***: partially acid-fast, Aerobic, GP branching rods (like fungi); causes cavitary pulm dis in immunocompromised pt's, can spread hematogenously to brain causing brain abscesses; **tx'd w./TMP-SMX DOC***

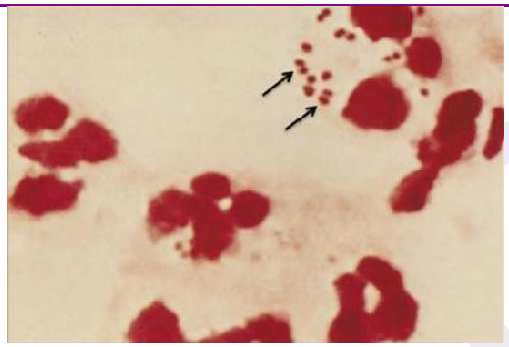


Gram Negative Algorithm

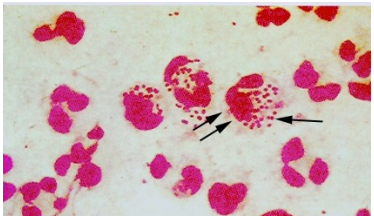


- ***Neisseria meningitidis***: GN diplococci, Ferments maltose & glucose, Culture on Thayer-Martin media; **dis's -**
  - **Meningococcemia:** form of sepsis, abrupt onset, fever, chills, malaise, petechial rash
  - **Waterhouse-Friderichsen syndrome:** fulminant meningococcemia, bilateral hemorrhage into adrenals, shock, DIC, coma, death in 6-8 hours
  - **Meningitis:** MC in infants, non-specific findings of infection

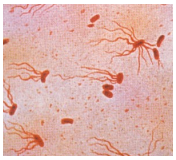
Ceftriaxone, cefotaxime	**PnG**



- ***Neisseria gonorrhoeae***: GN diplococcus seen w/in WBCs on urethral smear, Ferments glucose but not maltose, Culture on Thayer-Martin media; causes STD- Men (high fever, urethritis, prostatitis, epididymitis), Women (high fever, endocervicitis, PID, creamy, purulent discharge), Neonatal conjunctivitis, Septic arthritis & Fitz-Hugh-Curtis syndrome; PID complications: Infertility à tubal scarring; Ectopic pregnancy; Perihepatitis: (Fitz-Hugh-Curtis syndrome), & Inflammation of liver capsule; tx w/ **ceftriaxone or ciprofloxacin; prevent by** Prophylaxis procaine penicillin; often resistant to penicillin;



- **E. Coli:** GN bacilli w/virulence factors- P-fimbrae (Urinary tract), LPS –endotoxin -septic shock, K capsule (pneumonia & meningitis); causes UTI, Neonatal meningitis, & Diarrhea; classic triad- anemia, thrombocytopenia, acute renal failure; swelling of endothelium narrows lumen leading to hemolysis, ↓ renal BF, ↓ platelets as damage is repaired; tx w/ **TMP-SMX***, CS-1st or 2nd GEN, or alternatively AG's, Fluoroquinolones**
  - EPEC diarrhea ("pediatric")
  - EIEC invasive, dysentry, virulence factor is *shared* by Shigella
  - ETEC ("traveler") Diarrhea (watery)
  - EHEC dysentry Shiga-*like* toxin, HUS, O157:H7 strain associated
- **Salmonella typhi**: GN bacilli, NLF, Vi Ag detected w/Widal test, motile (salmon swim) ⊔ fever, abdominal pain, diarrhea, headache, rose spots on abdomen & chronic carrier state is possible; tx w/**Ceftriaxone, Cipro, or alternatively Chloramphenicol, cotrimoxazole**



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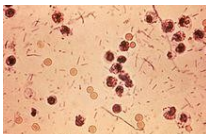
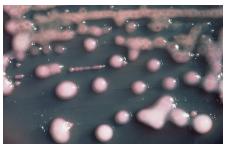
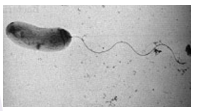




- **Shigella dysenteriae:** GN bacilli, Non-motile, Non-H_2S producing, Non-lactose fermenting ⊔ enterocolitis – bloody diarrhea w/mucus & pus, fever, tenesmus, lower abdominal cramps
- **Klebsiella:** GN bacilli, Causes UTI, sepsis; & Lobar Pneumonia in diabetics, alcoholics, red currant jelly sputum; 4 A's – aspiration pneumonia, abscesses in lungs, alcoholics, di-A-betics; Tx w/DOC cefazolin: ***Cefazolin (parenteral)** **DOC for surgical prophylaxis & Klebsiella pneumonia, or tx w/TMP-SMX*** or CS-1st or 2nd GEN, alternatively AG's, Fluoroquinolones**

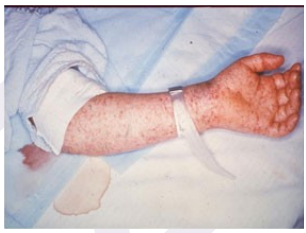


- **Vibrio cholera**: GN bacilli, curved rods w/polar flagellae; fecal-oral transmission, Oxidase +ve, Can survive on alkaline media, causing rice-water stools & diarrhea leads to death by dehydration; tx w/tetracyclines (doxycycline) or fluoroquinolones
- **Pseudomonas aeruginosa**: GN bacilli, causing, "BE PSEUDO" MC'ly afx immunocompromised; tx w/ **AG + pipericillin/ticarcillin; alternatively, Ceftazidime/cefoperazone+ AG, OR Aztreonam, imipenem**
  - Burns
  - Endocarditis- right valve in **IVDA's**
  - Pneumonia- in **CF**, in immunocompromised, ICU pt's on respirator, productive cough w/green sputum
  - Sepsis: ecthyma gangrenosum, can occur from catheter infection
  - External otitis: swimmer's ear, malignant otitis externa in diabetics
  - UTI: esp w/Foley catheters
  - Drug use
  - Osteomyelitis: trauma (ie. puncture wounds to foot), diabetics, drug addicts, hot tub folliculitis

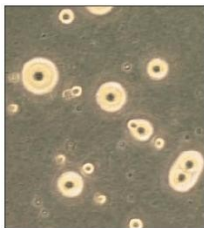
- **H. pylori**: GN bacilli, motile, has flagella, invasive; dx: urease breath test; causes duodenal ulcers (up to 90% of cases), Chronic gastritis, Gastric (stomach) ulcers; associated w/gastric adenocarcinoma or lymphoma
- **Amoxicillin** DOC for H.Pylori infection (peptic ulcers in duodenum or stomach w/nausea, vomiting, confirmed w/urea breath test; given w/this, metronidazole, PPI); **Tx: omeprazole (PPI) + amoxicillin (B-lactam) + clarithromycin (macrolides); MUST GIVE ALL 3 together!* for 10-14 days (or PPI + busthmol) +metronidazole; tx w/Tetracycline+ Metronidazole+PPI, OR Metronidazole +amoxicillin+PPI, OR Unless allergic to penicillin ⊔ Clarithromycin/amoxicillin+PPI**

- **Bacteroides fragilis**: GN bacilli, anaerobes; can cause Septicemia, Peritonitis, Abdominal abscesses, Wound infections; Infection often results from abdominal trauma or emergency abdominal surgery; tx w/**Metronidazole (1st choice), or Clindamycin (more toxic – pseudomembranous enterocolitis), or alternatively Chloramphenicol (very toxic – bone marrow suppression – aplastic anemia)**
- **H. influenza**: coccobacillary rods, Culture on chocolate agar -requires factors V (NAD+) & X (hematin) for growth; Satellite phenomenon- grows near *S. aureus* on blood agar; Causes "EMOP"= Epiglottitis- "cherry red" in kids, Meningitis, Otitis media, & Pneumonia (adults MC'ly); does not cause flu! - influenza virus does; tx w/ **Cefuroxime, ceftriaxone, alternatively Chloramphenicol**
- **Legionella pneumophilia**: weak GN, stain w/silver instead, Culture on charcoal yeast extract (CYE) w/ ⩲ iron & cysteine, dx via detection of Ag in urine; causes severe atypical pneumonia- "fever, cough, & diarrhea, esp in smoker"; OR Pontiac fever- mild flu-like syndrome; Tx w/floroquinolone (respiratory), erythromycin, tigecycline
- **Treponema pallidum**: spirochetes, dark-field micro or fluorescent Ab's; tx w/penicillin G, or alternatively tetracyclines; causes 3 stages –
  - **Primary**: painless chancre, indurated edge, dx w/dark-field or fluorescent micro of lesion

- **Secondary** systemic: diffuse copper-color maculopapular rash, condylomata lata, dx w/VDRL or FTA-ABS
- **Tertiary**: Gummas, aortitis (vasa vasorum destruction), neurosyphilis (ie. tabes dorsalis), Argyll-Robertson pupil: "prostitutes pupil" "accommodates but does not react" (to light), dx w/FTA-ABS



- **Rickettsiae rickettsi**: Tick –Vector, Weil-Felix test; Triad sx: petechial rash on palms & soles STARTS distally, MIGRATES proximally to wrists, ankles, then trunk, headache, fever; tx w/ **Doxycycline, OR Erythromycin, Ceftriaxone**



- **Mycoplasma pneumonia**: insidious onset, pharyngitis, headache, persistent, non-productive, dry hacking cough; X-ray looks worse than pt- diffuse interstitial infiltrate; Lab w/Mulberry-shaped colonies on media containing sterols, requires cholesterol to grow; +ve cold agglutinins test; Culture on Eaton's agar w/"fried-egg" appearance, Not seen on Gram stain, dx w/ELISA or IF; tx w/ **Macrolides**, OR **Tetracycline, doxycycline OR Fluoroquinolones**

What is your Diagnosis and Name organisms causing CSF finding in column A, B and C

- **Presents with: fever**, **neck stiffness (meningismus - cant touch chin to chest)**, **photophobia**, **altered mental status**, & **seizures**
- **Physical Exam shows: positive Kernig and Brudzinski signs**

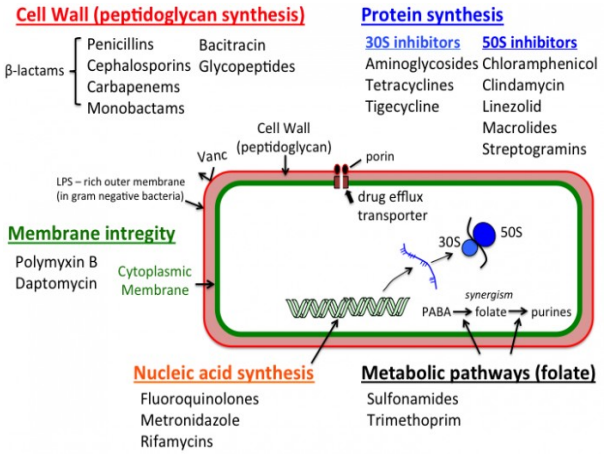
	A	B	C
Protein	incr.	incr.	normal to incr.
Glucose	decr.	decr.	normal
Pressure	incr.	incr.	normal
Cells	incr. neutrophils	incr. lymphs	incr. lymphs

involuntary flexion of hips when flexing neck (**Brudzinski's sign**)

L5 Anti-microbial – Intro & Cell Wall synthesis inhibitors

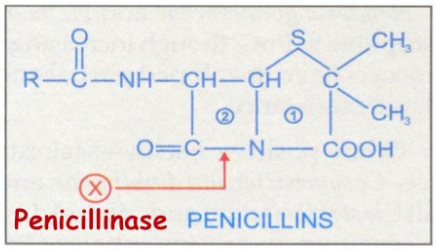
- Chemotherapy: tx of systemic infections w/specific drugs that selectively suppress infecting microorganism w/out sig'ly affecting recipient. Antibacterial agents can be:
  - Bactericidal: cause death of microorganism, Eg: Penicillins, AG's, Cephalosporins
  - Bacteriostatic: inhibits growth of microorganism, ex. Sulfonamides, Tetracyclines, Erythromycin

▭ Targets Axns of Antimicrobials –



Inhibitors of bacterial cell wall synthesis

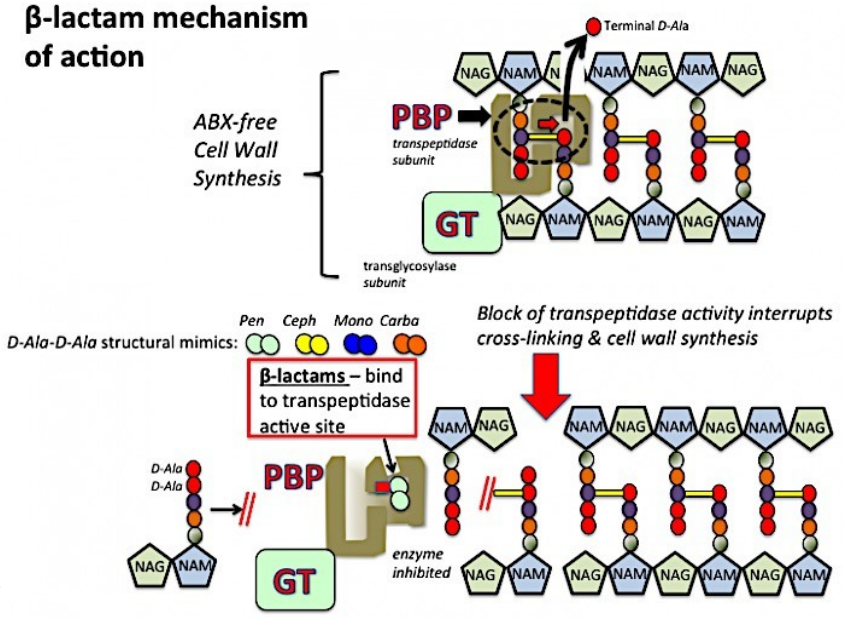
Betalactum antibiotics



1-Thiazolidine ring 2- Betalactam ring

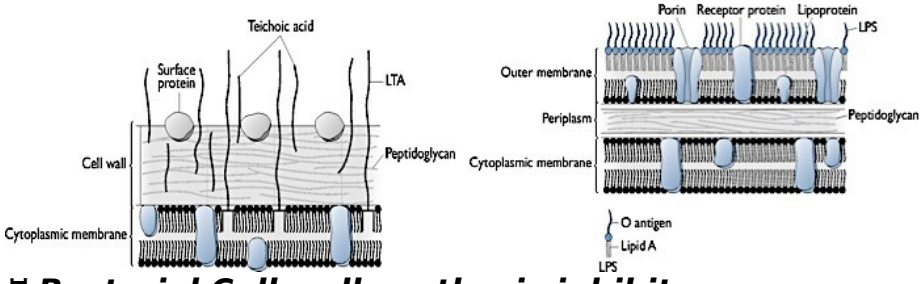
Cross-linking*** - bacteria will die of cross-linking not adequate/weak.
Peptidoglycan made up of 2 layers – NAM & NAG (N-acetylmuramic acid & N-acetyl glucosamine)
Terminal D-alanine removed to do cross-linking via trans peptidase. If this provides structural integrity to bacterial cell – this is best site of axn
Penicillins act on PBP.
Transglycolase does transglycosylation

β-lactam mechanism of action



Structure of bacterial cell wall

Gram positive *versus* Gram negative



⊔ *Bacterial Cell wall synthesis inhibitors:*

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␣ *B-lactam Antibiotics*: bind to transpeptidase & block cross-linking in bacterial cell wall

- #1 **Penicillins**: bactericidal; bind to penicillin binding proteins; Interfere w/synthesis of bacterial cell wall peptidoglycan (which is polymer containing alternating N-acetylglucosamine & N-acetyl muramic acid); final step in bacterial cell wall synthesis is cross-linking of peptidoglycan polymers; bind & inactivate transpeptidase (Penicillin-binding proteins; bacterial enzyme which cross-links peptidoglycan chains to form rigid cell walls) ␣ results in loss cell rigidity & cell death; GP w/thick cell wall esp susceptible; can't be used against Penicillinase/b-lactamase enzyme containing bacteria
  - Mechanisms of resistance –
    - Penicillinases (b-lactamases) break betalactam ring, *eg staphylococci*
    - Alteration of PBPs – *eg. S. Aureus – ***prefer methicillin/nafcillin but if MRSA –due to altered PBP so drug can't bind to transpeptidase – then vancomycin***, penicillin resistant pneumococci*
    - ¬permeability in GN cell memb's, *Eg.pseudomonas – CC of hospital acquired pneumonia*
  - ␣Penicillin Types & spectrum of activity
  - ***Narrow spectrum (penicillinase susceptible):*** **Penicillin G** (parenteral) **Penicillin V** (oral) – target GP – *Streptococci, pneumococci, T. pallidum (Syphilis, DOC), actinomyces (DOC) & GN meningococci*
    - ***Penicillin G:*** acid labile, hence given IM, IV; DOC for actinomyces (sulfa granules & rash eroding abscesses of oral/face drain thru sinus tract in skin); **repository penicillin G (2 long acting forms): Procaine & Benzathine penicillin G**; penetrate CSF to sig extent only during inflammation; eliminated via active tubular secretion, works against Streptococcal, meningococcal, GP bacilli, & DOC for Syphilis T. palidum (strains of pneumococci, S. Aureus & N. Gonorrhoeae are resistant tho*)
      - ***Procaine penicillin*** – 1/day injection; lasts for 24 hrs; DOC for T. pallidum, Gonorrhoae & Syphillis in sexual partner
      - ***Benzathine penicillin*** – 1/mo; lasts for 1 mo; DOC for T. pallidum; rheumatic fever, Gonorrhoae & Syphillis in sexual partner
      - Probenecid*: for gout to enhance uric acid excretion, but competitively inhibits renal tubular secretion of penicillin, Thus ␣[penicillin]* & prolongs its activity* b/c both have same route of elimination
      - Neurosyphilis, endocarditis, streptococcal; but tx w/risk Jarish Herxheimer (arthus) rxn
      - Pen V – S. pharyngitis
  - ***NARROW spectrum (penicillinase resistant):*** **Methicillin**, **nafcillin**, **oxacillin**, **cloxacillin**, **dicloxacillin ONLY target** *Staphylococci (except MRSA):* resistance to inactivation by b-lactamases so treat infections caused by S. aureus (MSSA) – endocarditis (murmur), endovascular infection, septic arthritis, skin & soft tissue infections (SSTI), BUT NOTE – Methicillin No longer commonly recommended for use b/c its nephrotoxicity) but still for determining drug resistance to penicillins (ie. MRSA: Methicillin Resistant S. Aureus); side efx - methicillin & nafcillin – interstitial nephritis (nephrotoxicity); methicillin worse so not used anymore
  - ***BROAD spectrum (penicillinase susceptible):*** **Ampicillin** & **Amoxicillin** target *GP cocci, H. influenza, listeria monocytogenes, H.pylori, enterococci, E coli, Proteus Mirabilis;* ***Both these drug's activity enhanced if used in combo w/b-lactamase inhibitors***: (clavulanic acid, sulbactum, tazobactam)
    - ***Ampicillin:*** DOC for Listeria Monocytogenes (tumbling motility ␣bacterial meningitis in kids, elderly & immunocompromised – confirm by cloudy CSF w/neutrophils); DOC for Bacterial endocarditis prophylaxis in pt's w/prosthetic heart valves, cyanotic heart dis, previous endocarditis dx- who're planning to undergo dental or respiratory tract or genitourinary or GI procedures [Amoxicillin or ampicillin]; adverse efx:

maculopapular rash & diarrhea- pseudomembranous enterocolits (super infection/supra infection caused by C. difficile), ¬¬OCT efx b/c eradicate colonic bacteira so estrogen process won't happen

- ***Listeria monocytogenes***: GP bacilli, facultative IC, non-spore forming, Tumbling motility; transmitted via Foodborne (cold growth in cheese, deli meats, coleslaw, hotdogs, unpasteurized milk), crosses placenta as vaginal transmission during birth; causes (1) In pregnant women (amnionitis, septicemia, spontaneous abortion), (2) neonatal meningitis (3) In immunocompromised (Meningitis, septicemia) & (4) In healthy (mild gastroenteritis)

▪ ***Amoxicillin:*** DOC for H.Pylori infection (peptic ulcers in duodenum or stomach w/nausea, vomiting, confirmed w/urea breath test; given w/this, metronidazole, PPI) & preferred prophylactic for bacterial endocarditis b4 major procedures; DOC for Bacterial endocarditis prophylaxis in pt's w/prosthetic heart valves, cyanotic heart dis, previous endocarditis dx – who're planning to undergo dental or respiratory tract or genitourinary or GI procedures [Amoxicillin or ampicillin]

▪ (clavulanic acid, sulbactum, tazobactam) – widens their spectrum [B lactams + B lactamase inhibitors]; alone w/no antibacterial activity; potent & irreversible B-lactamase inhibitors; improved against **ß lactamase producing *staphylococci, H.influenza, N.gonorrhoea, E.coli, Proteus****; inactive at inhibiting bacteria on OWN so always used w/cell-wall active penicillin**) available as fixed dose combos –

- **Ampicillin + sulbactum**
- **Piperacillin + Tazobactum:** used against bacteria w/penicillinases
- **Ticarcillin + Tazobactum**
- **IV Ampicillin + Gentamicin:** for serious infections in hospitals (until etiologic agent & antibiotic sensitivity ascertained)
- **Amoxicillin/ticarcillin + clavulanic acid/Clavulanate= Augmentin**:** for bacterial strains w/penicilinase; S. Aureus + best for sinusitis & otitis media (if original tx didn't work, seen from S. Pneumonia, H. influenza (non-typeable) GNB & Morazella catarrhalis GNC

○ ***Extended spectrum or antipseudomonal (penicillinase susceptible):*** **Ticarcillin**, **piperacillin**, **azlocillin** **target** *GN rods – Pseudomonas aeruginosa (burn wounds or hospital acquired pneumonia, green color), & enterobacter infections; synergistic axn w/AG's against pseudomonal & enterococci;*

○ **Adverse efx of Penicillins**: safe but HSR's 5-7% incidence itching, flushing, rash, urticaria, angioedema, bronchospasm, hypotension, Cross-sensitivity btwn ind penicillins possible (caution in those w/allergic history to any of these)

▪ Methicillin & nafcillin - interstitial nephritis (nephrotoxicity); methicillin worse so not used anymore

➢ #2 **Cephalosporins**: isolated from fungus Cephalosporium, 4 generations based on chronology of discovery & antibacterial spectrum – similar mechanism to penicillins, all bactericidal, less susceptible to inactivation by penicillinases, possible resistance as some bacteria produce cephalosporinase (another b-lactamase type) & due to ¬¬in memb permeability & change in PBP structure; b-lactam antibiotics, inhibit cell wall synthesis*** bactericidal & less suspectible to penicillinases; resistance if bacteria (1) produces b-lactamases & cephalosporinases & (2) alters their PBPs

○ **1st GEN Cephalosporins:** narrow spectrum – PEcK = GP cocci, Proteus, E.coli, klebsiella

▪ **Cephalexin(oral)**

▪ ***Cefazolin (parenteral)** **DOC for surgical prophylaxis & Klebsiella pneumonia**

○ **2nd GEN Cephalosporins**: More active on GN bacteria; Cefoxitin, Cefotetan, Cefaclor, Cefamandole & Cefuroxime against HEN PEcKS (*H. influenza, Enterobacter, Neisseria, Proteus, E.coli, Klebsiella pneumoniae, Serratia*)

▪ Except Cefuroxime others do NOT enter CSF

- **Cefoxitin, cefotetan** – *Bacteroids fragilis (anaerobes*; mild intra-abdominal & pelvic infections)
- **Cefuroxime** (only drug for H. influenza bacterial meningitis), cefaclor, cefamandole – *H.influenza*

- ***3rd GEN Cephalosporins**: 1st DOC for bacterial meningitis***, esp adults; ↓activity against GN bacteria; Good penetration into BBB (except Cefoperazone & Cefixime). BUT not effective for Listeria
  - **Cefotaxime**: tx of bacterial meningitis (except Listeria) b/c attain [high] in CSF
  - **Ceftriaxone** (IM): tx of bacterial meningitis (except Listeria) b/c attain [high] in CSF
  - **Ceftazidime**: good activity against *Pseudomonas*
  - **Cefoperazone**:
  - **Cefixime** (oral):
  - **Cefotaxime, Ceftriaxone** - tx of bacterial meningitis (except Listeria) b/c attain [high] in CSF
  - **Cefoperazone, Ceftazidime** –good activity against *Pseudomonas*
  - **Ceftriaxone** (parenteral) & **Cefixime** (oral) – 1st DOC of gonorrhoea
  - **Ceftriaxone, cefotaxime, cefoperazone**- Rx of S. typhi (typhoid/enteric fever)
- **4th GEN Cephalosporins: Cefipime (IV), cefpirome**; resistant to inactivation by beta lactamases; excellent penetration into GN bacteria – ↓activity against *pseudomonas aeruginosa*; wider spectrum than 3rd GEN (both GP & GN)
- Adverse efx of Cephalosporins: HSR – rashes, fever, Cross-HSR btwn cephalosporins completely possible, Cross-rxn btwn penicillins less likely (5-10%) caution still needed; contraindicated in Hx of anaphylaxis to penicillin; Superinfection- C. difficile diarrhea (pseudomenbraneous colitis) – tx'd w/metronidazole; If given w/aminoglycosides- ↓chances of nephrotoxicity
  - **Cefamandole, Cefoperazone & Cefotetan** contain methylthiotetrazole group (MTT group) may cause dusulfiram like rxns w/alcohol or ethanol (reddening face, aldehyde syndrome b/c accumulated acetaldehyde) & Vit K def causing hypoprothrombinemia & bleeding disorder

➢ #3 **Carbapenems**: **Imipenem**, **Meropenem**, **ertapenem**, **Doripenem**; broad spectrum: GP & GN bacteria, anaerobes- Bact. fragilis (intra-abdominal, peritoneal infection, diverticulitis), clostridia; reserved for Severe Life Threatening Infections: Intra-Abdominal & Pelvic Infections, UTI's, Complicated Skin & Soft Tissue Infections (SSTI), Bone & Jt Infections (ie. diabetic foot infections), Meningitis, Sepsis, Endocarditis, VAP (Ventilator-Associated Pneumonia)

- **Imipenem**: rapidly inactivated by renal dehydropeptidase I; always combined w/cilastatin to prevent hydrolysis by enzymes in renal brush border
- **Cilastatin**: inhibitor of renal dehydropeptidase thus ↓plasma ½ life of imipenem
- Side efx: GI distress, rash, allergy (Cross reacts w/penicillins), seizures in pt's w/renal dysfunc

➢ #4 **Monobactum**: **Aztreonam (IV):** structure has single ring; active only against GN rods; no effect on GP & anerobes (ie. Bacteroides); Same MOA as penicillins & cephalosporins; resistant to ß-lactamases; no cross HSR btwn penicillins & aztreonam; used in GN infections esp in pt's allergic to Penicillins/Cephalosporins;

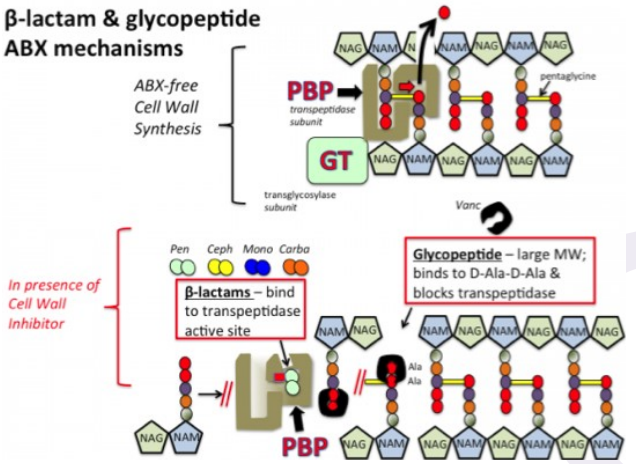
⊟ *Glycopeptide: #5* *****Vancomycin: Glycoprotein, bactericidal (1) primary efx – binds D-Ala-D-Ala terminal thus inhibiting transpeptidase ⊟ prevents further elongation & cross-linking peptidoglycan; (2) secondary efx - inhibits **transglycosylase (Glycosyl transferase-GT)**, 2nd enzyme responsible for cross-linking sugar residues; **treats against GP cocci (**Strep, Staph (S. aureus, coagulation—ve Staph), Enterococci (most E. faecalis, variable E. faecium; bacteriostatic so add AG to obtain bactericidal activity), **Endocarditis due to S. viridans or enterococci**, **GP bacilli** Listeria, & **GP anaerobes** C. difficile,

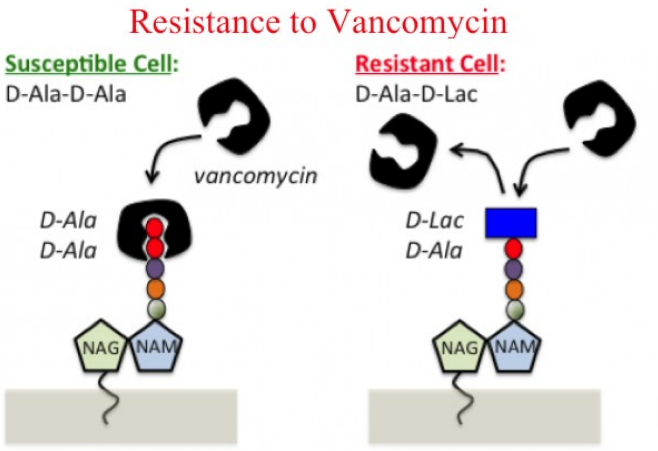
MRSA, **Pseudomembranous enterocolitis due to C. difficile (orally)**. NOTE: Metronidazole 1st choice for mild C. difficile, but vancomycin also effective in absence of drug resistance & for **pt's allergic to β-lactams;**

Adverse efx of vancomycin: *No cross sensitivity w/Pn/CS*, *but others due to long half life!*

- **Red mans syndrome b/c released histamine (flushing, face redness, hypotension); prevented by slow IV infusion & pre tx w/antihistamines**
- **Nephrotoxicity:** ⏚risk if giving w/other nephrotoxic drugs such as AG's
- **Ototoxicity:** ⏚risk if giving w/other nephrotoxic drugs such as **AG's or furosemide**
- **Notes:** Use of vancomycin reserved for bacterial infections resistant to other antibiotics, or pt's w/severe HSR to other indicated antibiotics. If resistant to vancomycin, only few other drugs may be effective
- Resistance in strains of enterococci & staphylococci (VRE & VRSA) via ¬affinity of vancomycin for binding site by replacing terminal D-Ala by D-Lactate****; just like monobactum, can use in penicillin HSR pt's; ie. CA pneumoniae w/S. Aureus – tx w/Methicillin but if MRSA go for Vancomycin – but if this pt has HSR to penicillin, can still use it b/c no cross sensitivity

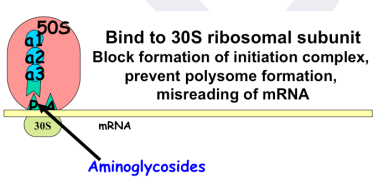
Vancomycin MOA

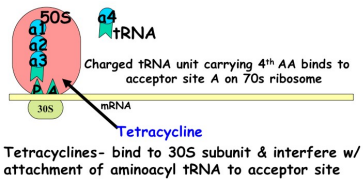


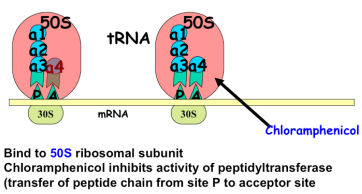


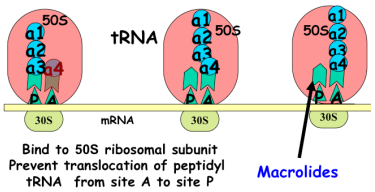
L6 Bacterial Protein Synthesis Inhibitors:

- ***Bacterial protein synthesis:*** takes place in ribosomes ⏚translation ⏚AA's incorporated into protein in order predetermined by mRNA sequence; requires tRNA to carry AA's in activated form to ribosome to form peptide-bonds ⏚ribosome has 2 binding sites for tRNA – A (Acceptor) & P (Peptidyl) sites; steps– (rmr, 70s ribosomal mRNA complex has 50s & 30s subunits – assembly inhibited by AG's)
  - 1: Charged tRNA unit carrying 4th AA binds to acceptor site A on ribosome; inhibited by tetracyclines & Dalfopristine
  - 2: Peptidyl tRNA at donor site w/AA's 1 to 3, then binds growing AA chain to 4th AA (transpeptidation); inhibited by chloramphenicol
  - 3: Uncharged tRNA left at donor site is released
  - 4: New 4 AA chain w/its tRNA translocates from acceptor to donor site; inhibited by macrolides









⏚ *50S PS INHIBITORS:*

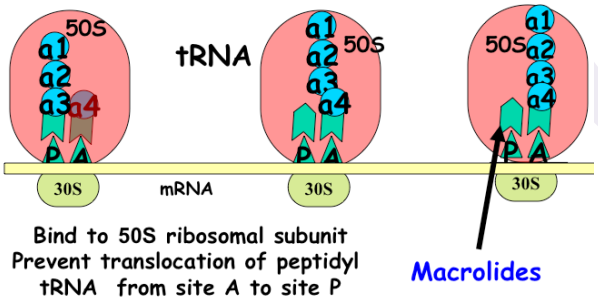
- **Macrolides**: reversibly bind 50S subunit; protein synthesis inhibited b/c aminoacyl translocation rxns; DOC for tx'ing atypical pneumonia like Mycoplasma pneumonia;

resistance in GP via efflux pump (throws out drug from w/in cell) & producing ***methylase***, In *Enterobacteriaceae* resistance due to forming drug metabolising esterases, & Acquired resistance via specific mutation in ribosomal RNA of 50S ribosomal subunit

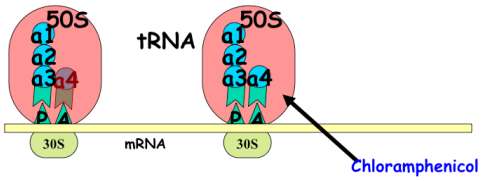
- **MAP**
- **Erythromycin**: for atypical Mycoplasma pneumoniae, C. diphtheria 1st line, Chlamydia (Chancroid), Legionella Legionnaire's pneumoniae, Bordetella pertussis whooping cough, alternative to penicillin for S. pyogenes infections (pharyngitis, tonsillitis, if can't give amoxicillin for penicillin allergic pt's since also cross sensitivity w/cephalosporins then); 8 hr half life so given 3X/day so least preferred! But DI below; acid labile enteric coated tablets; short plasma t1/2 1.5 hr; adverse efx: diarrhea (motilin receptors (ANSWER) not superinfection like from tetracyclines), rashes, fever, cholestasis, jaundice w/erythromycin estolate; DI*** – **Inhibit CYP P-450 (DI's) but not w/azithromycin, QTc prolongation & Torsade de pointes** by high [ ]'s (after IV boluses)**, use of other drugs that prolong QT interval w/ erythromycin or clarithromycin should be done cautiously,**

Newer macrolides

- **Clarithromycin**: given 2X/day, for Chlamydia (eye infections, STD), MAC in AIDS, H. Pylori; acid stable w/better GI absorption than erythromycin; for URT & LRT, skin infection, Atypical pneumonia, H.pylori tx in recurrent peptic ulcer (Note: 1st DOC for H. pylori ulcer is amoxicillin + metronidazole + bismulth in pt's w/out penicillin allergy), Leprosy; use of other drugs that prolong QT interval w/erythromycin or clarithromycin should be done cautiously; also CYP inhibitor – ie. contraindicated in pt's on warfarin!
- **Azithromycin/zithromycin**: prefer for CA pneumonia, Legionnaire's pneumonia, 1X day b/c longer half-life $t_{1/2}$ *2-4 day*; for Chlamydia (highly active*, infection of urogenital tract, pneumonia, trachoma), MAC in AIDS (can also use rifabutin instead), H. influenza, Neisseria; only macrolide free of DI's (doesn't interact w/hepatic CYP enzymes); Acid stable, *[High] inside MO's & fibroblasts;* safe in pregnancy
- **Telithromycin**:



- **Chloramphenicol (ANSWER)**: bacteriostatic, broad spectrum, BARELY USED SO ASK MORE ABOUT TOXICITY; binds to 50S ribosomal subunit to inhibit peptidyl transferase & transfer peptide chain from site P to acceptor site; spectrum highly active against Salmonella typhi (w/petechial rose spots on abdomen), H. influenza meningitis, N. meningitis meningitis, anaerobic infections (Bacteroides fragilis), less active on GP cocci & Spirochetes Rickettsia; Most frequently used outside US, rarely in US b/c concerns about aplastic anemia; for Enteric fever or salmnellosis (1st line ciprofloxacin, ceftriaxone/cefotaxime), H.Influenza meningitis & Anaerobic infections- *Bacteroides fragilis*; Bone marrow suppression causing Aplastic anemia & Grey baby syndrome***(in neonates- due to def hepatic glucuronosyltransferase- lack effective glucuronic acid conjugation degradation of chloramphenicol C/F: vomiting, limp body tone, abdominal distension, cyanosis (blue lips & skin) , refusal to feed, CV collapse, death)



Bind to 50S ribosomal subunit
Chloramphenicol inhibits activity of peptidyltransferase
(transfer of peptide chain from site P to acceptor site

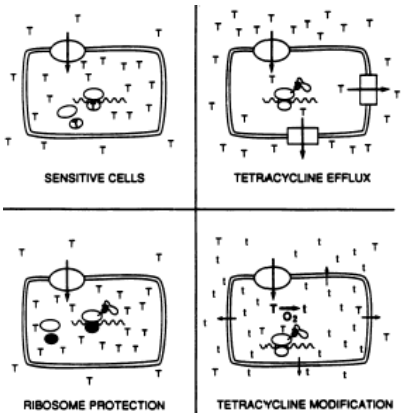
- **Lincosamides**: **Clindamycin**: same as macrolides, spectrum for *Bacteroides fragilis, PCP Pneumocystis jiroveci* pneumonia*;* used for Anaerobic infections- *Bacteroides fragilis,* Prophylaxis of endocarditis in valvular dis pt's allergic to Penicillin; for Clostridia perfringes, Clostridia tetani; Toxicity: pseudomembranous enterocolitis caused by C. difficile (which can be fatal) (6% incidence)

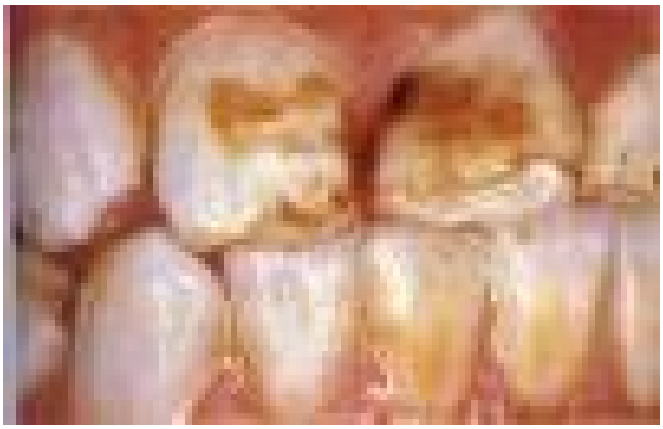
These 2, focus on clinical indications –

- **Streptogramins (Quinupristine-Dalfopristine)**: bind 50S ribosomes, inhibit aminoacyl t-RNA interaxn w/acceptor site & stimulates its dissociation from tertiary complex; for pt's w/serious or life-threatening infections of VRE (Enterococci faecium) bacteremia; last resort for VRSA; CYP450 inhibitor; A/E: arthralgia- myalgia syndrome;
- **Linezolid (ANSWER)**: MAO-I, bind 23S ribosomal RNA of 50S ribosomes; **for Hospital acquired (nosocomial) pneumonia caused by MRSA, MSSA & S. pneumoniae**; **reserved for MRSA**, infections caused by **VRE (Enterococcus faecium), s**kin & skin structure infections like diabetic foot ulcers (w/out osteomyelitis): S. aureus (MSSA & MRSA), S. pyogenes, S. agalactiae, infections caused by MDR GP; **A/E: thrombocytopenia;** last resort VRSA bacteria

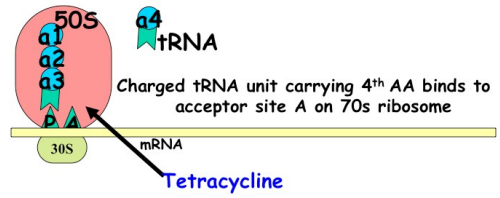
30S PS INHIBITORS:

- **Tetracyclines**: reversibly bind 30S subunit & block binding aminoacyl-tRNA to acceptor site on mRNA-ribosome complex prevent addition of AA's to growing peptide; broad spectrum for GP – Clostridia, Listeria, Corynebacterium, B. anthracis & GN – Y. Pestis, H. Pylori, Spirochetes – 2nd DOC T. Pallidum (for those allergic to penicillin), Borrelia, atypical bacteria – Rickettsia, Chlamydia & mycoplasma – highly sensitive, & Protozoa (E. histolytica, Plasmodium falciparum); DOC for RMSF Rickettsi; has chelating property – binds Ca^{2+}, Mg^{2+}, Fe^{2+} - which ↓their absorption, so *don't* give w/milk products, antacids; bind to tissues like teeth, bones which undergoing calcification (permanent brown discoloration & illformed teeth) during dev't (<8 yrs age or pregnancy), can cross placenta & concentrate in fetal bones & teeth, stunted bone growth, phototoxicity on exposure to UV light – demeclocycline, doxycycline superinfections – C. difficile diarrhea, candida; epigastric pain, abdominal distention, nausea, vomiting, hepatic injury, nephrotoxicity (doxycycline safe), Fanconi syndrome (renal tubular acidosis attributed to using outdated tetracyclines or Ag's), contraindicated in pregnancy, children <8 yrs; IV admin produces thrombophlebitis due to local irritation; IM injections painful, cause local irritation & result in poor absorption; elimination by kidney for most- dose ↓in renal dysfunc; except doxycline – eliminated thru liver so only 1 safe in renal dysfunc (contraindicated), Minocycline w/best CSF penetration for meningococcal carrier; Concentrate in saliva & tears; resistance via efflux pumps & activity of uptake systems;
- ***Primary use***: Doxycycline- Atypical pneumonia by mycoplasma; Chlamydial infections (Lymphogranuloma venereum, Granuloma inguinale), Cholera by *Vibrio cholera,* Spirochetal infection (Lyme dis (Borelia burgdorferi) & Relapsing fever (Borelia recurrentis)), Ricketsial infections as DOC of RMSF (, typhus, Q fever), Brucellosis & Bubonic Plague
- ***Secondary uses***: Alternative to penicillin in syphilis, H-pylori peptic ulcers, Chloroquine resistant falciparum malaria- doxycycline; Meningococcal carrier - minocycline - during epidemic, but prefer Rifampin, Acne, Leptospirosis, & SIADH (demeclocycline)

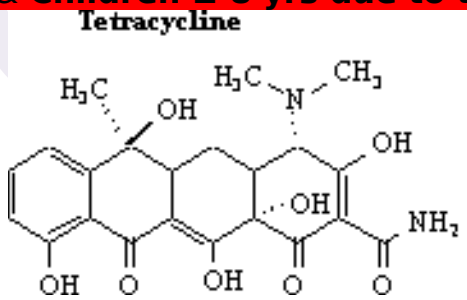




- **Chlortetracycline**:
- **Oxytetracycline**:
- **Demeclocycline**: DOC ADH antagonist used to treat SIADH as blocks ADH axns on CD; phototoxicity on exposure to UV light
- ***Doxycycline: MC'ly used among group; effective against atypical Mycoplasma pneumonia 2nd DOC; DOC for Chloroquine resistant falciparum malaria; eliminated thru liver…so ONLY tetracycline safe in renal dysfunc & doesn't cause nephrotoxicity; phototoxicity on exposure to UV light
- **Minocycline**: best CSF penetration for meningococcal carrier state in epidemic but prefer Rifampicin
- **Tigecycline**: **binds to 30S ribosomal subunit blocking binding of tRNA, inhibiting protein synthesis**. **Very broad spectrum** & active against many tetracycline-resistant strains; **Spectrum of GP** MRSA, Streptococcus, Pneumococcus, **Anaerobes (**Bacteroides specie), **GN (except Pseudomonas),** active against some MDR Acinetobacter, **Atypicals (**Legionella CA Pneumonia); **FDA Indications:** Complicated skin/skin structure infections, complicated intra-abdominal infections, CA pneumonia; **Contraindicated in Pregnancy (Category D)** (¬¬fetal weight & delayed bone formation in animal studies) & **Children ≤ 8 yrs due to teeth staining**



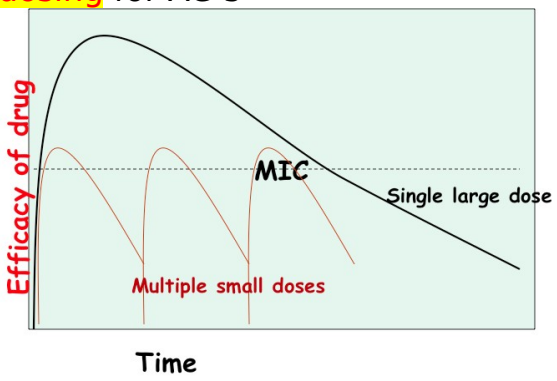
Tetracyclines- bind to 30S subunit & interfere w/ attachment of aminoacyl tRNA to acceptor site



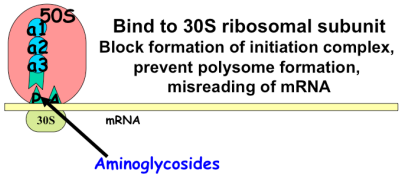
- **Aminoglycosides**: structure rel'd amino sugars attached by glycosidic linkages; obtained from *Streptomyces*; ***more effective on GN aerobic bacilli vs GP, only on aerobes not aenerobes (b/c drug afx O_2 dependent process); initial passive diffusion across outer memb thru porin channels; **NOTE: Transport across cell wall enhanced by cell-wall inhibitors like penicillin or vancomycin, which can make synergistic efx w/this; Oxygen dependent active transport** (anaerobic bacteria are thus resistant to AG's); Bind 30S ribosome & inhibit bacterial protein synthesis ⌴ ---| initiation complex of peptide formation- by blocking association of 50s subunit w/mRNA-30s; induce misreading mRNA ⌴ incorporating wrong AA into peptide ⌴ nonfunc'al/toxic protein; polysomes break into nonfunc'al monosomes**;** polar compounds so not effectively absorbed by GIT, always admin'd Parenterally, usually IV or IM w/minimal metabolism; EC distribution (Vd (L) = 25% BW); most cleared by kidney; monitor & adjust blood lvls in pt's w/renal failure/elderly; Maintenance doses must be adjusted if creatinine clearance not normal; attain [high]'s in otic perilymph, & renal cortical tissue so can cause Ototoxicity & nephrotoxicity; toxicities - Nephrotoxicity: 6-7% incidence [Proteinuria, elevated BUN, acidosis, & Acute tubular necrosis..usually reversible, enhanced by other nephrotoxic drugs..vancomycin, cyclosporin

(immunosuppresant), amphotericin, cisplatin], Ototoxicity [b/c Cochlear damage results in deafness (irreversible) & Vestibular damage as Headache appears 1st followed by nausea, vomiting, dizziness, nystagmus, vertigo & ataxia (reversible)] – ototoxicity can be enhanced by loop diuretics (frusemide), Neuro muscular blockade w/high doses, may result in respiratory paralysis (reversible by admin of Ca^{2+} & neostigmine)

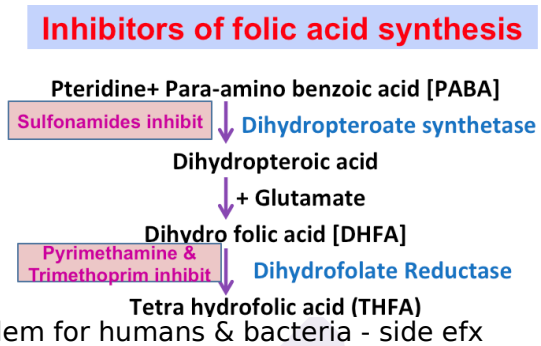
- Concentration-dependent killing: ⏚ [ ]'s kill ⏚proportion of bacteria & at more rapid rate so single large dose more effective than multiple small doses; ie. Gentamicin
- **Postantibiotic efx: antibacterial activity persists beyond time during which measurable drug present; postantibiotic efx of AG's can reach several hrs; Hence it's given Once daily dosing for AG's



- AG's have Synergistic axn w/b-lactam antibiotics
  - *Enterococcal* infections (AG + PenicillinG / vancomycin)
  - *P. aeruginosa* infection (AG + extended spectrum penicillin/cephalosporin)
- **Mechanism of resistance**: (1) **bacteria produce transferase (ANSWER) to inactivate AG's by** phosphorylation, acetylation & adenylation (**2) Drug's impaired penetration into cell or (3) receptor protein on 30S ribosomal subunit may be deleted or altered b/c mutation; *Streptococci* & *enterococci* resistant to AG's (due to ↯ penetration)**
- **Amikacin, Gentamicin & Tobramycin**: used topically – TOPICAL GAT
- **Gentamicin**: very nephrotoxic & vestibulotoxic
- **Streptomycin & gentamicin: most vestibulotoxic**
- **Streptomycin**: used for TB, brucellosis, bubonic plague & tularemia
- **Neomycin*****: AG w/exception available in oral formulation, not sig'ly absorbed from GI tract, after oral admin, intestinal flora suppressed or modified & drug excreted in feces; for hepatic encephalopathy/ hepatic coma to ↓↓coliform flora which ↓↓production of ammonia (ANSWER) that causes lvls of free nitrogen to ↓↓in bloodstream; very toxic, now replaced by Lactulose
- **Neomycin, tobramycin, gentamicin** most nephrotoxic.
- **Kanamycin**
- **Netilmicin**



L7 Inhibitors of Bacterial Nucleic Acid Synthesis:

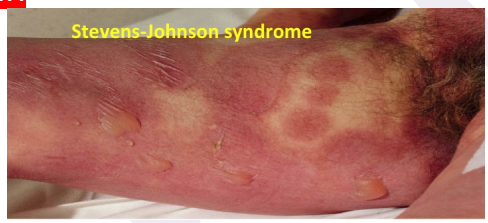


Folate synthesis: Humans can't synthesise folate, must be provided in diet. But Bacteria can synthesize their own folate (folic acid). Bacteria use precursor PABA (p-aminobenzoic) – to make it–SO ANTIBIOTICS – esp sulfonamides compete for active site w/PABA for utilization of folic acid –so bacteria won't be able to make folic acid- *competitive* substrate – sulfonamides inhibit this DHPS (dihydropteroate synthase)

- **Folic acid *synthesis* is diff – but *utilization is same* in bacteria & humans.** Any drug that disrupts utilization – can be problem for humans & bacteria - side efx occur. These drugs have more affect on bacterial enzymes then human enzymes- humans little more protected.
- THF Synthesis (further reduced form of folic acid) requires DHFR. This enzyme can be inhibited by folate antagonists… thus can inhibit DNA synthesis by interrupting folate utilization. This enzyme is many times more sensitive to folate antagonists in bacteria than in humans. Thus bacterial cells affected sparing human cells.

Bacterial Folic acid synthesis inhibitors:

- **Sulfonamides**: *competitively* inhibit DHPS (dihydropteroate synthase) & so folic acid synthesis; Resistance by 1. Altered bacterial DHPS enzyme (ANSWER) mutates causing affinity for sulfonamides – imp for Sulfamethoxazole IN QUES; 2. uptake – permeability to sulfonamides may be ; 3. PABA synthesis – enhanced PABA production can overcome inhibition of DHPS; Adverse efx– MC – type III HSR…mostly rashes, can be severe…Stevens-Johnson syndrome*** (20% fatal; generalized eruption of lesions that initially w/target-like pattern but then became confluent, brightly erythematous, showed crinkled surface & became bullous. If lesions touched, epidermis'll be dislodged & erosions appear (Nikolsky sign), extensive mucous memb involvement & tracheobronchitis. May show pic, common on face, lesions large after therapy w/sulphonamides), Folic acid def (megaloblastic anemia), contraindicated in newborns & pregnant F's esp in 3rd trimester (displaced from plasma proteins – bilirubin accumulated in brain b/c BBB & placental barrier not well dev'd kernicterus), Nephrotoxicity (crystalluria can cause obstruction of kidneys & AIN – allergic interstitial nephritis), ****Hemolysis in G6PD def (rmr Heinz bodies, hemolytic anemia); also Highly plasma protein bound – DI efx (toxicity) of methotrexate, phenytoin & warfarin



  - Intermediate acting (8-12 h)
    - ***Sulfadiazine***: combo w/pyrimethamine treats toxoplasmosis;
    - ***Sulfamethaxazole***
  - *Systemic sulfonamides*
    - ***Sulfasalazine***: in RA as DMARD, U. Colitis – colonic bacteria splits this into sulfapyridine + ASA (5-amino-salicylic acid aka aspirin) to have intended efx; via inhibiting PGs & LTs (mediators of inflammation)
    - ***Sulfisoxazole***: short acting (4 hr)
    - ***Sulfamethoxazole***: intermediate acting (8-12 hr) combined w/TMD
    - ***Sulfadoxine***: long acting; combo w/pyrimethamine to treat malaria – long acting so preferred
  - *Topical sulfonamides* –
    - **Silver sulfadiazine**: intermediate acting (8 – 12 hr) as 1% cream treats burns,
    - ***Sulfacetamide***: as eye drops treats Conjunctivitis,
    - ***Mafenide***

Dr. Chanz

- **Urinary tract infections** –uncomplicated mild = TMP-SMX
- **Conjunctivitis** = Sulfacetamide eye drops
- **Malaria** = Sulfadoxine + pyrimethamine
- **Burns** = Silver sulfadiazine 1% cream
- **Toxoplasmosis** = Sulfadiazine + pyrimethamine
- *Other sulfa drugs but w/diff MOA*: do not inhibit DHPS & not folate antagonists, thus All sulpha drugs not folate antagonists, & all folate antagonist are not sulpha drugs
  - Thiazides, frusemide, Acetazolamide used as diuretics
  - Sulfonyl ureas used as oral hypoglycemic drugs
  - Sulfasalzine useful in tx of U. colitis & RA via inhibition of PGs & LTs (mediators of inflammation)

➢ **Trimethoprim**: inhibits DHFR & provides sequential blockade of THF synthesis; Resistance via mutated gene for DHFR; hence hardly used alone; can cause Megaloblastic anemia via folic def

➢ ****TMP-SMX (Cotrimoxazole = Trimethoprim-Sulfamethaxazole): (ANSWER)** fixed dose combo of sulfamethaxazole & trimethoprim (ratio 5:1); Eg: Single strength 400 mg + 80 mg; Double strength 800 mg + 160 mg; causes sequential block of folate metabolism; ind'ally bacteriostatic but Together Bactericidal & Synergistic; less resistance to combo than w/either alone; 50,000X more selective for bacterial enzymes; **treats uncomplicated mild UTI'S**, Nocardiosis – DOC, *P. jirovecii PCP* infections in AIDS* 1st line drug for prophylaxis & tx*** based on CD4+ count <200, GN (E.coli, salmonella, H.influenza) ID'd by GMS stain & cause Uncomplicated UTI (SMX-TMP is 1st line), Salmonella typhoid fever (1st line drugs - cipro/ cefotaxime/ceftriaxone), meningitis, Listeria (ampicillin is 1st line), GP infection *staph +MRSA (sometimes, prefer vancomycin);* *adverse efx: contraindicated in pregnancy b/c NTD's*

➢ **Pyrimethamine**: inhibit DHFR & so block THF synthesis

Direct Nucleic acid synthesis inhibitors:

➢ ***Quinolones/Fluoroquinolones***: synthetic Fluorinated analogues of nalidixic acid (old drug still used in UTI); thus inhibits bacterial DNA gyrase/ Topoisomerase II, after binding to subunit 'A' interferes w/strand cutting & resealing; also inhibits topoisomerase IV (N separates replicated DNA in cell division); Drug Resistance may occur by **drug efflux** *(P.aeruginosa)* or changed sensitivity of target enzymes topoisomerase IV *(GP bacteria)* & topoisomerase II *(GN bacteria)*; Adverse efx: cause tendonitis, tendon rupture in all ages esp CI in kids (<18 yrs) & pregnancy, due to depositing cartilage & disrupting matrix (may damage growing cartilage & interfere w/collagen metabolism); *Antacids- ↓absorption FQ (same as TC); &* grapefloxacin – w/drawn in 200 for cardio toxicity

DNA gyrase has 2 subunits A & B
- Subunit 'A' Nicks dsDNA
- Subunit 'B' introduces –ve supercoils

  - ***1st group:* Norfloxacin** – least active; treats UTI's
  - ***2nd group (CPOLL)***: excellent activity on GN, moderate activity on GP; **Ciprofloxacin**, **Lomeflaxacin**, **Ofloxacin**, **Levofloxacin**, **Pefloxacin**
    - ***Ciprofloxacin (ANSWER)**: excellent high activity against Pseudomonas in Osteomyelitis aka bone – wide distribution, substrates for active tubular secretion… so lower dose in renal failure; treats 1st typhoid enteric fever, Gonorrhea & Bacillus Anthracis (also tx'd w/penicillin, tetracyclines)
    - ***O*floxacin**: treats gonorrhoea, ***o*nly Fluoroquinolone for Chlamydia***
    - **Levofloxacin**: for drug resistant pneumococci/S. pneumoniae
  - ***3rd group***: active on both GP & GN: **Sparfloxacin**, **Moxifloxacin Travofloxacin**, **Gatifloxacin**
    - ***Sparfloxacin***: for drug resistant pneumococci; prolonged QT interval– esp pt's on CYP inhibitors – *Procainamide, sotalol, amiodarone*

- ***Gatifloxacin***: prolonged QT interval – esp in pt's on CYP inhibitors – *Procainamide, sotalol, amiodarone*
- **RESPIRATORY FLUOROQUINOLONES** (***levofloxacin, Moxifloxacin, Gemifloxacin***) w/enhanced GP activity & against atypical pneumonia agents (chlamydia – 1 week tx, mycoplasma & legionella)
- Ceftriazone & cefaperazone – S typhi
- Uses of Fluoroquinolones –
  - **UTI's** = Norfloxacin
  - **Typhoid (enteric fever)** = Ciprofloxacin
  - **Gonorrhea** (ciprofloxacin, ofloxacin for gonorrhea – single dose, but ceftriaxone is 1st line drug)
  - **Chlamydia** …Only fluoroquinolones used is Ofloxacin
  - **Atypical pneumonia** (chlamydia, mycoplasma & legionella) = respiratory fluoroquinolones – Levofloxacin, Moxifloxacin, gemifloxacin
  - **Pseudomonas infections**…. Ciprofloxacin very effective FOR burns??
  - **Drug Resistant pneumococci** = levofloxacin, Sparfloxacin
  - MDR cases of TB

➢ Rifampin

L8 General Principles of Microbiotics:

➢ Empiric Antimicrobial therapy: initiation of drug tx b4 ID of specific pathogen

Class	Organism	First choice	Alternative
GP aerobic	S. pneumoniae, S. pyogenes	Penicillin	Erythromycin, doxycycline & quin
	Enterococcus	Penicillin (broad spectrum – ampillicin, amoxicillin) or extended, not narrow) + gentamicin	Vancomycin (VSE) + Gentamicin; If VRE ⊣ Streptogramins (Quinupr Dalfopristine) OR Linezolid
	S. aureus Penicillinase producing*****	Penicillinase resistance Penicillins: Oxacillin, nafcillin, dicloxacillin	1st generation CS if MRSA ⊣ vancomycin (MRSA) if VRSA ⊣ Streptogramins (Quinu Dalfopristine) OR Linezolid
	MRSA	Vancomycin	Linezolid, streptogramins
	Bacillus anthracis	Ciprofloxacin, Penicillin	Erythromycin
	Listeria	Ampicillin DOC*	TMP-SMX (Cotrimoxazole), Vancomycin, Tetracycline
	Nocardia	TMP-SMX DOC*	
	Actinomyces	Penicillin DOC*	
	Corynebacterium diphtheria	Erythromycin	Penicillin
Anaerobic GP	Cl. perfringes, Cl. tetani	Penicillin, Clindamycin	Vancomycin
	Clostridia difficle	Metronidazole	Vancomycin
	Bacteroides fragilis***	Metronidazole (1st choice) Clindamycin (more toxic – pseudomembranous enterocolitis)	Chloramphenicol (very toxic – bon marrow suppression – aplastic an
	Mycoplasma pneumoniae	Macrolides (Erythromycin) tetracycline	Fluoroquinolones

Class	Organism	First choice	alternative
Gram - ve	N gonorrhoea	Ceftriaxone (3rd GEN cephalosporin)	ciprofloxacin
	N meningitidis	Ceftriaxone, cefotaxime	PnG
	E.coli, proteus, klebsiella	TMP-SMX*** CS-1st or 2nd generation	Aminoglycosides (AG), Fluoroquin
	H.influenza	Cefuroxime, ceftriaxone	Chloramphenicol
	Pseudomonas	AG + pipericillin/ticarcillin	Ceftazidime/cefoperazone+ AG Aztreonam, imipenem
	Brucella	Doxycycline + rifampin/ AG	
	H.pylori	Tetracycline+ Metronidazole+PPI Metronidazole +amoxicillin+PPI Unless allergic to penicillin ⊟	Clarithromycin/amoxicillin+PPI
	S.typhii	Ceftriaxone Ciprofloxacin	Chloramphenicol cotrimoxazole
	Vibrio	Tetracycline	Fluoroquinolone
Spirochetes	Borrelia recurrentis Borrelia burgdorferi Rickettsia (RMSF)	Doxycycline Doxycycline	Erythromycin Ceftriaxone
	T. pallidum (Syphilis)	Penicillin G	Tetracycline
Chlamydia	Chlamydia trachomatis	Tetracycline, azithromycin	Clindamycin, ofloxacin

- **Susceptibility testing**: testing bacteria in vitro for their susceptibility to given drug – done by disk diffusion & broth dilution tests; results establish drug sensitivity of organism & predict MIC (Minimum inhibitory concentration). Lowest [antibiotic] which prevents visible growth of bacterium in cultured plates is called MIC; Least the MIC more potent the drug
- Bactericidal agents can be divided into 2 groups –
  - 1. Agents that exhibit concentration-dependent killing (eg, *AG's* & quinolones). Maximizing peak plasma lvls-Rate & extent of killing, *single large dose admin*
  - 2. Agents that exhibit time-dependent killing (eg, Penicillin, vancomycin). Antimicrobial axn depends on length of time [plasma] is above MIC; *Divided daily dose*
- **PAE (Postantibiotic efx):** persistent suppression of bacterial growth after lmtd time exposure to antimicrobial; means – antibiotic efx continues after [blood] has fallen; ex's of such antibiotics – AG's ***(given 1/day), Streptogramins & Carbapenems
- ***Antibacterial drug use in Pregnancy & neonate***; Safe: Penicillins, Erythromycin
  - Unsafe
    - Tetracyclines – bone & teeth deformity
    - Sulfonamides – kernicterus
    - Chloramphenicol – causes Grey Baby syndrome
    - Fluoroquinolones – cartilage damage
    - Methicillin – interstitial nephritis
- Antibiotics of special mention which requires dose modification in
  - renal dis: AG's, cephalosporins, vancomycin, amphotericin B (antifungal); CAVA=R
  - liver dis: erythromycin, chloramphenicol; CE=L
- Drug interaction
  - Never use AG's w/furosemide ⊟ Ototoxicity/nephrotoxicity

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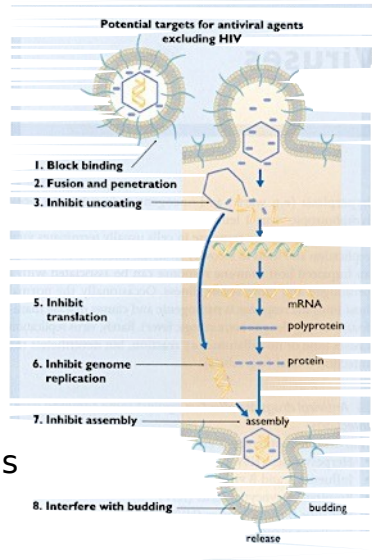
- Metronidazole, Cephalosporins ▭ Disulfiram like rxn w/alcohol
- CYP enzyme inhibitor like Erythromycin, azole antifungal, HIV protease inhibitors
- CYP enzyme inducer – rifampin

➢ **Superinfection**: prevent by using narrow spectrum antimicrobials, not using antimicrobials to treat self limiting infections & not prolonging tx; new infection w/antimicrobial therapy via suppressing normal microbial flora; common in immunocompromised – on Corticosteroids, AIDS & Leukemias – on anticancer drugs; drugs known to cause suprainfections: Tetracyclines, Ampicillin, Cephalosporins; ex's of super(supra) infection –
- Monilial Diarrhea, oral thrush, vulvonaginitis caused by *Candida albicans;* tx w/Clotrimazole
- Pseudomembranous enterocolitis by *C. difficile* (via clindamycin, tetracycline), tx w/metronidazole, vancomycin
- UTI's, enteritis by *Pseudomonas;* Rx: Piperacillin/Cefoperazone, ceftazidime

➢ ***COMBO OF ANTIMICROBIALS***:
- To achieve synergism
  - TMP-SMX/Cotrimoxazole = Sulfonamide + Trimethoprim (sequential blockade)
  - Augmentin = Amoxicillin+Clavulanic acid (blockade of drug inactivating enzyme)
  - Gentamicin + penicillin in Bacterial endocarditis
  - Amphotericin B + flucytocine in Cryptococcal meningitis
  - Extended spectrum Penicillin+AG in pseudomonal infections (⏚drug uptake)
- To ⏚⏚severity/incidence of adverse efx
- To prevent emergence of resistance: INH+ Rifampin+pyrazinamde in TB, Leprosy
- To broaden spectrum of antimicrobial axn: in tx of mixed infections like UTI, bronchiectasis, diabetic foot & for Initial tx of severe infections

➢ **Antimicrobial chemoprophylaxis**: to prevent/suppress contacted infection b4 it clinically manifests
- Prophylaxis against specific organisms
  - Rheumatic fever – streptococci – Benzathine Penicillin
  - Tuberculosis – give INH to contacts
  - Gonorrhoea/Syphillis w/Procaine penicillin
  - *PCP Pneumocystis jiroveci* pneumonia in AIDS pt's w/Cotrimoxazole
- In high risk situations
  - **Endocarditis** prophylaxis in pt's w/valvular heart dis's undergoing dental extraction, upper respiratory procedures- give amoxicillin/clindamycin
  - Genitourinary/GI procedures give ampicillin/vancomycin+gentamycin
  - Surgical prophylaxis - Cefazolin commonly used drug

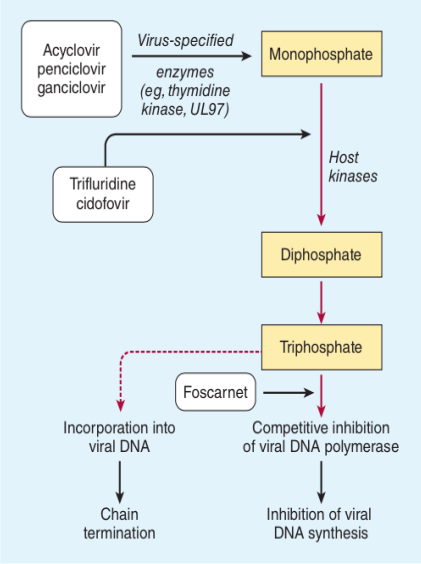
L9 Antivirals:
1. **HSZ**, **VZV**: Acyclovir, cidofovir, foscarnet
2. **CMV**: Gancyclovir, Cidofovir, foscarnet, fomiversin (Antisense oligonucleotide)
3. **HIV**: NRTI, NNRTI, PI (protease inhibitor)
4. **Influenza**: Oseltamivir, zanamivir, Amantadine, Rimantadine
5. **Hepatitis B**: Interferon –α, Lamivudine
6. **Hepatitis C**: Interferon –α, Ribavarin



Steps for Viral Replication
1. Absorption & penetration into cell
2. Uncoating of viral nucleic acid
3. Synthesis of regulatory proteins, RNA or DNA, then structural proteins
4. Assembly of viral particles
5. Release from host cell

Anti-Herpes virus drugs: acyclovir, ganciclovir, famciclovir, cidofovir, foscarnet, vidarabine, fomovirsen

- All herpes drugs
- **Acyclovir**: **prodrug** à must be activated by **phosphorylation** (by **viral enzyme** = **Thymidine Kinase**), forms **acyclovir monophosphate** ␣then forms diphosphate & triphosphate
  - **triphosphate form inhibits DNA polymerase competitively**
- **DNA Polymerase** is target of all herpes drugs.
- **Resistance** to acyclovir à **Viruses that don't have viral Thymadine kinase****. (less commonly is DNA Polymerase change)
- Will be asked about the resistance
- Foscarnet is not a prodrug à directly inhibits
- Need phosphorylation à all besides foscarnet
- All inhibit viral DNA polymerase
- Resistance: no thymidine kinase
- Nephrotoxic: Cidofovir and Fosconet
- Bone marrow suppression: Gancyclovir



- **Acyclovir**: prototype; activity against *HSV & VZV ONLY* – Genital herpes, H.simplex keratitis, H.simplex encephalitis (IV), Chicken Pox, *Topical, oral, IV* forms; ***resistance via Lack of viral thymidine kinase & changes in viral DNA pol****; doesn't work against CMV; safe drug à no real se, should be well hydrated – otherwise nephrotoxic
- **Ganciclovir**: treats CMV, HSV, VZV; same MOA as acyclovir (…) 1st step in phosporylation w/viral thymidine kinase in HSV, whereas also phosphotransferase in CMV—triphosphate form inhibits viral DNA pol hence DOC for CMV, esp immunocompromised; for prophylaxis & CMV infections (retinitis) in AIDS & transplants recipients; A/E: haematoxicity- leukopenia, thrombocytopenia, Mucositis, Crystalluria; & in OD ␣ seizures; Bone marrow suppression (Leukopenia, thrombocytopenia) can see oral ulcers; If someone on gancyclovir à see neutropenia (GM-CSF) àtx w/filgrastim. Anemia à EPO α, or Antibacterial where we see thisà Chloramphenicol
- **Famciclovir**:
- **Cidofovir**: needs to be phosphorylated to active form inside cell – but doesn't need viral enzyme thus *Independent* of viral enzymes; inhibits DNA pol to inhibits *HSV, CMV (alternative, DOC – ganciclovir), adenovirus, HPV* & for tx of CMV retinitis, genital warts; adverse efx: Nephrotoxicity
- **Foscarnet**: synthetic organic analog of inorganic pyrophosphate interferes w/DNA synthesis & replication of CMV & HSV1&2; doesn't need phosphorylation…so not prodrug, inhibits DNA pol, viral RNA pol & HIV RT (secondary efx on HIV RT (don't use as monotherapy in HIV tho); for CMV retinitis & *Acyclovir resistant strains of HSV (normally use acyclovir)*; adverse efx: Nephrotoxicity- ATN (continuously assessment renal func), seizures b/c electrolyte imbalances – HYPOCALCEMIA, hypophosphatemia, hypomagnesemia, hypokalemia; HENCE DON'T USE

- Vidarabine:
- **Fomivirsen**: antisense oligonucleotide, binds to mRNA of CMV – inhibits protein synthesis; injected intravitreally in CMV retinitis; not commonly used

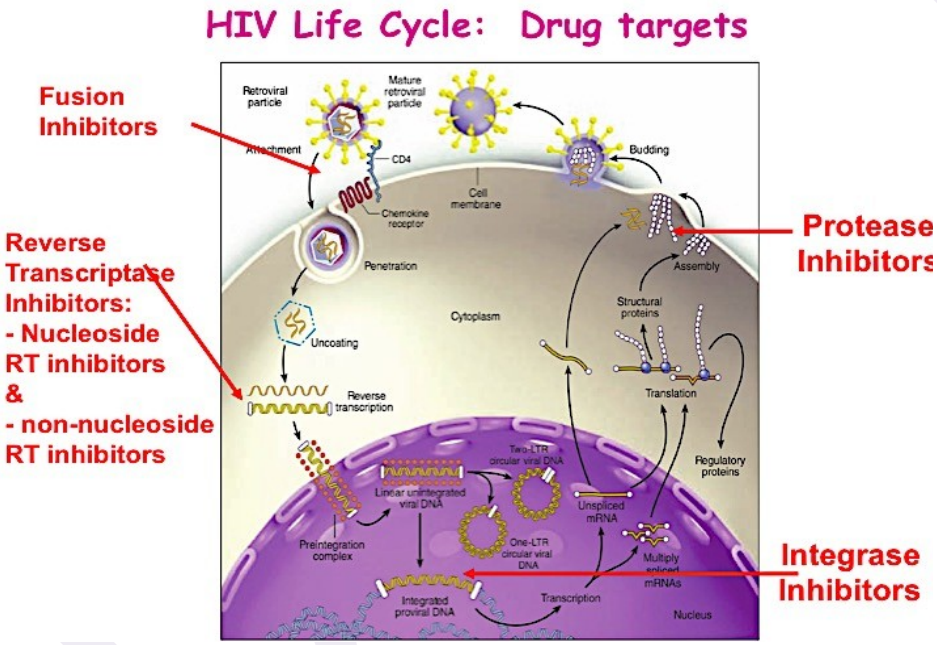
HSZ, **VZV**: Acyclovir, cidofovir, foscarnet

CMV: Gancyclovir, Cidofovir, foscarnet, fomiversin (Antisense oligonucleotide)

HIV: NRTI, NNRTI, PI (protease inhibitor)

HIV Life cycle: Drug targets

- Replication of HIV. First step = absorption
- HIV has envelope protein (GP41 & GP120); GP41 = attachment & fusion
- CD4 is target cell.
- CXCR & CCR5 à chemokine receptors
- GP41 brought in close contact w/chemokine receptors. à fusion of viral to host cell memb.
- Uncoating
- Reverse transcription: ssRNA à dsDNA.
- Viral DNA gets incorporated or integrated into host DNA. Later there is transcription/translation.
- Protease needed to release. Once released they affect other T helper lymphocytes.
- Most research now targeted twds attachment & penetration.
- RT inhibitors (AZT à Ziduvadine = acidothymadine) thymidine analog. Competes by incorporating into DNA
- RTI, NRTI, NNRTI & PI. Now there are also integrase inhibitors.
- Then came fusion inhibitors. (fusion of viral & host) à GP41 allows fusion.

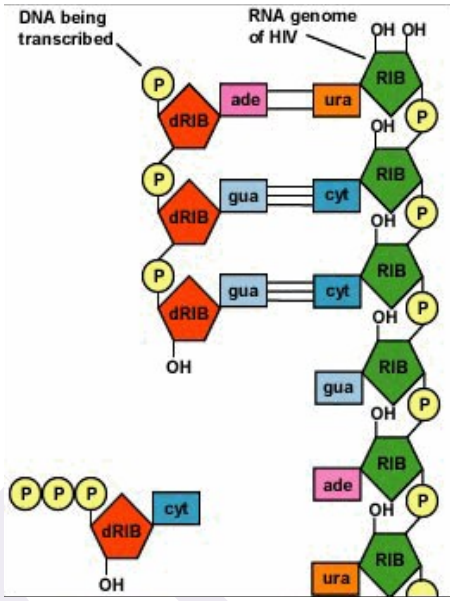


- **HAART** (Highly active anti retroviral therapy): always combo of at least 3 drugs; usually has AZT. All of these nucleotide analogs. Thymidine or Cytosine.

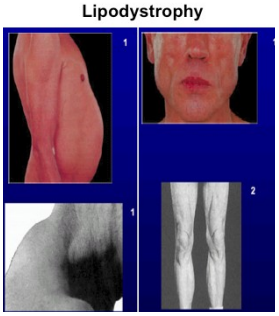
Antiretroviral drugs:

- **NRTI (Nucleoside reverse transcriptase inhibitors)**: prodrugs must be converted by host cell enzymes to active Zidovudine triphosphate; competitively inhibit Reverse transcriptase so HIV can't go from ssRNA to dsDNA; B/c lack 3′-hydroxyl group on ribose ring, attachment of next nucleotide is impossible, thus interrupt DNA chain elongation; imp pt of HAART (highly Active Antiretroviral Therapy) in combo w/PI's
  - Not all HIV pt's have AIDS à look for **CD4 count** & **HIV Viral Load**. Based on CD4#, treat or use prophylactic drug
  - for **post exposure prophylaxis** à needle stick or exposure to body fluids. (2 drugs or just AZT)

- Vertical transmission = mom to baby (transmission usually happens during time of labor) – start tx by 2nd trimester at least. Must be continued 6 weeks in fetus after delivery, liquid form. Can prevent in 98% cases.
- ****Zidovudine (AZT):** NRTI converted to active form (triphosphate); Only acronym might be tested on is AZT; used w/protease inhibitors; for Prophylaxis – following needlestick injury (Post exposure prophylaxis) & prevent Vertical transmission (ie. mom to baby during pregnancy); usually used w/PI's; causes ***bone marrow suppression**** à even in [therapeutic]'s à not w/NNRTIs; also myopathy & peripheral neuropathy; tx w/F-stim (GM-CSF) & EPO
- **Stavudine (D4T):** adverse efx: peripheral neuropathy
- **Didanosine (ddI):** adverse efx: **pancreatitis****, peripheral neuropathy (ie. shooting pain down leg)
- **Lamivudine (3TC) & Emtricitabine/FTC;** both least toxic, only some GI efx & neutropenia
- **Zalcitabine (ddC)**



- **NNRTI (Nonnucleoside reverse transcriptase inhibitors):** don't need phosphorylation to triphosphate form; directly bind site on & inhibit HIV-1 reverse transcriptase; used synergistically w/NRTI &/or PI in HAART; prevents vertical transmission; not myelosuppressant
  - **Nevirapine**: sulfa drug; adverse efx: steven Johnson syndrome
  - **Delaviridine**
  - **Efavirenz**: adverse efx – CNS dysfunc, only RT inihibitor contraindicated in pregnancy ▭ seizures
- **PI's (Protease inhibitors)**: Saquinavir, Ritonavir, indinavir, Nelfinavir; *inhibit HIV protease (pol gene encoded) needed for viral assembly* which cleaves precurssor polypeptide in HIV to form virus structural proteins; *thus* cause production of immature, non infectious viral particles; often used in combo w/NRTIs (to greater lower viral load); resistance via specific point mutations in *pol* gene b/c Polymerase highly mutagenic so always use in combo to prevent resistance; SSRI & protease **inhibitors are CYP inhibitors** à DI's so Monitor other drug à ie. monitor Warfarin; Adverse efx: **Lipodystrophy**: as Body Habitus Changes w/Fat deposition in Intrabdominal, Dorsocervical & Breasts; & w/Fat atrophy as extremity wasting & Facial lipoatrophy, hyperglycemia due to insulin resistance, & hyperlipidemia



  - **Indinavir**: adverse efx: diarrhea, kidney stones, hyperbilirubinemia
  - **Nelfinavir**: advere efx: both CYP inducer & inhibitor +diarrhea
  - **Ritonavir:** imp, used in some therapeutic doses (not much antiretroviral efx) à skip to kinetic boost aka used w/other NRTI's to have better [therapeutic]'s – MC'ly use 2 NRTI & 1 PI; adverse efx: GI irritation, CYP3A4 & CYP2D6 inhibitors

HIV entry divided into 3 basic steps, & inhibitors for each being dev'd/been dev'd:

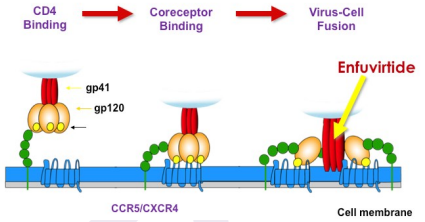
- 1st step is specific binding of HIV gp120 to CD4 molecule. Following gp120-CD4 binding, conformational change occurs in gp120; so virus can then bind coreceptor on cell surface – chemokine receptor, either CCR5 or CXCR4 ▭ results in further conformational changes in gp120 that exposes gp41 protein. This protein mediates fusion of viral & cell memb's. [GP120 = attachment of virus to CD4; comformational change in GP120 to allow viral to bind chemokine receptors]

Each of these steps now targeted by investigational/approved antiretroviral agents:

- Binding of CD4 & gp120 inhibited by series of small molecules designed by BMS that bind to gp120. BMS-488043 is 1st of these compounds to show activity in HIV-infected ind's, on next slide

- Antagonists that bind to CCR5 or CXCR4 & inhibit 2nd step are in dev't. CCR5 inhibitors, including SCH C, SCH D & UK 427,857, shown activity in pt's
- 3rd step inhibited by **enfuvirtide** (T-20): peptide molecule that binds directly to HR1 region of gp41 & stop fusion of viral & host memb

HIV Attachment and Fusion Inhibitors

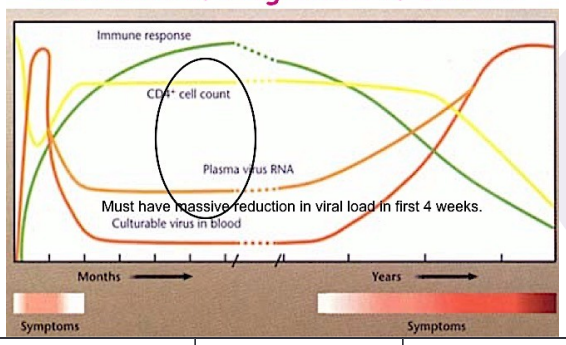


New Antiretroviral drugs (add on drugs)

- **Fusion inhibitor: Enfuvirtide (T-20):** peptide molecule that binds directly to HR1 region of gp41 & stop fusion of viral & host cellular memb's (surface protein & attachment); current indication in combo w/other antiretrovirals on pt's failing tx; new drug add on; blocks viral penetration/uncoating
- Chemokine Receptor (CCR5 Receptor) antagonist: **Maraviroc**
- Integrase Inhibitor: **Raltegravir**: inhibits integrase necessary for integration of HIV DNA to host cells

NRTI (all cause lactic acidosis & peripheral neuropathy***)	NNRTI	PI (CYP inhibitors): all cause Hyperglycemia due to insulin re hyperlipidemia, lipodystrophy
Zidovudine: BM suppression, Myopathy, Peripheral neuropathy	Nevirapine: stevens johnsons syndrome	Indinavir: diarrhea, Kidney stones (crystals), hyperbiluribinemia
Didanosine: Pancreatitis, Peripheral neuropathy	Efavirenz: CNS dysfunc; teratogenic	Ritonavir: GI irritation, CYP3A4 &2D6
Stavudine Peripheral neuropathy		Nelfinavir: both CYP inducer & inhibitor, +causes diarrhea

HIV Infection:
Predictors of Progression of Disease



Guidelines: When to start HAART tx?
Criteria to make decision –

1. Clinical – symptomatic or asymptomatic
2. Immunologic: CD4 cell counts
3. Virologic: viral load

Clinical Category	CD4+ T Cell Count	Plasma HIV RNA	Recommendation	Common infections
Symptomatic (AIDS, severe sx)	Any value	Any value	Treat	➢ MAC – treats w/Azythromycin (once a day)
Asymptomatic	<200/mm³	Any value	Treat Start retroviral tx	

Common dis's in HIV +ve pt's & their tx:****

- **CD4 <200:**
  - **Cryptosporidium** (MCC diarrhea in AIDS) w/HAART
  - **PCP** w/TMP-SMX
- **CD4 <100:**
  - **Esophageal candidiasis** (oral thrush) – Fluconazole
  - **histoplasmosis** – Itraconazole - Antifungal Azole
  - **Toxoplasmosis** – Sulfadiazine + pyrimethamine, or TMP-SMX? (Kaplan)
- **CD4 < 50:**
  - **CMV retinitis:** see cotton wool spots on retinoscope; perivascular hemorrhage, exudate & even retinal detachment; dx w/hisoltog large intranuclear bodies & cytoplasmic inclusions in tissie; tx w/Cidofovir (+prophylaxis) or Gancyclovir
  - **Cryptococcal meningitis – rmr Cryptococcus neoformans: fungi that** can cause meningitis in AIDS; seen as soap bubble appearance, India ink stain; predominantly reactive lymphocytes; tx w/Fluconazole (+prophylaxis) + flucytosine
  - **MAC/Mycobacterium avium** - azithromycin

Possible combos for tx:
2 NRTI + 1 NNRTI

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2 NRTI + 1 PI
1 NRTI +1 NNRTI + 1 PI
3 NRTI
Combinations to avoid:
Didanosine+ zalcitabine b/c additive toxicity
Stavudine + zidovudine b/c they both compete for same kinases

- **Kinetic boost**: **Ritanovir**: potent anti HIV w/pronounced inhibitory efx on CYP3A4; co-admin w/other anti HIV drugs ↓[plasma] of these drugs; Lopinavir is PI w/low oral bioavailability; SOOO L+R ↓anti-retroviral effect of Lopinavir; often in combo w/other PI; in small doses (subtherapeutic) for pharmacokinetic boost
- **HIV prophylaxis:**
  - ***Needle stick:*** AZT (zidovudine) + 3TC (lamivudine) for 1 month, +PI for 4 weeks
  - ***In high risk cases***: AZT + 3TC + Indinavir PI
  - ***Pregnancy***: AZT full dose in trimester 2 & 3 (high risk during labor) + 6 weeks to neonate (high prevention rate)

Influenza: Oseltamivir, zanamivir, Amantadine, Rimantadine

- **Amantidine & Rimantidine**: inhibit 1st step in replication of influenza A (viral *uncoating*) by blocking M2 protein; toxicity – atropine like peripheral side efx, livedo reticularis (modeled discoloration of skin reticular net-like/cyanotic, lace like surrounding pale central skin, mostly in legs, esp cold weather)
- **Amantidine**: for Influenza A only; Parkinson's dis
- **Zanamivir (intranasal)** & **Oseltamivir**: neuraminidase inhibitors (enzyme required for preventing clumping of virions) made from influenza virus; for both influenza A & B as most strains respond to these

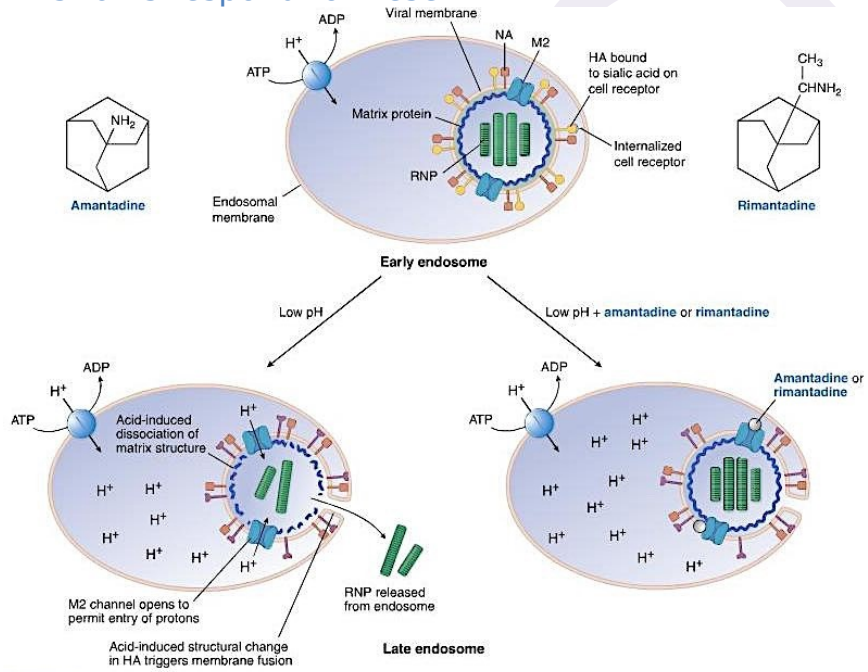

FIGURE 37-4. Uncoating of influenza virus and effect of amantadine and rimantadine. The structures of the adamantanes, amantadine and rimantadine, are shown. Influenza virus enters host cells by receptor-mediated endocytosis (*not shown*) and is contained within an early endosome. The early endosome contains an H^+-ATPase that acidifies the endosome by pumping protons from the cytosol into the endosome. A low pH-dependent conformational change in the viral envelope hemagglutinin (HA) protein triggers fusion of the viral membrane with the endosomal membrane. Fusion alone is not sufficient to cause viral uncoating, however. In addition, protons from the low-pH endosome must enter the virus through M2, a pH-gated proton channel in the viral envelope that opens in response to acidification. The entry of protons through the viral envelope causes dissociation of matrix protein from the influenza virus ribonucleoprotein (RNP), releasing RNP and thus the genetic material of the virus into the host cell cytosol. Amantadine and rimantadine block M2 ion channel function and thereby inhibit acidification of the interior of the virion, dissociation of matrix protein, and uncoating. Note that the drug is shown as "plugging" the channel (lower right panel, upper channel graphic); however, there is also evidence that the drug may bind to the outside of the channel instead (lower right panel, lower channel graphic). NA, neuraminidase.

- Uncoating & release (site of axn for some of these drugs)
- Influenza virus in early endosome à certain events cause release of viral DNA.
- Early endosome à has proton pump à cause influx of H^+ (acidification) à cause changes w/in M2 protein
- M2 protein allow proton into virus
- Once protons inside à viral matrix dissociates
- Hemaglutanin à help in attachment
- M2 à help in matrix break down.
- Amantidine blocks uncoating. (M2)
- Neuraminidase à viral

Drugs for hepatitis – IFN-α, Adefovir, Lamivudine, Ribavarin

- **IFN-α**: glycoproteins produced by WBC; activate host cell ribonuclease that preferentially degrades viral mRNA; for Hep B (*alone or w/Lamivudine*), Hep C (*w/ribavarin*), Kaposi's sarcoma, Pappilomatosis, genital warts; Toxicity: GI irritation, flu like syndrome, bone marrow suppression

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- **Ribavarin**: triphosphate form inhibits viral RNA pol, used for RSV (aerosol), Influenza A&B & Chronic hep C infection (w/IFN);

Hepatitis B: Interferon –α, Lamivudine
Hepatitis C: Interferon –α, Ribavarin

MOA	Drug groups
Blocks viral penetration/uncoating	Amantadine, rimantadine, enfuvirtide, maraviroc
Inhibiting viral DNA polymerases	Acyclovir, foscarnet, ganciclovir
Inhibit viral RNA polymerases	Foscarnet, ribavarin
Reverse transcriptase inhibitors	Zidovudine, didanosine, zalcitabine, lamuvidine, stavudine, nevirapine
Integrase inhibitors	Raltegravir
Inhibit protease	Indinavir, ritonavir, saquinavir
Inhibit viral neuraminidase	Zanamavir, oseltamavir

Drug combos –

(1) Piperacillin & Ticarcillin for pseudomonas, enterobacter; synergistic w/AG's

(2) Amoxicillin DOC for H.Pylori infection (peptic ulcers in duodenum or stomach w/nausea, vomiting, confirmed w/urea breath test; given w/this, metronidazole, PPI); **Tx: omeprazole (PPI) + amoxicillin (B-lactam) + clarithromycin (macrolides); MUST GIVE ALL 3 together!* for 10-14 days (or PPI + busthmol) +metronidazole**
   a. **Tetracycline+ Metronidazole+PPI**
   b. **Metronidazole +amoxicillin+PPI**
   c. **Unless allergic to penicillin → Clarithromycin/amoxicillin+PPI**

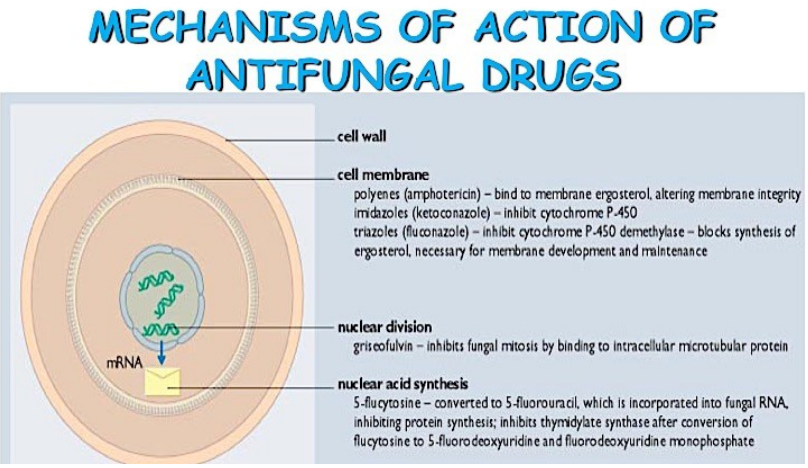
(3) **Imipenem + Cilastin [Carbapenems**: Imipenem, Meropenem, ertapenem, Doripenem; broad spectrum: GP & GN, anaerobes- Bact.fragilis (intra-abdominal, peritoneal infection, diverticulitis), clostridia]
   a. Imipenem: rapidly inactivated by renal dehydropeptidase I; always combined w/cilastatin to prevent hydrolysis by enzymes in renal brush border
   b. Cilastatin: inhibitor of renal dehydropeptidase thus ↑plasma ½ life of imipenem

(4) **AG's have good activity against GN aerobic bacilli but lack activity against anaerobes.** AG's have Synergistic axn w/b-lactam antibiotics
   a. *Enterococcal* infections (AG + PenicillinG / vancomycin)
   b. *P. aeruginosa* infection (AG + extended spectrum penicillin/cephalosporin)

(5) Antifolates**: Sulfadoxine +pyrimethamine (Fansidar)**: Chloroquine resistant serious/complicated *P.falciparum* Malaria tx'd by IV Quinidine

L10 Antifungal drugs & Fungal infections:

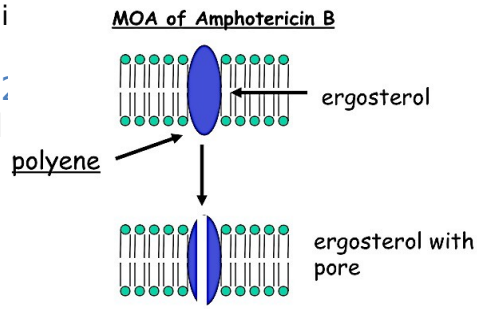
- ***Superficial mycosis***: Tinea versicolor, tinea nigra (Surface infections), candidiasis, Dermatophytosis like tinea corporis, tinea cruris, tinea pedis (cutaneous infections)
- ***Systemic mycosis***: candidiasis, cryptococosis, aspergillosis, mucormycosis, blastomycosis, histoplasmosis, coccidiodomycosis, paracoccidiodomycosis



A. Inhibitors of Fungal Memb Stability

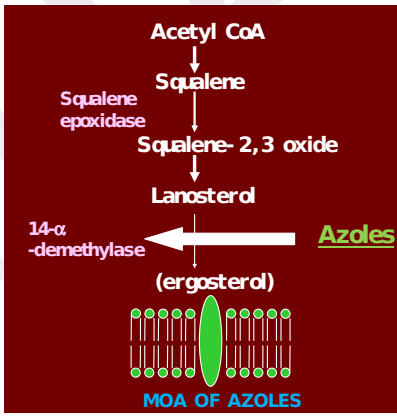
- **Amphotericin B**: polyene antifungal binds ergosterol in fungal cell memb to alter its memb permeability allowing leakage of IC components; rmr Ampho*TER*icin *tears* fungal cell memb; fungicidal w/broad spectrum of axn against *Aspergillus, candidia, cryptococcus, histoplasma,*

mucor, sporothrix; remains DOC for ~all life threatening fungal infections so shouldn't be used to treat noninvasive forms of fungal dis such as oral thrush, vagi candidiasis & esophageal candidiasis in pt's w/normal neutrophil counts; not absorbed orally, IV form must be admin'd slowly over period of ~2 hrs; or given intrathecally for CNS infections, but poorly tolerated newer therapies usually preferred; Liposomal formulations also for pt's intolerant to amphotericin B; Adverse efx:



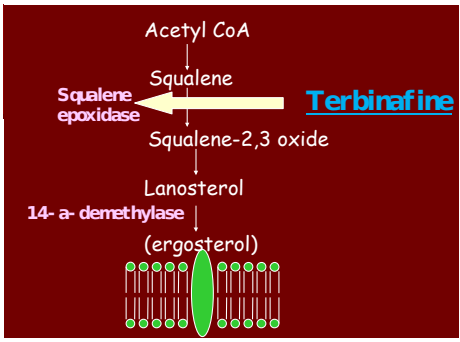
- Infusion rel'd: fever chills, m rigor, hypotension (release of histamine)
- Nephrotoxicity: dose dependent, ↓↓GFR, tubular acidosis, Hypokalemia, anemia by ↓↓EPO, can be avoided by using liposomal amphotericin B, combining w/flucytosine permitting ↓↓in AMB dose
- Uses for Aspergillosis, candidiasis, Cryptococcal meningitis (synergistic combo of amphotericin B/fluconazole+ Flucytosine)

- **Nystatin**: polyene antifungal; MOA similar to amphotericin B, disrupts fungal memb by binding to ergosterol; used Topically (as cream) to vaginal candidiasis; & orally to treat oropharyngeal candidiasis (swish & swallow); TV & OO;



B. Inhibitors of Ergosterol Synthesis

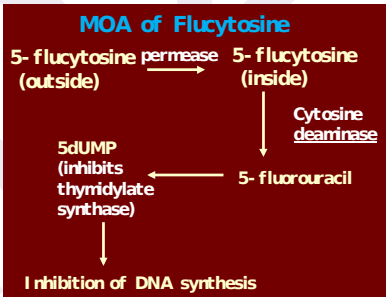
- **Azoles**: synthetic fungistatic agents w/broad spectrum activity; inhibit fungal CYP3A (lanosterol C-14-a-demethylase) that converts lanosterol to ergosterol; specifically inhibit at step of ***14α-demethylation of lanosterol;
  - Hypae: invasive & pathogenic form of fungi.
  - CYP 450 enzyme inhibitor, ESP **CYP3A4** – major drawback in KTZ
  - ***Topical Azoles***: **Clotrimazole**, **econazole**, **miconazole**: for candidiasis, dermatophytosis
  - **KTZ Ketoconazole**: azole inhibits fungal CYP3A (lanosterol C-14-a-demethylase) that converts lanosterol to ergosterol; when given orally, need acid env to dissolve drug; antacids can inhibit this; can't use for meningitis b/c doesn't enter CNS; systemic KTZ fallen out of clinical use in USA. But currently used as topical antifungal in creams for tx'ing dermatophytosis & candidiasis & as shampoo for tx of seborrheic dermatitis; **Also Endocrine use – Cushing's dis b/c blocks synthesis of GC's**; Adverse efx: gynaecomastia, loss hair & libido, oligospermia; DI's: CYP3A4 inhibitor inhibits metabolism of warfarin, sulfonylureas, cyclosporine, terfenadine; Rmr!!! Key to DI's (KTZ causes several ADR) thus Disadv: w/greater propensity to inhibit mammalian CYP450 vs other azoles
    - Oral absorption ↓↓by H_2 blockers, omeprazole PPI & antacids
  - **Fluconazole**: azole that inhibits fungal CYP3A (lanosterol C-14-a-demethylase) that converts lanosterol to ergosterol; well absorbed orally, enters CNS, least efx on liver enzymes, used orally, IV, eye drop as DOC in esophageal & oropharyngeal candidiasis, DOC for infections caused by Coccidioides, +vaginal candidiasis (single dose) & **cryptococcal meningitis** (in AIDS); less ADR & DI's vs KTZ (b/c not CYP inhibitor)
  - **Itraconazole**: azole that inhibits fungal CYP3A (lanosterol C-14-a-demethylase) that converts lanosterol to ergosterol; absorption ↓by food; CYP inhibitor - Drug-drug interaxns, similar to KTZ but to lesser degree; broad spectrum antifungal for fungal infections in immunocompromised & non-immunocompromised: Blastomycosis, pulm & extrapulm; Histoplasmosis, including chronic cavitary pulm dis & disseminated, non-meningeal histoplasmosis; Aspergillosis, pulm & extrapulm, in pt's intolerant of or refractory to amphotericin B; A/E: Minor GI upset
  - Miconazole, clotrimazole: azole that inhibits fungal CYP3A (lanosterol C-14-a-demethylase) that converts lanosterol to ergosterol; both used as topical cream
- Non-Azoles



- **Terbinafine**: prevents ergosterol synthesis as inhibits squalene epoxidase (for synthesis of ergosterol from squalene in fungal cell wall ▭ squalene accumulation ▭ toxic to organism ▭memb disruption & cell death); 1st line of therapy for Dermatophyte infections – tinea pedis/corporis/cruris/capitis & pityriasis versicolor concentrated in dermis, epidermis & given for longer time (6-12 weeks) for fungal infections of nails (Onychomycosis); orally & also available topical

C. Inhibitors of Fungal Cell Wall Synthesis: Echinocandins: Capsofungin, Micafungin; inhibit Fungal cell wall by **inhibiting synthesis of β-glucan**; used for tx of invasive Aspergillus in pt's who can't tolerate, or have failed therapy w/amphotericin B, & for oral & esophageal Candidiasis refractory to azoles & amphotericin B

D. Inhibitors of Fungal DNA synthesis



- **Flucytosine/5-Fluorocytosine (5-FC)**: anticancer drug which afx pyrimidine synthesis aka Pyrimidine antimetabolite rel'd to anticancer 5-FU; given orally, enters CNS rapidly; accumulated in fungal cells & converted to 5-FU by cytosine deaminase ▭5-FU inhibits thymidylate synthase (afx 5dUMP) thus inhibits fungal DNA synthesis; only for tx of serious infections caused by susceptible strains of Candida &/or Cryptococcus; fluconazole/amp B + Flucytosine (cryptococcal & candidial meningitis); Mechanism of resistance: ¬deaminase activity;Adverse efx: Bone marrow suppression (anemia, leukopenia & thrombocytopenia aka pancytopenia) ▭ aplastic anemia hence why lmtd to only severe fungal infections

E. Inhibitors of Fungal mitosis

- **Griseofulvin**: binds MT's comprising spindles & inhibits fungal mitosis, incorporates into affected keratin **so fungistatic in Dermatophyte infections of skin, hair, nails & feet**; **needs prolonged therapy (2-6 weeks) for efx** (rmr, standard tx always 6 weeks); CYP Enzyme inducer- induces metabolism of drugs (warfarin, OCT's); A/E Disulfiram like rxn w/alcohol

L11 Antimycobacterial drugs: 4 drugs, 4 mechanisms, 4 toxicities.

First line drugs – RIPES

- **Isoniazid (H): inhibits mycolic acid synthesis & mycobacterial cell wall; resistance: high lvl - due to deletions of *katG* gene -encodes catalase needed for bioactivation of INH bioactivation ; A/E: Hepatotoxicity (for all TB drugs! So close monitoring of liver enzymes imp***); side efx even in therapeutic dose, Peripheral neuropathy due to Vit B6 def (pyridoxine) as tingling & numbness in toes so supplement B6; Haemolysis in pt's w/G-6-PD def aka Hemoglobinuria; DLE (rashes, fever, arthraligia; similar to procainamide & hydralazine)…Plasma half-life in fast acetylators is 70 min & in slow acetylators is 2-5 hr…Slow acetylators develop more toxicity; INH can inhibit phenytoin metabolism so ⁷⁷ phenytoin efx**
- **Rifampicin/Rifampin (R)**: **inhibits DNA dependent RNA pol** (just like all Herpes drug & secondary from metronidazole); *Urine / body secretions/sclera becomes orange red but harmless just rel'd to chem'al nature so educate;* Uses: TB, Leprosy; 1st choice Prophylaxis of menigococcal & H.Influenza meningitis (to prevent carrier state), MRSA (1st choice is vancomycin), as alternative to isoniazid (1st choice) for TB prophylaxis (for close fam members & contacts of TB pt's); A/E: Hepatitis major side efx; Interaxn: CYP 450 (CYP 3A4) enzyme inducer - ▭Warfarin metabolism (causing coagulation failure) & oral contraceptive failure
  - **Rifabutin:** chemically rel'd to rifampin, for Prophylaxis of MAC infections in HIV pts
- **Pyrazinamide (Z):** prodrug … converted to active form pyrazinoic acid by pyrazinamidase (metabolically activated by bacteria); inhibits FAS I that makes FA from acteyl co A needed to

synthesize mycolic acid; esp effective against IC form of M. TB; A/E: Hepatotoxicity (1-5%) & ***Hyperuricemia*** (Gout)

- **Ethambutol (E):** inhibits synthesis of arabinogalactan (cell wall component); Mechanism of resistance– mutation in arabinosyl transferase gene; A/E: Optic neuritis – ¬¬visual acuity / colour blindness unable to distinguish b/w red and green traffic light, not used in children; & so monthly eye exam mandatory to track vision changes & is reversible! Optic neuritis & blindness are texicity of ethambutol. E for eye toxicity; resistance via mutated EMB gene
- **Streptomycin (S)**: 1st clinically available drug for tx of TB; now least-used 1st-line drug b/c toxicity (ototoxicity, nephrotoxicity), difficulty to achieve adequate CSF lvls & inconvenience of parenteral admin; AG that inhibits protein synthesis; A/E: Has to be given IM everyday – disliked, Painful, ototoxicity- deafness or vestibular dysfunc & nephrotoxicity; used only in resistant, severe, disseminated tubercular meningitis or when other drugs cannot be used

Second line –used in resistant cases (MDR tuberculosis) refractory cases which cannot be cured after therapy, pt's not tolerating standard therapy, defaulters, or in AIDS

Ethionamide
Cycloserine
Kanamycin
Capreomycin
Aminosalicylic acid (PAS)

Newer drugs: **Amikacin, Ciprofloxacin, Levofloxacin, Ofloxacin**, **Azithromycin, Clarithromycin**

- Treatment of TB:
  - Conventional regimen for 12-18 months, cheaper, high failure rate rarely used
  - Short course chemotherapy (SCC) for 6-8 months
  - *Direct observed therapy (DOT):* direct observation of each dose taken by pt in presence of observer, usually representative of health dept. In U.S. DOT is standard of care for TB tx.
- Short course chemotherapy:

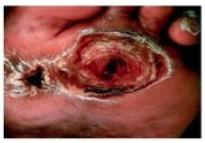
Six months

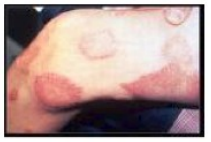
- **1st phase: 2 mo's (Induction) – HRZE – 4 drugs together in 1st 2 mo's; always w/B6 to prevent peripheral neuropathy**
- **2nd phase 4 mo's (Continuation) – HR..**
- 1st 2 mo's intensive therapy w/daily 4 drugs ..HRZE, aimed to rapidly kill mycobacteriae, cause sputum conversion, & give symptomatic relief (Sputum positivity indicates infective stage)
- Last 4 mo's maintenance therapy w/daily 2 drugs ..HR..to prevent relapse

Tuberculosis in AIDS**

- Lifelong prophylaxis w/**Rifabutin** to prevent MAC infection AIDS
- Tx of MAC in AIDS = Clarithromycin (or Azithromycin) + Ethambutol given life long

Drugs for Rx of Mycobacterium Avium complex infection
Azithromycin
Clarithromycin
Ethambutol
Rx : Clarithromycin/azithromycin + Ethambutol
given life long
Prophylaxis(CD4<50): 1st choice- azithromycin alternative- Rifabutin Lifelong****



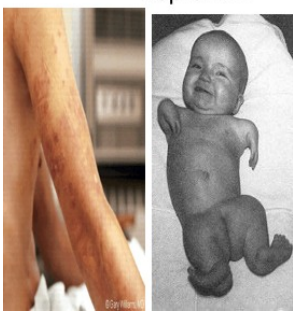


LEPROSY : (Hansen's disease)

- ***Leprosy (either Lepromatous Leprosy or TB Leprosy):*** chronic granulomatous infectious dis caused by Mycobacterium Leprae afx skin, mucus memb & peripheral n's; **dx via** clinical exam & Smear exam
  - **Sulfones: Dapsone:** MC'ly used, Highly active drug; chem'ally rel'd to sulfonamides & same MOA (inhibits folic acid synthesis – dihydropteroate synthase); also treats Pneumocystis pneumonia in HIV pt's
    - Adverse efx: HSR's, Hemolytic anemia in G-6-PD def pt's, & Lepra rxn
    - *Lepra rxn:* Jarish Herxheimer (arthus) rxn due to release of Ag's from killed bacilli via TNF* ⇒ Fever, malaise, enlarged LN's, extreme jaundice, anemia, severe form called *Erythema Nodosum Leprosum;* Tx w/***Clofazamine** or **Chloroquine** or **Thalidomide** or **Corticosteroids***
      - **Thalidomide:** immunologic efx rel'd to: **suppression of excessive TNF-α production, down-reg of selected cell surface adhesion molecules involved in leukocyte migration, &** anti-angiogenic efx; i**ndications:**
        - **multiple myeloma**: tx w/combo of thalidomide & dexamethasone effective 1st-line induction regimen
        - skin manifestations of **lupus erythematosus**
        - tx of **cutaneous manifestations of moderate to severe Erythema Nodosum Leprosum (ENL), condition associated w/tx of leprosy (Hansen's dis)**.
        - ENL is rxn caused by immune resp to Ag's produced by destruction of mycobacterium bacilli; typically includes signs & sx of fever, painful skin nodules, arthralgia & peripheral neuritis.

        Contraindications: Pregnancy category X; IF THALIDOMIDE IS TAKEN DURING PREGNANCY

Lepra rxn



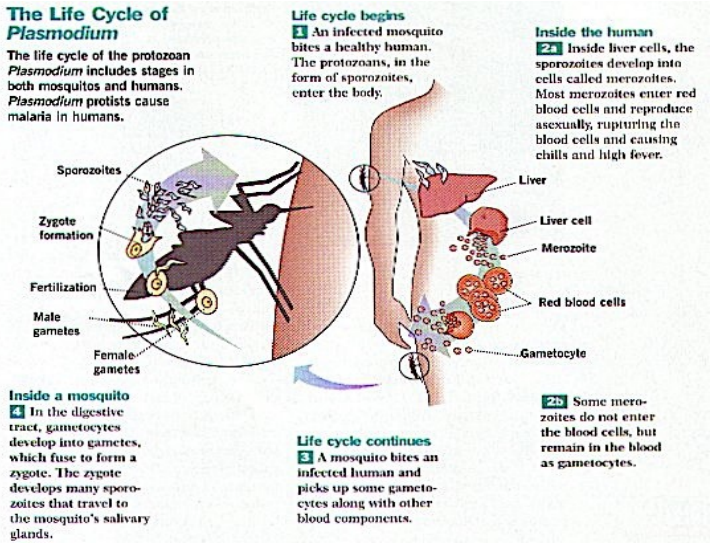
  - **Dye: Clofazimine:** dye w/leprostatic & anti-inflammatory axns; binds to DNA & inhibits template func, generates cytotoxic oxygen radicals toxic to bacteria; long half life------70 days; also used in lepra rxns; cause Reddish Black discoloration of skin.
  - **Anti tubercular: Rifampin**
  - LEPROSY TX: Till 1981 Dapsone alone used as mono therapy. Now Multi Drug Therapy (MDT)
  - Multibacillary Leprosy (MBL): infectious, Lesions w/lot of bacilli *(Rx for 24 months)*
    - Dapsone - daily once
    - Clofazimine--- once a day, self admin
    - Rifampin---once month under supervision
  - Paucibacillary Leprosy (PBL): Noninfectious, Lesions w/less bacilli (*Rx for 6 months)*
    - Dapsone -daily once
    - Rifampin---once month under supervision

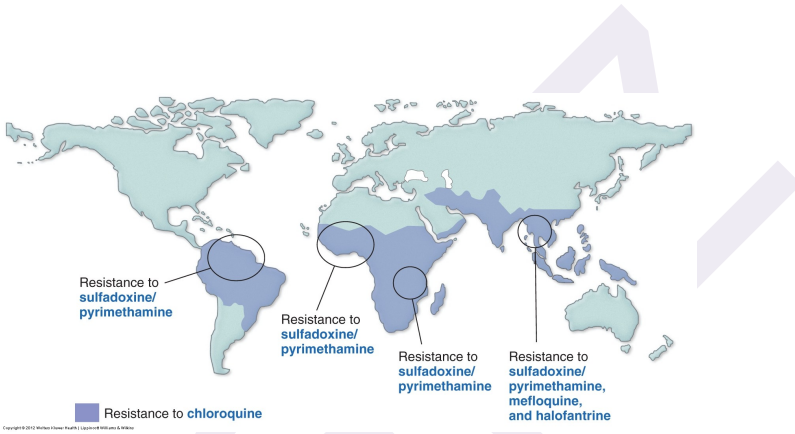
L12 Antiprotozoal (focus on tx & prophylaxis***), Antihelminthics

- **Malaria: via mosquito bites ⊔ introduce sporozoites ⊔ go in blood cells as merozoites ⊔ once rupture out rbc's ⊔ fever spikes! These merozoites can enter back to liver & remain dormant – these are hypnozoites (seen in vivax & ovale);**

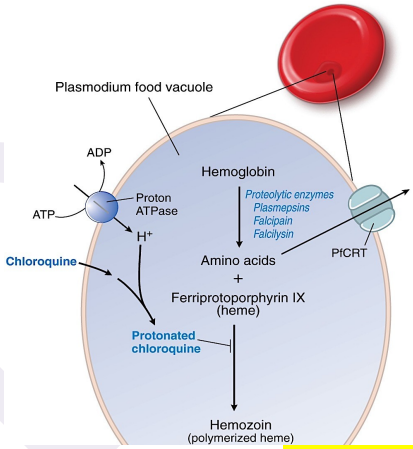
asexual cycle in host; sexyal cycle in mosquito; rbc form are erythrocoites; hypnozoites are dormant forms – must give drugs to kill both forms; can be caused by –

- **P.falciparum (severe, carebral malaria), P.malariae (quartan malaria)**
- **P. Vivax, P.ovale (tertian malaria, Relapses) – only these can remain dormant in liver**





- **Drugs used – ALL antimalarials kill plasmodia in rbc's – blood/erythrocytic schizontocides – used for clinical cure & chemo prophylaxis**
  - 4-Aminoquinoline: **Chloroquine/Hydroxychloroquine**: **given for 3 days**; undergoes protonation that accumulates in food vacuole of parasite & prevents conversion of heme to hemozoin. Heme accumulation leading to death thus for **tx of chloroquine sensitive malaria (explained below), & also** Amoebic liver abscess (but used for 10-15 days), RA (longer duration); ***resistance to via Mutated P. falciparum chloroquine resistant transporter (pfcrt) (K76T) pumps protonated chloroquine out food vacuole; Adverse efx: Retinal damage – periodic retinal exam mandatory in long term use (as immunosuppressant in RA or Amoebiasis)
    - *P.falciparum & P.malariae tx w/*Chloroquine alone
    - *P. Vivax & ovale tx w/*Chloroquine + Primaquine (to prevent relapses) – ONLY 2 TO REACTIVATE – VIVAX MOST ASKED ABOUT*



Mechanism of heme metabolism in plasmodial food vacuole:
Plasmodium has food vacuole in which it uses human Hb to form AA's. Degradation of Hb releases heme which plasmodia polymerize into nontoxic hemozoin.

Chloroquine – freely enters food vacuole, in acidic env it's protonated making it unable to diffuse out of vacuole (it accumulates in [high] in food vacuole) & prevents polymerization of heme to hemozoin

Mechanism of Chloroquine resistance: mutated

  - 8-Aminoquinoline: **Primaquine:** only antimalarial as tissue schizontocides (kills exoerythrocytic hypnozoites), thus ONLY drug that prevents relapse of infection; tissue schizontocide; only active agent against dormant liver forms of **vivax & ovale** (HYPNOZOITES); only drug used to prevent relapse of vivax & ovale; adverse Efx: Hemolysis & Methemoglobinemia in G6PD def pt's

Remaining drugs below: mainly for Tx of Chloroquine resistant cases:

- **Cinchona alkaloids: Quinine, Quinidine** (+anti-arrythmic): oral quinine primary drug for chloroquine resistance P. falciparum; derived from bark of cinchona (alkaloid); QUINIDINE is d-isomer of Quinine; Quinidine given IV'ly in tx of severe, complicated Chloroquine resistant P. falciparum malaria; A/E: CINCHONISM [Tinnitus, vertigo, double vision, headache, flushed & sweaty skin, dizziness, visual disturbances, hypoglycemia, arrhythmias], Hemolysis in G6PD def pt's & rarely BLACKWATER FEVER (massive Intravascular haemolysis – fatal complication)
- **Mefloquine**: given only orally, long half life of 20 days; Adverse efx: Syncope, extrasystoles; Contraindicated – psychosis, seizures, cardiac conduction dfx
- Artemisinin derivatives**: atresunate, artemether**: from Chinese herb; best in MDR; not prophylaxis
- Antifolates**: Fansidar = Sulfadoxine +pyrimethamine**: for Chloroquine resistant malaria of serious/complicated *P.falciparum* tx'd by IV Quinidine initially

Others:

- Tetracyclines **Doxycycline**:

- Malaria Prophylaxis (recommended by CDC):
  - 1. *Chroroquine sensitive regions*: Chloroquine +/- Primaquine: 1-2 weeks b4 departure, weekly during stay & 4 weeks after leaving endemic area
  - 2, *Chloroquine resistant regions*:
    - **Mefloquine**: 1-2 weeks b4 departure, weekly during stay & 4 weeks after leaving endemic area; don't give Quinine for such a long time b/c causes cynchonism & toxic
    - **Proguanil+Atovaquone (Malarone)**: 1-2 days b4 departure, daily during stay & 7 days after leaving endemic area
  - In Pregnancy: all drugs used except doxycyline & primaquine

Pneumocystosis Jiro: tx w/Drugs used TMP-SMX (Cotrimaxozole)- first choice, Pentamidine (2nd), Pyrimethamine plus sulfadiazine, Atovaquone, Primaquine + Clindamycin

Amebiasis & their tx's

Tissue amoebicides

- *****Metronidazole**: given orally & IV infusion, generates & accumulates free radical toxic metabolites in bacterial cell which damage DNA; for All Amebiasis forms (in colon & liver) +Trichomonas vaginalis, Giardiasis (diarrhea) & 1st choice for Anaerobic bacteria – B.fragilis, Cl.difficile, H.pylori peptic ulcers; DI's: *disulfiram like rxn* w/alcohol, Metallic taste, GI distress, convulsions, insomnia, peripheral neuropathy & thrombophlebitis
- ***Tinidazole*, Chloroquine, Emetine, Doxycycline**

Luminal amebicides

- ***Diloxanide furoate*: tx w/Iodoquinol or Paromomycin**
- **Amoebic colitis: tx w/Metronidazole + Diloxanide furoate**
- **Asymptomatic amoebic: tx w/Diloxanide furoate alone**
- **Hepatic Amebiasis: Metronidazole + Chloroquine (combo very effective in killing liver forms) + Diloxanide furoate**

Leishmaniasis: tx w/sodium stibogluconate
Giardiasis: tx w/Metronidazole/tinidazole
Toxoplasmosis: tx w/Pyrimethamine + Sulfadiazine, or TMP-SMX

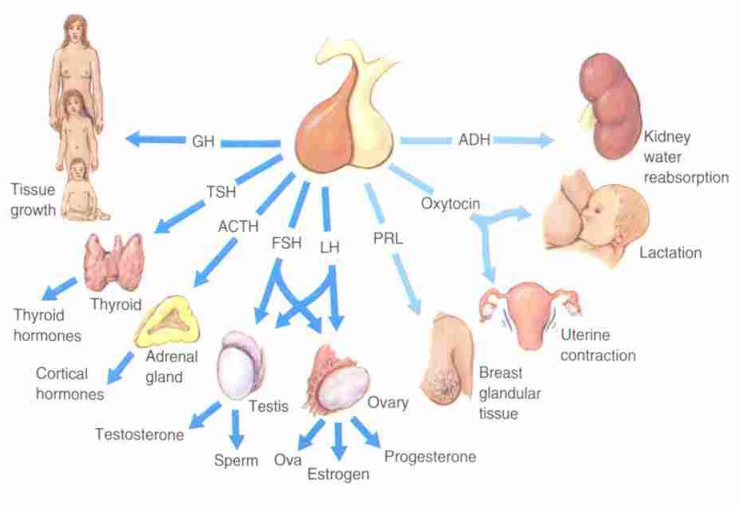
Trypanosomiasis tx w/

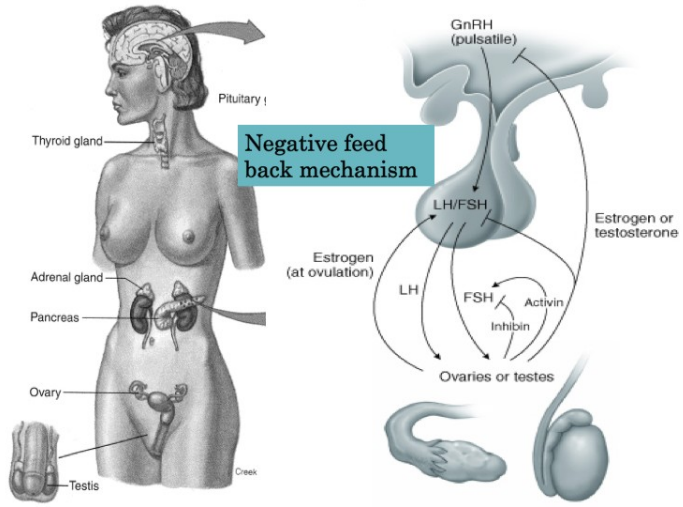
- **Melarsopral for African sleeping sickness (late CNS stage of trypanosomiasis)**
- **Suramin, Pentamidine for haemolymphatic stage of trypanosomiasis**
- **Nifurtimox for *T. Cruzi (Chagas' dis)***

Drugs for Helminthic infections:

- Drugs for intestinal nematodes (*ascaris lumbricodes, Ankylostoma duodenale, strongolides stercoralis, Trichinella spiralis, enterobius vermicularis*) tx w/*Mebendazole, albendazole* & *Pyrantel palmoate (MAP)*
- Drugs for tissue nematodes
  - *W.bancrofti (Filariasis), Loa Loa, Toxocara canis*: Diethylcarmazine
  - *Onchocerca Volvulus*: Ivermectin
  - *Drancuncula medinensis*: Niridazole
- Drugs for Cestodes (tapeworms- *taenia solium, Diphyllobothrium latum, Echinococcus*) & trematodes (flukes-*Schistosoma*)
  - *Praziquantel* preferred (for both cestodes & trematodes)*
  - *Niclosamide (for cestodes)*

L13 Endocrine Pituitary





JAK STAT for GH & PRL???

▭ Ant pituitary ▭ makes* & releases GH, PRL, & Gn's (FSH & LH) ▭ Post pituitary ▭ stores & releases vasopressin/ADH & Oxytocin	Negative feedback by these hormones: ▭ GRIH (GH release inhibitory hormone) ▭ GnRH (Gonadotropin releasing hormone ▭ PRIH (PRL release inhibitory hormone/ D

▭ Thus 8 imp hormones:

1. **GH**: MOA thru releasing **IGF**/Somatomedins (IGF-Insulin Like GF's; made in liver),
   1. ▭▭▭GH causes Gigantism, Acromegaly
   2. ▭▭▭GH Def causes pituitary dwarfism
   3. Drugs: recombinant forms of GH. Eg: Somatropin & Somatrem; uses GH drugs –
      1. Pituitary dwarfism
      2. *Laron's dwarfism*: AR mutant GH receptor ▭ insensitivity to GH; causes short stature & ▭sensitivity to insulin; unlikely to develop DM type 2; tx w/Somatomedin or IGF-1 analogues Mecasermin
      3. Catabolic states w/excess protein loss: Severe burns, CRF, osteoporosis, bed ridden pt's
      4. Prader-Willi Syndrome: rare genetic 7 genes on chr 15 (q 11–13) deleted or unexpressed on paternal chr. CF's: low m tone, short stature, incomplete sexual dev't, cognitive disabilities, behavior problems & chronic feeling of hunger that can lead to excessive eating & life-threatening obesity
      5. Turners
      6. Idiopathic Short Stature (ISS): controversial
   4. **GH receptor antagonist: Pegvisomant**: used for acromegaly; rmr it won't ▭GH lvl (instead ▭efx of it & blocks its receptors*** so ends up, rather ▭GH in serum b/c can't use it)

2. **GRIH (inhibitory/GHRIH)/Somatostatin**: released from hypothalamus (& also pancreas) & inhibits GH secretion from pituitary; Preparation of Somatostatin has very Short half life (1-3 mins); wonder if its excess released in Carcinoid syndrome/tumors
    1. **Octreotide**: synthetic somatostatin analogue, overcomes very short half life (1-3 mins) problem of somatostatin; 45X more potent & longer half-life (80 mins) than somatostatin; side efx: gall stones, steatorrhea; both used *for acromegaly, carcinoid tumors/carcinoid syndrome, esophageal varices*, diabetic diarrhea (can ¬¬secretions, in diabetic diarrhea is highly secreted)
3. **PRL (Prolactin):** released from Ant pituitary; stimulated by TRH (that also ↑TSH) excess PRL produces Hyperprolactenemia charac'd by amenorrhea, infertility, galactorrhea, gynecomastia **&** loss of libido, due to prolactinoma (MC pituitary adenoma) & also caused by drugs like DA antagonists (ie. haloperidol)
4. **PRIH/DA (inhibitory):** released from Hypothalamus; inhibit PRL release from pituitary; so DA agonists **Bromocriptine** & Cabergoline used as PRIH in tx'ing Hyperprolactenemia
    1. **Bromocriptine & cabergoline**: potent DA agonists, act like PRIH; ¬¬PRL release, ⏚GH in normal persons but ¬¬GH in Acromegaly (2nd choice/add on, 1st choice always octreotide); **treats** Hyperprolactenemia, Galactorrhea, Acromegaly, Parkinsonism, to suppress milk production in stillborn
5. Gonadotropins (Gn)- FSH, LH,
6. Oxytocin: secreted from post pituitary gland along w/ADH, required for Initiation /facilitation of labour; contracts upper pt & relaxes lower pt of uterus thus facilitates fetal expulsion b/c produces Intermittent contractions, won't cause foetal asphyxia. Why do you prefer this over ergots for induction of labor?? **USED** in addition to PG's, IV infusion of oxytocin **induces labour** to have early vaginal delivery in PET, postmaturity, Rh problems, uterine inertia & incomplete abortion, just to deliver baby at time mother wants; Used in PPH (Post partum haemorrhage too) but **Ergonovine best choice over oxytocin, otherwise use oxytocin; Adverse efx: uterus rupture in excess dose or in obstructed labour
    1. **Ergonovine**: ergot alkaloid, has nothing to do w/these hormones; produces continuous contractions of uterus & contracts both upper & lower pt which for normal birth delivery, can lead to foetal asphyxia. thus not good for induction of labour; hence used IM'ly in PPH & Placental retention only; MOA: Acts thru α or 5-HT receptors, & H
    2. ***OXYTOSICS*** or ***ECBOLIC*** agents = drugs used to induce labor. or *Abortifaciants* if used for abortion. Eg: Oxytocin & PG's like Dinoprostone, Ergonovine as 2ndary
    3. ***Tocolytic*** agents: (toco = tone; lytic = break/¬¬) hence uterine relaxants, Eg: Beta-2 agonists, alcohol & CCB's: used to postpone labor in premature deliveries
7. **Vasopressin/ADH:** post pituitary hormone secreted along w/Oxytocin (Both hormones made in hypothalamus), acts thru V_1 (in blood Vessels) & V_2 (kidney Collecting duct)
    1. ****Desmopressin- 12X more potent, predominantly acts on V_2, longer acting, intranasal spray; more commonly used; **for ****central/neurogenic DI**, Nocturia, Bleeding oesophageal varices, Haemophilia & vonWillbrand's dis (b/c extrarenal V2 receptors when stimulated ⏛ release Factor VIII & vWF);
    2. Lithium induced Nephrogenic/Peripheral DI (mutated V2 receptors) often caused by Lithium in pt's being tx'd for Manic Bipolar disorder; tx'd by amiloride (interferes w/sodium channels causing oddly paradoxical efx) promoting anti-diuresis
    3. **Non-specific induced Nephrogenic/Peripheral DI**: tx'd w/thiazide diuretics causing oddly paradoxical efx) promoting anti-diuresis

L14 Gonadotropins (Gn), GnRH & Gonadal hormones

⏛***FSH func's***: induce follicular growth, dev't of ovum, secretion of estrogen, regulates spermatogenesis in men; ↑conversion of androgens to estrogens by granulosa cells

⏛***LH func's***: ovulation, maintain corpus luteum, progesterone secretion & testosterone secretion; ↑androgen production by theca cells in follicular stage of menstrual cycle

▫ ***hCG (Human chorionic gonadotropin):*** placental glycoprotein identical w/LH; mediated thru LH receptors
▫ In ovary, LH ↑androgen production by theca cells in follicular stage of menstrual cycle, whereas FSH ↑conversion of androgens to estrogens by granulosa cells. In luteal phase of menstrual cycle, estrogen & progesterone production primarily under control 1st by LH & then, if pregnancy occurs, under control of hCG

Recombinant human FSH, LH & hCG are the drugs

1. Follicle stimulating hormone
    1. Urofollitropin (uFSH) – human FSH obtained from urine of post menopausal women
    2. Recombinant human FSH- follitropin α & follitropin β
2. Lutenizing hormone
    1. Lutropin
3. Menotropins: FSH + LH
4. Human Chorionic gonadotropin: hCG

▫ Use of Gonadotropins: Recombinant human FSH, LH & hCG are drugs

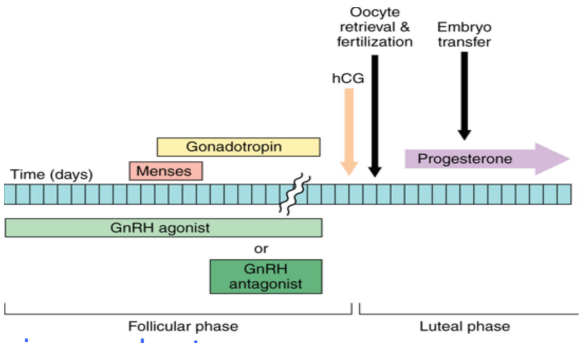
- Infertility due to anovulation, Polycystic ovarian dis, In Vitro Fertilization
- Male infertility- Hypogonadism in males-hCG
- hCG promotes descent of testes in cryptorchism (undescended testes)

▫ LH & FSH have complex efx on reproductive tissues in both sexes. In women, these efx change over time course of menstrual cycle as result of complex interplay among concentration-dependent efx of gonadotropins, cross-talk of LH, FSH, & gonadal steroids & influence of other ovarian hormones. Coordinated pattern of FSH & LH secretion during menstrual cycle is required for normal follicle dev't, ovulation & pregnancy.
▫ During 1st 8 weeks of pregnancy, progesterone & estrogen required to maintain pregnancy & produced by ovarian corpus luteum. For 1st few days after ovulation, corpus luteum maintained by maternal LH. However, as maternal [LH]'s fall owing to ⏚ [progesterone & estrogen], corpus luteum will continue to func only if role of maternal LH taken over by hCG produced by syncytiotrophoblasts in placenta.

▫ GnRH: Main func of this hormone is to stimulate release of FSH & LH from ant pituitary; released from hypothalamus in *PULSATILE* manner

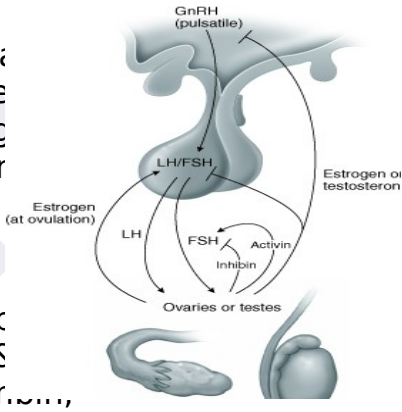
- **GnRH preparations**: (GnRH Agonists): Commercially available preparations are of 2 types –

1. ***Drugs released in body in pulsatile manner***, just like physio'al GnRH. Thus axns of this drug similar to GnRH – stimulation of gonads. Eg: Gonadorelin; Uses of **Gonadorelin** (& relins): Used in clinical conditions **to stimulate gonads**, used for Hypogonadism, Delayed puberty & Cryptorchism
2. ***Drugs released in body in continuous manner unlike physio'al GnRH***. *Eg: Leuprolide*. Continuous release of GnRH has opposite axns of pulsatile release of GnRH. Thus axns of leuprolide opp of normal GnRH which is **suppression of gonadal func's** ****Note: Initially ↑gonads but eventually suppresses gonads; **used in many clinical conditions wherever suppression of gonads is required**
    - Carcinoma of prostate & breast
    - IVF (In vitro fertilization): **prevent premature surges of natural LH**; Controlled ovarian stimulation in preparation for assisted reproductive technology such as IVR. Follicular phase: Follicle dev't stimulated w/gonadotropin injections that begin ~2 days after menses begin. When follicles ready, assessed by US measurement of follicle size, final oocyte maturation induced by injection of hCG. Luteal phase: Shortly thereafter oocytes retrieved & fertilized in vitro. Recipient's luteal phase supported w/progesterone injections. To prevent premature LH surge, endogenous LH secretion inhibited w/either GnRH agonist or GnRH antagonist. In most protocols, GnRH agonist started midway thru preceding luteal cycle



- Precocious puberty
- Fibroid uterus
- Endometriosis but ******Note: Actually ****_Danazole_ is better DOC in endometriosis
  - **Danazol: acts on ovaries to inhibit LH & FSH? & inhibits P-450c17**

➢ **GnRH antagonists**: block GnRH receptors so only suppress & no initial stimulation of gonads (unlike leuprolide); **Eg: *Cetrorelix & Ganirelix***; uses similar to leuprolide



Gonadal hormones: estrogen, progesterone, testosterone; normal ova produces small amts **androgens**, including testosterone androstenedione dehydroepiandrosterone. Of these, only testosterone has sig amt of biolog activity, altho androstenedione can be converted to testosterone or estror peripheral tissues. Ovary also produces **inhibin** & **activin. Relaxin** is another peptide that can be extracted from ovary.

➢ **Estrogen** & its physio'al efx: dev't of female reproductive tract, secondary sex charac's, proliferative changes in endometrium, retard b resorption, sodium & water retention, Cardioprotection (↓LDL ↑HDL), & enhance coagulability of blood by ↑factors II, VII, IX & X & ↓ anti-throm..., used in primary hypogonadism, ***used as hormonal contraceptives, ***used as **HRT**) in menopause; estrogen preps –

- **1. Natural estrogens:** Estradiol, Estrone, Estriol
- 2. Synthetic estrogens (Synthetic steroidal): Ethinyl estradiol*****, Mestronol**** & Quinestrol*****
- 3. Synthetic Non steroidal estrogens: Diethyl Stilbesterol
- Adverse efx: Nausea, vomiting, migraine, ↑risk of MI, stroke, gall stones, pulm embolism, ****Ca Breast, & most imp'ly endometrial hyperplasia w/↑risk of endometrial cancer****** - Progesterone preparations have opp efx on endometrium, so prevent endometrial proliferation. Rather makes endometrium more secretary. SO along w/estrogen we add progesterone in HRT. So estrogens efx on endometrium is counteracted by progesterone

➢ **HRT**: supplementation of very low dose estrogen to prevent or treat menopausal syndrome; Conjugated estrogens/ ethinyl estradiol– first 21-25 days of each month + progestin (medroxy progesterone acetate) – last 10-14 days; b/c estrogen will compensate endometrial hyperplasia**** (ANSWER)

➢ **Post menopausal syndrome**: charac'd by irritability, loss skin turgor, dry skin, dry vagina, mood instability & fragile bones, osteoporosis, frequent bone fracture, vasomotor disturbances, urogenital atrophy, Skin changes, depression, ↑ risk MI, stroke

Anti estrogens & SERMS

➢ **Antiestrogen** = substance that blocks production or utilization of estrogens or inhibits their efx; **3 imp drugs in this class are**:

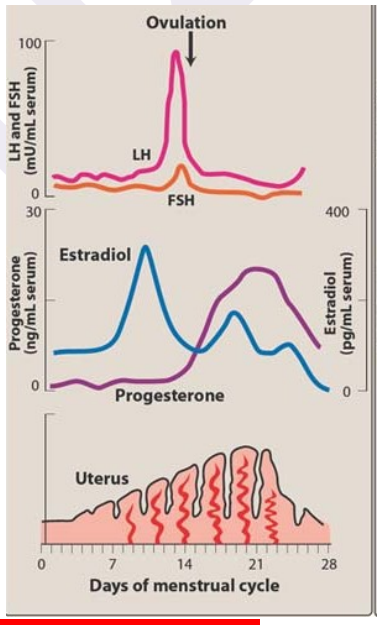
- **Clomiphene citrate** (Clomid, Serophene): *antiestrogen* competitive antagonist at estrogen receptors *↑follicular dev't for ovulation induction;* blocks –ve feedback receptors in hypothalamus & pituitary ↓↑GnRH secretion ↓↑FSH & LH thus ↑chances ****ovulation**, used for anovulatory cycles – woman not passing on ovum even tho

menstruating regularly; facilitates release of ovum & overcomes infertility anovulatory cycles cause. Uses: **Infertility w/anovulatory cycles, IVF & Sterility**

- **Tamoxifen**: blocks estrogen receptor on breast thus best used in ****Breast cancer (esp estrogen/ Her2/neu receptor +ve) b/c agonistic efx on endometrium, but risk of **endometrial hyperplasia & cancer**
- **Raloxifen**: treats ***osteoporosis in post menopausal women; no risk of carcinoma of endometrium or breast, b/c has *agonistic* axn only on bone (¬¬bone resorption & improving bone mineral density) & *antagonistic* axns *on breast & uterus so excellent choice for preventing breast Cancer & OP*

➢ **SERMS:** selective Estrogen Receptor Modulators: Estrogens acting as agonist at some tissues & partial agonist or antagonist at other tissues; includes Tamoxifen & Raloxifene; adverse efx: hot flashes, VTE, & endometrial hyperplasia & cancer (only Tamoxifen)

➢ **Anastrozole**: aromatase inhibitor; also, loosely labeled antiestrogen; inhibits aromatase (that converts androgens into estrogens via aromatization); used in estrogen-sensitive breast cancers, following surgery or metastasis, more so in postmenopausal women



➢ *****Natural: Progesterone & physio'al efx**: secretory changes in Endometrium, Alveolobular dev't of secretory apparatus in breast, ovulation inhibition, ⏚body temp & Antineoplastic axn prevents endometrial carcinoma; preps used as hormonal contraceptives & in HRT (to counteract adverse efx of estrogens, ie. endometrial cancer); **has 2 main types of Synthetic –**

1. ***Progesterone derivatives*** –
   a. Megestrol
   b. Hydroxy progesterone caproate
   c. Medroxy progesterone acetate
2. ***19-nortestosterone derivatives*** –
   - Norethindrone, Levonorgestrel
   - Desogestrel, Norgestimate

⏚ Adverse efx: breast engorgement, irregular bleeding, ¬¬HDL lvls – atherogenesis seen mostly w/more androgenic progestins such as Medroxyprogesterone

➢ **Antiprogestins**: **eg. Mifepristone (RU486): MOA**: competitively inhibits progesterone receptors; GC receptor antagonist; **Used as (1)** Medical termination of early pregnancy: given along w/misoprostol, dislodges fetus, ↓hCG, causes Cervical softening **& (2)** Used as postcoital emergency contraceptive pill

➢ **Hormonal contraceptives (OCT's):** contain estrogen or progesterone or both in varied dose; inhibit release of FSH & LH, change Cervical mucus – thick & hostile for sperm penetration, Endometrium – hypersecretory – no implantation; Uterine & tubal contractions – prevent fertilization; & High dose estrogen – dislodge blastocyst (no period! Oddly can be used for that too)

1. **Combined pills:** *Ethinyl estrodiol* or *Mestronol plus* 1 of progestins (**19-nortestosterone derivatives**)
   1. diff types of combined pills – Monophasic, Biphasic & Triphasic
   2. **monophasic** forms (constant dosage of both components during cycle) & **biphasic** or **triphasic** forms (dosage of 1 or both components is changed once or twice during cycle).
   3. **Contraception w/Progestins Alone**: small doses of progestins admin'd orally or by implantation under skin can be used for contraception; particularly suited for use in pt's for whom estrogen admin is undesirable
2. **Post coital pill** (morning after pill): ****High doses of *estrogen* for 5days or single dose of *Mifepristone***

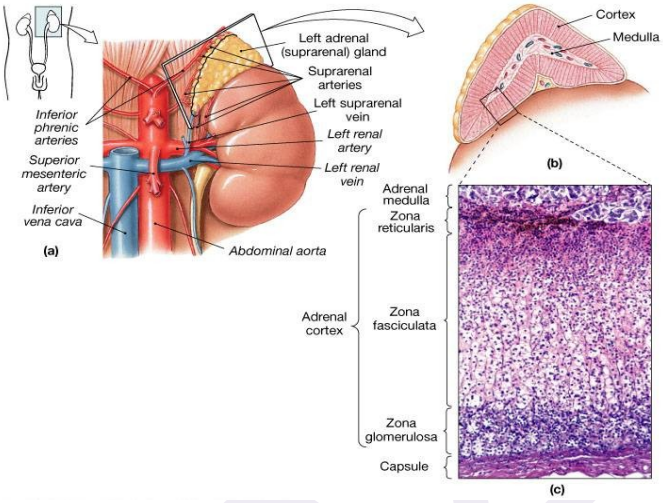
serious Adverse efx of contraceptive pills: DVT, ↑in BP, Gall stones, ↑chances of MI, esp w/smoking
↓ Mild side efx: Nausea, vomiting, mastalgia –related to estrogen amts; Headache, worsening of migraine sx
↓ Moderate side efx: Breakthru bleeding – common w/progestin only preparations, Weight gain & Acne –exacerbated - common w/androgen like progestins, ↑skin pigmentation, Hirsutism – common w/19-nortestosterone derivative progestins
Severe side efx: Venous thromboembolic dis- overall incidence is 3X ↑ in women taking contraceptives, Attributed to estrogens- ↑coagulability of blood ¬↓ATIII; MI- progestional component- ¬↓HDL; Cerebrovascular dis, Cholestatic jaundice, hepatic adenomas- progestin containing drugs

- **Androgens: Testosterone** & physio'al axns: 2ndary sexual charac's, Spermatogenesis in testes, ↓HDL, anabolically ***Rapid bone growth***, ↑m mass, promotes nitrogen retention, ↑appetite; **drugs: Methyl testosterone, Testosterone propionate & cypionate**
- **Anabolic steroids*****:** synthetic androgens w/higher anabolic & lower androgenic activity; relative androgenic: anabolic activity of testosterone 1:1; same for some other drugs could be 1:3, 1: 4 1:13 etc; Eg: **Nandrolone decoanate, Oxandrolone & oxymetholone**; used in Osteoporosis, ACD seen w/malignancy, renal failure & aplastic anaemia, Catabolic states & Abused in sports (MCC of erectile dysfunc)
  - **Oxandrolone:** for males w/primary androgen def; when abused however causes impotence after pt stops abusing it –

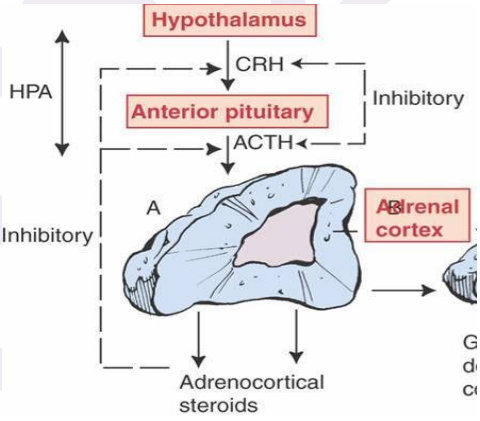
******Antiandrogens or Testosterone Antagonists:**
- **Finasteride**—5-α reductase inhibitor for BPH & hirsutism. 5-α reductase need for activating testosterone to DHT, so can't activate testosterone to DHT
- **Flutamide**— testosterone Receptor blocker/antagonist on prostate for prostate Ca; leprulide also used along w/this which initially ↑GnRH receptors ↓ ↑LH & FSH w/testicular androgen production & bind androgen receptors on tumor cells, during this flare – exacerbate sx but then downreg GnRH receptors & ¬gonadotropin secretion ↓ testosterone [ ]'s equivalent to that after castration
- Other drugs w/antiandrogen axn:
  - **Spironolactone:** competes w/DHT for androgen receptors in target tissues; also ¬17α-hydroxylase activity ↓¬plasma lvls of testosterone & Androstenedione; used in tx of hirsutism in women
  - **Cyproterone acetate:** used in women to treat hirsutism & in men to ¬excessive sexual drive
  - **KTZ:** doesn't affect ovarian aromatase, but ¬human placental aromatase & displaces estradiol & DHT from sex hormone-binding protein in vitro & ↑estradiol:testosterone ratio in plasma in vivo by diff mechanism; inhibits P-450c17

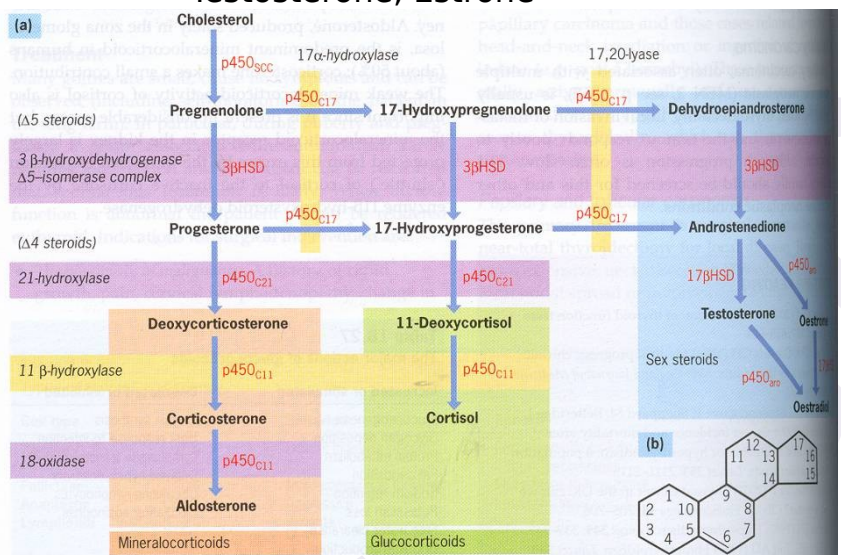
L15 Corticosteroids

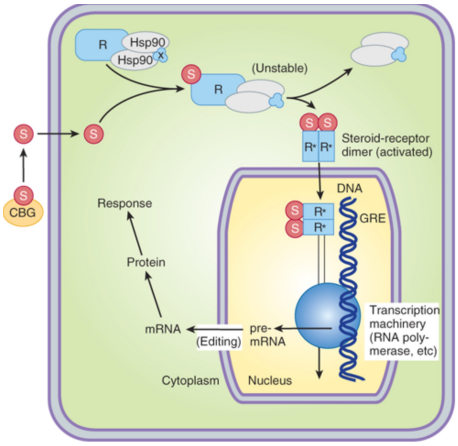
- Salt, sweet, sex = G F R
- HPA (Hypothalamic Pituitary Adrenal Axis) as Autoreg in Adrenals ↳ as Corticotropin releasing factor (CRF) from hypothalamus ↳ Adrenocorticotropic hormone (ACTH) from pituitary ↳ Cortisol from adrenal cortex
  - Don't know cause for Cushings initially. Could be ACTH or too much CRH or just adrenal releasing too much Cortisol.



- Corticosteroids: secreted by outer cortex of adrenal gland, derived from Cholesterol precursor; MOA: Acts thru intracytoplasmic steroid receptor. Drug-Receptor complex enters nucleus, binds to GRE on gene, regulates transcription leading to altered mRNA & protein synthesis. Thus delayed efx categorised into 3 groups –
  - 1. Glucocorticoids.....Cortisol (Hydrocortisone)
  - 2. Minerelocorticoids = Aldosterone
  - 3. Sex steroids = estrogens, progesterone Testosterone, Estrone







- Estrogen can come from testosterone.
- 21 beta hydroxylase à lead to bilateral adrenal hyperplasia.

Pharmacological axns of steroids:

Mineralocorticoid actions:

1. ↓renal Na^+ reabsorption & water retention: results in Edema
2. ↓K^+ & H^+ excretion in urine

Glucocorticoid axns:

1. **ON Carbs:** ↑gluconeogenesis ↳ hyperglycemia by inhibiting peripheral utilisation & stimulating glucose release from liver
2. **ON Proteins:** Catabolic axn— ↓breakdown ↳Mobilize AA's for glucose production ↳-ve nitrogen balance ↳ m wasting, loss of bone, thinning skin
3. **Fat:** ↑Lipolysis, redistribution of body fat, subcutaneous tissue over extremities loses fat ↳ deposited over face, neck & shoulder, moon face, fish mouth & buffalo hump
4. **CVS:** ↓↓capillary permeability, ↓adrenaline mediated vasoconstriction - ↓BP
5. **Lymphoid tissue:** ↓lymphoid cell destruction, specially 'T' cells in Lymphoma
6. **Anti Inflammatory efx:** Corticosteroids ↑**lipocortins/annexin** ↳ inhibit ↑PL-A2 & PGs synthesis. Thus suppresses all components of inflammation

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7. Immunosuppresent efx: suppresses ↓CMI & allergic rxns, inhibits ↓cytokines release (IL-1, IL-6, TNF-α)
8. Lungs: production of lung surfactant ↑helps lung maturation in infants
9. Negative Ca balance by inhibiting ↓stomach absorption & facilitating ↑renal excretion
10. Gastric ulcerations
11. CNS: mild euphoria

↑ Corticosteroids = GC's unspecified. Both natural hormones & synthetic steroids in market w/various amt of gluco & mineralo corticoid activity. *Classification based on DOA, G:M activity & route of admin –*

- **Short acting**: **Hydrocortisone**: G:M::1:1: equal GC & minarlocorticoid; name for cortisol when used as med; treats ppl who lacks adequate naturally generated cortisol; DOC in all acute or emergency situations; **short** & **quick acting** & better than cortisol & cortisone b/c it's the **active form**.
- **Intermediate acting**: Prednisolone: Mainly GC activity
- **Long acting**: Betamethasone, Dexamethasone: Only GC activity
- **Pure Mineralocorticoids**: Fludrocortisone: only Minaralocorticoid activity
- ***Inhalation preparations (ICS):** Beclomethasone, Budesonide, Flunisolide, Fluticasone, Triamcinolone
- **Skin preparations**
- **ACTH preparation:** Cosyntropin
- Cortisone is prodrug of Cortisol
- Cortisol is major natural glucocorticoid.
- Prednisone is prodrug of Prednisolone

↑ Endocrinal USES of corticosteroids:

- Chronic adrenal insufficiency (Addison's dis): Weakness, fatigue, wt loss, ↓↓BP & hyperpigmentation
- Acute adrenal insufficiency (addisonian crisis)
- Cushing's syndrome: during & after surgical procedure.
- Congenital adrenal hyperplasia (CAH): due to def 21-β-hydroxylase: ↓↓GC's & mineralocorticoids & ↑androgens= Virilization & ambiguous genitalia
- Dx'ic purpose: Dexamethasone suppression test.

↑ Nonendocrinal uses: Asthma, RA, OA, Gout; Collagen dis's: SLE, PAN; Severe allergic rxns such as anaphylaxis, angioneurotic edema, urticaria & drug rxns – BUT in anaphylaxis, always select Epinepherine. Steroids have role but no immediate efx; Eczematous skin dis, Autoimmune dis's, Ulcerative colitis, Crohn's dis, Organ transplantation (Graft rejection), Septic shock, Meningitis

↑ Uses of steroids: ALL, Lyphomas, Ca Breast, & Cancer chemo induced vomiting

↑ Uses of steroids in pregnancy to prevent respiratory distress in new born, esp in premature labor (b4 34th week). Betamethasone is DOC. Dexamethasone is 2nd choice.

1. Why betamethasone preferred over dexamethasone? Why not prednisolone at all? Betamethasone relatively less protein bound than dexamethasone. Fetal placental 11-beta-HSD type-II converts prednisolone to prednisone which is inactive form. Inside fetus, this inactive form can't be get activated b/c fetal liver lacks required enzyme 11-beta-HSD type-I. That's why prednisolone can't be used. Beta/dexamethasone remain unaffected by 11-beta-HSD type-II.

Adverse efx of corticosteroids: *Peptic ulcers, *Osteoporosis, *Precipitate diabetes, HTN, *Edema, Hypokalemic alkalosis, *M wasting, fragile skin, purple striae, *precipitates infections (TB, candidiasis), *cataract (↑glucose), *Cushing's habitus, *Delayed wound healing, Psychiatric problems ↑ euphoria; HPA axis suppression

↑ General principles of corticosteroids therapy:

- Use short acting, lowest possible dose for short period

- Gradual tapering of dose …**NEVER withdraw abruptly**
- **Start w/higher dose & taper it slowly**
- Single dose better than multiple divided doses
- In Infection, severe stress & trauma— dose
- Try to use more locally applicable preparations first before systemic.

Antagonists of GC's: for Cushing's syndrome, inhibit enzymes needed for steroids synthesis; most inhibit P450 & inhibit steroid synthesis

- Metyrapone: safer in pregnancy Aminoglutethimide
- KTZ: in high doses, for Adrenal tumor Cushings
- Mitotane:
- Trilostane:
- Mifepristone (RU 486)

Antagonists of mineralocorticoids

***Spironolactone (Also Diuretic)**: for Primary hyperaldosteronism (Conns syndrome), Hirsutism & acne

L16 Antidiabetics

- **Type 1 diabetes/IDDM (Insulin dependent DM):** less common, lack insulin due to destruction of beta cells, commonly in children, obesity not seen, insulin only tx option, more prone to ketoacidosis
- **Type 2 diabetes:** more common (~90%), adequate insulin, but tissues resistant to insulin axn, in elderly & obesity common; usually tx'd w/oral antidiabetic drugs. Failure of oral therapy requires additional Insulin therapy; Ketoacidosis rare. May develop hyperosmolar coma
- **Type 3 diabetes** – Other causes like Drug induced
- **Type 4 diabetes** – Gestational DM

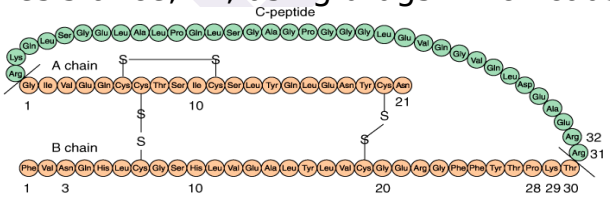
- **Insulin**: esp Mechanism of insulin release & insulin axn; polypeptide hormone w/2 chains A & B, linked by 2 disulfide bridges; has 51 AA's (chain-A w/21 AAs & B-chain w/30 AAs) w/mw-5808; release inhibited by α_2-adrenergic receptors & stimulated by β_2-adrenergic receptors. Ach, CCK, GIP, GLP-1 release; to treat all type 1 DM, type 2 DM pt's who're not adequately controlled w/diet & oral antidiabetics, gestational diabetes, post pancreatectomy pt's, diabetic ketoacidosis & hyperosmolar coma; binds to α subunits β subunit – Tyrosine Kinase (TK) by Phosphrylation Insulin Receptor substrate IRS-1 & 2 Ras & MAP (Mitogen activated protein) kinases translocate glucose transporters to cell memb glucose uptake & glycogen synthesis

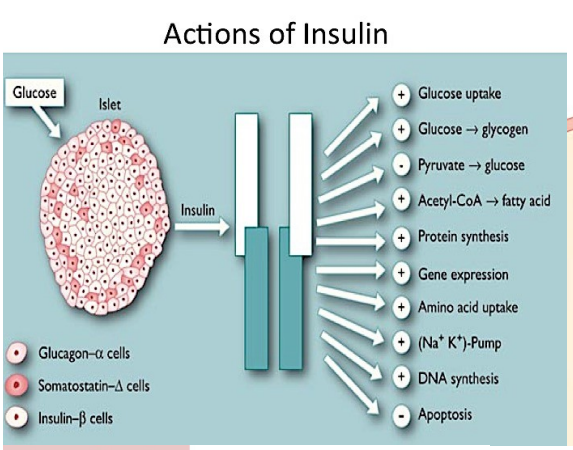
Sources of Insulin: ****Human insulin made by recombinant DNA techniques thus allergy & resistance to human insulin less likely

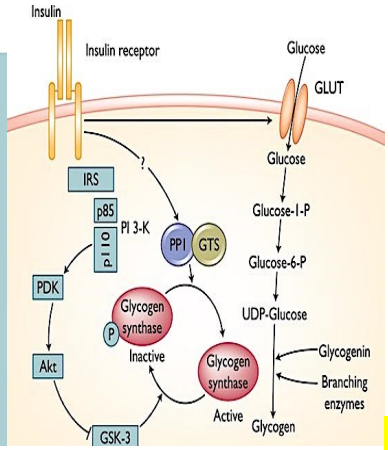
Route of Admin: Subcutaneous injection is MC route

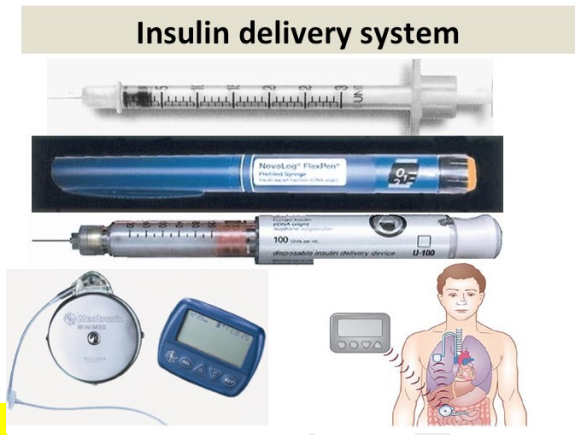
Regular insulin only insulin that can be admin'd IV, esp useful (given by IV infusion) for management of diabetic ketoacidosis & other emergencies *****

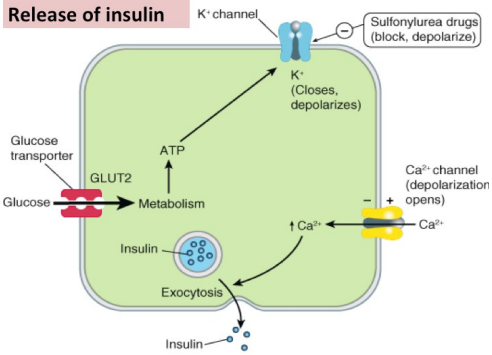
Situations requiring more insulin: DKA, Infections, Acute poisoning, High fever, Trauma, surgeries, certain neoplasms, Serious psych'al stress, Pregnancy, Hyperthyroidism, Insulin resistance, MI, using drugs which cause hyperglycemia

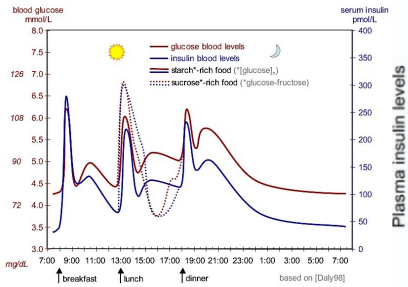


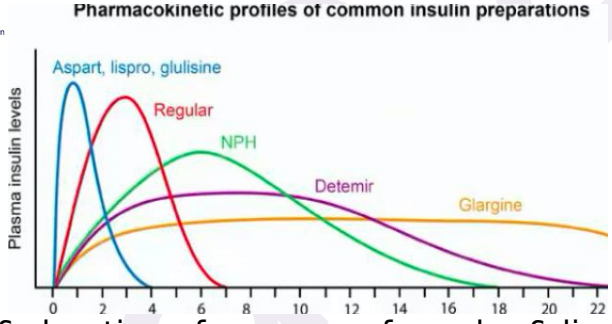












- Diff types of insulin preparations: sig of their onset & duration of axn, esp of regular & lispro insulins

Classification of insulin preparations given S.C.

TYPE ★ ★	**Onset of action** **S.C injection**	**peak**	**Duration of action**
Ultra-rapid-acting Lispro insulin** Aspart insulin** Glulisine insulin	15 min 15 min 15 min	1-2 h 1-2 h 1-2 h	3-4 h 3-4 h 3-4 h
Rapid-acting Regular insulin**	45min	2-4 h	5-8h
Intermediate-acting NPH insulin (isophane)	1-2h	6-12h	16-24h
Long-acting Insulin detemir** Glargine insulin**	1-2h 1-2h	6-7h 4-5h	13-17h >24h

- **Ultra-rapid onset & very short acting Insulins**: **Lispro, Aspart & Glulisine**: taken 5 mins b4 meal & their short duration of axn ¬risk late postmeal hypoglycemia relative to long-acting

insulin preps; used to control postprandial hyperglycemia; admin'd w/intermediate acting preparation to control baseline glucose

- **Lispro**: very short acting, insulin analogue w/interchange of lysine & proline at 28 & 29 pos's of β-chain; w/structure of Lys(B28), Pro(B29) – transposition allows lispro to dissociate more rapidly into monomers & faster absorption (ultra rapid onset axn), Suitable to inject just b4 meal*****, Less hypoglycaemia; less risk of post prandial hypoglycaemia, used to control postprandial hyperglycemia

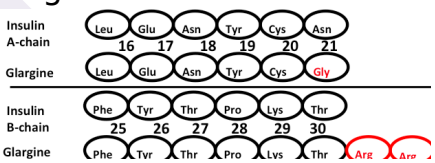
- **Regular Insulin**: *rapid onset – short acting insulin*, alone or mixed w/intermediate or long acting preps; given 30-45 mins b4 meal to control postprandial hyperglycemia; routinely given by SC, but in emergencies like Diabetic ketoacidosis, given IV'ly & is insulin preparation of choice ***** also in emergencies like coma

Intermediate acting insulins:

- **Isophane/NPH insulin [NPH-Neutral Protamine Hagedorn]:** suspension of insulin in complex w/zinc & protamine; given SC'ly, maintains basal insulin lvl to control blood glucose btwn meals; when mixing w/ regular/ultra-short insulins, good care should be taken; shouldn't be combined until time to inject, otherwise they bind to each other

Slow Onset & Long Acting Insulins

- **Glargine Insulin**: glycine substituted for asparagine at A21 pos & 2 arginines attached to B chain; designed to provide constant (peak less) basal insulin supply thru out day, slow onset axn, maintains flat lvl (no PEAK – ID on GRAPH) for prolong period (>24 hrs, similar to extended release) then fall in axn



- **Detemir**: FA myristic acid bound to lysine AA at pos B29

Adverse efx & DI's of insulins & preps:

- *****Hypoglycemia most frequent & serious adverse rxn due to delay in meal intake after insulin injection; Inadequate carb intake; physical exertion & high dose of insulin; *****CF's**: sweating, anxiety, palpitation, tremor dizziness, headache, beha'al changes, visual disturbances, fatigue & weakness; *mental confusion, seizures & coma occur in severe hypoglycemia*; **Tx** w/Oral glucose & if severe give IV glucose & glucagon injection; **Hypoglycemic unawareness** in some: Diabetic neuropathy & pt's on Beta-adrenergic blockers*****
- Allergic rxns, Lipodystrophy & Local rxns at site of injections, Weight gain, Insulin resistance

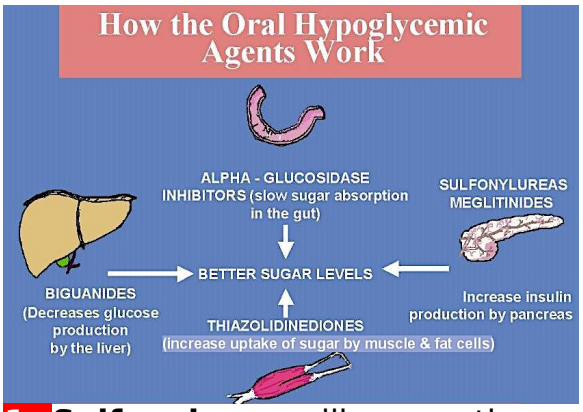
Insulin DI's

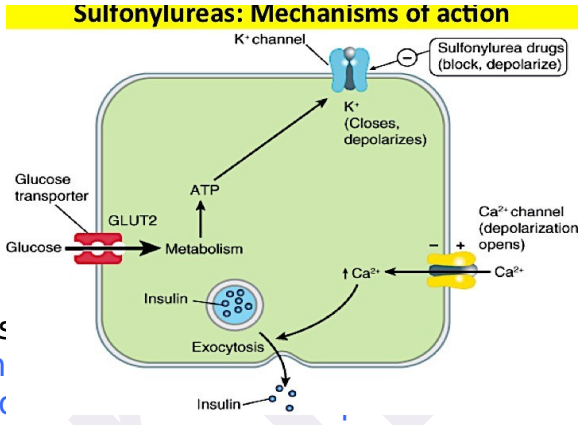
1.***** ß-blockers: masks warning signs of hypoglycemia like palpitation, sweating, tremor & anxiety which delays recog & tx, leads to prolong hypoglycemia; use carefully, not contraindicated b/c may be vital in tx

2. Alcohol: can precipitate hypoglycemia, thus worsens it!

3. Thiazides, Frusemide & Corticosteroids ↑↑blood sugar, so counteract insulin!!!

OHA's (Oral Hypoglycemic agents):





1. Sulfonylureas: like any other oral antidiabetic, needs func'al beta cells to produce efx, so not useful in type I DM; bind ATP-sensitive K^+ (KATP) channel of pancreatic beta cells memb to inhibit tonic, hyperpolarizing K^+ efflux, thus causin electric potential over memb to become more +ve aka depo voltage-gated Ca^{2+} channels ↓rise in IC Ca^{2+} leads to ↑fusion of insulin granulae w/cell memb & thus ↑insulin secretion; for Type-II DM, esp those who're NOT OBESE; Adverse efx: *****Hypoglycemia, allergic rxns, weight gain & contraindicated in *****Sulfa drug HSR, Hepatic or renal insufficiency (b/c delayed drug excretion makes it accumulate & cause hypoglycemia), Cautious use in CV dis's & elderly (hypoglycemia), Pregnancy (risk hypoglycemia in newborn), porphyrias; DI's w/**Warfarin, phenylbutazone & sulfonamides** – induce hypoglycemia by inhibiting sulfonylurea metabolism or displacing from plasma protein bind ↓ ↑sulfonylurea's efx

- **1st GEN Sulfonylureas:** Tolbutamide & Chlorpropamide
  1. **Tolbutamide**: short acting, less hypoglycemic episodes, so treats Type 2 DM in elderly
  2. **Chlorpropamide**: prolong hypoglycemia, treats Nephrogenic DI, so not good for elderly, ant-abuse /disulfiram like rxn
- **2nd GEN Sulfonylureas (more potent): *Glyburide*, *Glipizide*, *Glimepiride***
  3. **Glipizide**: shortest acting, less potent than glyburide so better; less incidence hypoglycemia–safe in elderly
  4. **Glimepiride**: long acting & most potent among sulfonylureas

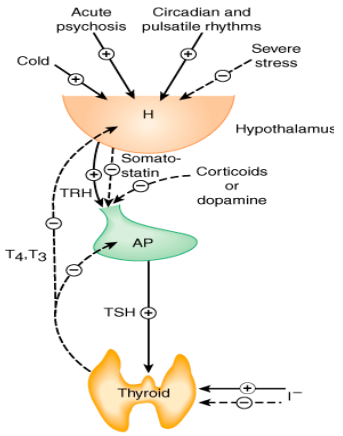
2. **Meglitinides/Non Sulfonylurea secretagogues**: **Repaglinide, Nateglinide**; similar to sulfonylureas, ↑insulin secretion by blocking ATP dependent K^+ channels of B-cells; best to control post-prandial hyperglycemia in type 2 DM; safe in sulfa allergic pt's; hypoglycemia main side efx, also renal & liver failure
3. **Biguanides: Metformin (Glucophage):** insulin sensitizer, ↓↓insulin, testosterone, BMI & promotes ovulation**;** ****1st-line therapy for pt's w/type 2 DM **esp in Obese** & PCOS for infertility; *****euglycemic– Don't cause hypoglycemia *****No **Weight gain**, so prefer in obese; ↓**HEPATIC GLUCONEOGENESIS**, slows glucose absorption from GIT, ↑glucose uptake & utilization by tissues (skeletal m) & ↓glucagon; Q: which is not mechanism of metformin???; **adv's over others:** promotes mild weight loss, ↓↓insulin, improves lipid profile slightly, ↓↓cancer risk & doesn't cause hypoglycemia when used as monotherapy; adverse efx: N/V, Metallic taste, Lactic acidosis***** but rarely (USMLE step 2), Vit B12 def & weight loss; contraindicated in all conditions that predispose to acidosis, Renal dis & CHF; synergistic w/sulfonylureas
4. **Thiozolidinediones/glitazones: *Pioglitazone & Rosiglitazone***: *bind nuclear receptor* PPAR *(peroxisome proliferator activated* receptor) that regulates transcription of several insulin responsive genes; insulin sensitizers as ↑target tissue sensitivity to insulin & ↓↓insulin resistance; no hypoglycemia (euglycemic just like metformin) & delayed efx; Hepatotoxicity major side efx & Cardiovascular dis's another major concern

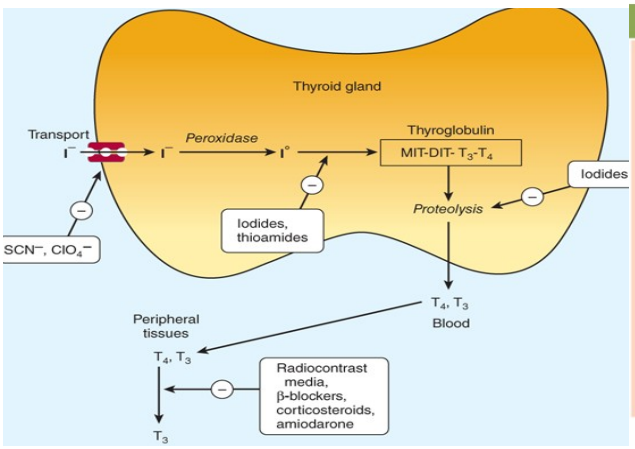
5. **α-glucosidase inhibitors: Acarbose & Miglitol**: **competitive inhibitors** of intestinal brush border **α-glucosidase** (breaks starches into simple sugars) ↓ so ↓↓ **monosaccharide formation** from carbs in upper small intestine & thus ↓↓absorption of monosaccharides from duodenum & upper jejunum; for type 2 DM, admin'd just b4 ingestion of 1st portion of each meal; **most suitable in** pt's w/predominantly postprandial hyperglycemia; adverse efx – Flatulence (up to 40%), Diarrhea (20%), abdominal pain (7%). Contraindicated in IBD, Hypoglycemia not sig (very rare, negligible)
   1. **Miglitol**: α-glucosidase inhibitor; more potent; make sure to differentiate from meglitinides
6. **Amylin analogues:** Amylin, small peptide hormone released into bloodstream by β-cells of pancreas along w/insulin after meal; amylin completely absent in ind's w/Type I DM
   1. **Pramlintide**: injectable amylin analogue, allows pt's to use less insulin, used as adjunct therapy to control postprandial glucose excursions (hypoglycemia?)
7. ***DPP-4 inhibitors as pt of Incretins***: gut hormones secreted from enteroendocrine cells into blood w/in mins after eating **&** stimulate ↓↓blood glucose by ↑insulin released from pancreatic β-cells after eating; also inhibit glucagon release; thus regulate amt of insulin secreted after eating; *2 types of incretins* – GLP-1 (Glucagon Like Peptide-1) & GIP (Gastric Inhibitory Peptide); Both rapidly inactivated by DPP-4 (Dipeptidyl Peptidase-4); drugs mimic GLP-1 & GIP or inhibit DPP-4; for type I DM
   1. ***GLP-1 agonists***: Liraglutide, Exenatide***** à ↑incretin
   2. ***DPP-4 inhibitors/Gliptins***: ***Sitagliptin***, ***Saxagliptin*** à inhibit incretin breakdown; ↑incretin which inhibit glucagon release ↓in turn ↓insulin secretion, ↓↓gastric emptying & blood glucose lvls
8. **SGLT2 inhibitors: Gliflozin (canaglifozin, dapaglifozin)**: block SGLT2 (sodium/glucose cotransporter 2 responsible for at least 90% glucose reabsorption in PCT; mutations in this gene also associated w/renal glucosurea) to eliminate blood glucose thru urine; monitor serum Cr for kidney func's
9. **Glucagon**: polypeptide w/29 AAs, secreted by α cells of pancreas; potent inotropic & chronotropic efx, similar to β-agonists w/out requiring func'ing β-receptors, relaxes intestine & ↑blood glucose via glycogen breakdown in liver & ↑gluconeogenesis & ↓insulin release; for severe hypoglycemia when oral & IV glucose not available; & for β-blocker poisoning b/c reverses cardiac efx by ↑cAMP & X-ray visualization of bowel

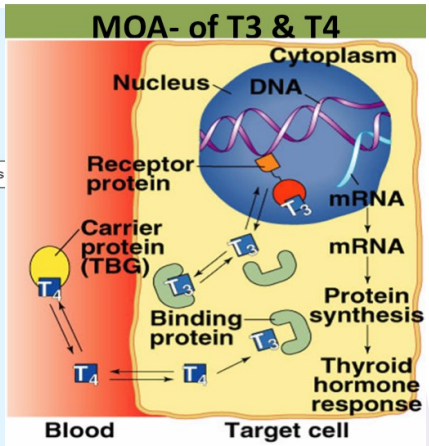
L17 Thyroid & Antithyroid drugs https://www.youtube.com/watch?v=uCjpGlnCjeA

↓ 2 imp hormones secreted by thyroid: & thus synthesized preps by humans for exogenous forms –

- ***Thyroxine T4****: 90% TH's*; $t_{1/2}$ 7 days, slow onset axn; converted to T3 in peripheral tissues; *MC'ly used TH prep;* **prep of choice** in – cretinism***, adult hypothyroidism***, myxedema coma***, non-toxic goiter, hyperthyroidism (w/levothyroxine)
- ***Triiodothyronine T3****: 10% TH's; $t_{1/2}$ 1 day, fast onset axn; converted to inactive metabolites; rarely used TH prep; T3 4X more potent than T4;* sometimes used in myxedema coma w/T4
- *>99% T4 & T3 bound to TBG. Both well absorbed on oral admin. T3 4X more potent than T4.* T4 converted to T3, T3 binds to intranuclear receptors. Know T4 not T3, used widely: common uses include hypothyroidism, cretinism & myxedema coma. T3 cardio toxic, sometimes used in myxedema coma







- **Hypothyroidism**: due to def TH's causes slowing of bodily func's w/or w/out goiter; MCC in adults is ***autoimmune thyroiditis*** **(Hashimoto's thyroiditis)**: Auto Ab's against thyroid peroxidase; Other causes – Iodine def, radiation, thyroidectomy & **drugs like** – iodides, lithium, thiomides, aminosalicylic acid, phenylbutazone, amiodarone etc
- **Cretinism**: Hypothyroidism in infants charac'd by irreversible MR & dwarfism; MC preventable cause of MR in the world AT birth. Tx w/thyroxine supplementation
- **Myxedema coma**: end state of severe, long-standing & untx'd hypothyroidism; medical emergency charac'd by deterioration of mental status; progressive weakness; hypothermia, hypoventilation, hypoglycemia, hyponatremia, water intoxication shock, stupor, coma, & death.
- **Thyroid storm****: acute form of hyperthyroidism (thyrotoxic crisis); due to inadequate tx of hyperthyroidism like Graves dis's or toxic goiters & precipitated by infection or stress; **CF's**: Fever, Tachycardia, Nausea, Vomiting, Diarrhea, Agitation & Confusion, Coma & death; **Tx w/**IV fluids, antipyretics, **propylthiouracil, iodides, propronolol,** dexamethasone; in over-hyperthyroidism need to make pt euthyroid; can't do surgery in pts who're hyperthyroid, hyperglycemic, hypertensive; If surgery performed you will get thyroid storm; so tx'd by propylthiouracil (thiomade) (ANSWER?)!

Thyroid hormone preps:
1.**Levothyroxine sodium (L-T4):** *Preparation of choice* in thyroid replacement therapy**
2.**Liothyronine sodium (L-T3**): not preferred for routine use; cardio-toxic, thus not preferred in CV dis's
3. **Liotrix**: mixture of T4 & T3, very rarely used
4. **Thyroid desiccated**: dried animal thyroid extract not recommended b/c of protein antigenicity

Therapeutic uses of TH's:
1. Cretinism***
2. Adult hypothyoidism***
3. Myxedema coma***
4. Non-toxic goiter
5. Hyperthyroidism (concomitant use of levothyroxine along w/anti-thyroid drugs rep'td to ⏤rate of remission of Graves' dis)

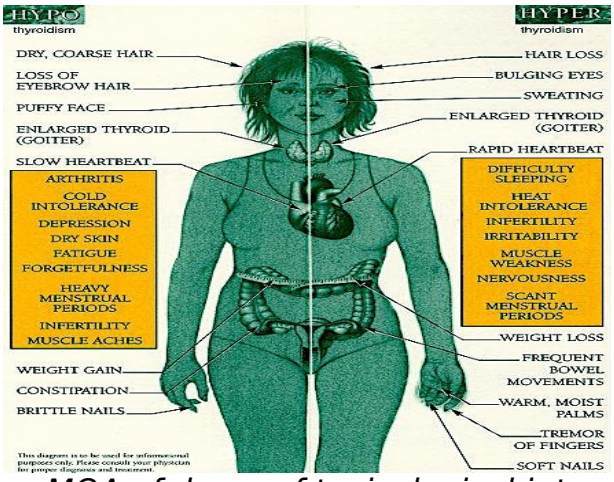
- ***T4: prep of choice** in – cretinism***, adult hypothyroidism***, myxedema coma***, non-toxic goiter, hyperthyroidism (w/levothyroxine). But in myxedema coma T3 may be given in addition to T4
- T4 converted to T3 ⏤binds to intranuclear receptors. Know T4 not T3, used widely: common uses include hypothyroidism, cretinism & myxedema coma. T3 cardio toxic, sometimes used in myxedema coma

⏤ Drugs used in HYPERthyroidism:

1. **Thioamides (Anti-thyroid drugs):** ****MOA**: *inhibit TH synthesis by* inhibiting TPO (thyroid-peroxidase); thus inhibit oxidation, iodination & coupling, +peripheral conversion; no effect on iodine uptake & release of TH's; used for Graves dis, toxic uninodular & MNGs, Non toxic goiter, Thyroid storm & Prep of thyrotoxic pt for thyroidectomy
    1. **Methimazole** more potent & longer acting vs. propylthiouracil, Hence **prefer over propylthiouracil** in tx'ing all hypothyroidism conditions (except pregnancy – can cause aplasia cutis congenita) b/c longer duration of axn so better compliance
    2. ***Propylthiouracil: relatively safe, don't cross placental barrier & hence ***prefer in pregnancy; also*** *inhibits* peripheral conversion of T4 to T3; CAN BE USED PREOPERATIVELY; in pregnancy DOC b/c shorter acting & prevent peripheral conversion T4 to T3; used in thyroid storm!!!!
    2. **Carbimazole**: pro drug converted to methimazole & widely used in UK; ADRs: **Common**: lupus-like rxn, Hypothyroidism (reversible), Arthralgia, **Rare**ly Agranulocytosis – tx w/**STOP DRUG &** G-CSF
2. **Iodides/iodine salts**: inhibits TH release thru blocking thyroglobulin proteolysis (most imp MOA), inhibits organification (Iodination of tyrosyl residues to form MIT & DIT), inhibit sodium-iodide symporter, ↓size & vascularity of hyperplastic thyroid (Goiter); gland become more firm & also less vascular; fast onset axn, preferred in emergencies like "**Thyroid storm**"; supplies iodine in non-toxic goiter due to iodine def, block TH release in thyroid storm & prepare thyrotoxic pt for thyroidectomy (admin'd for 7-10 days prior to thyroid surgery, makes gland more firm, less vascular & enables easier surgical excision), & disinfectant & fungicide (iodine tincture used)
    1. **Lugol's sol'n:** iodide salt as mixture of 5% Iodine & 10% Potassium iodide; given together w/thioamides b4 surgical resection of gland; adverse efx: HSR's, Chronic overdose leads to **iodism**** charac'd by inflammation & ulceration of mucous memb's; salivation, rhinorrhea, sneezing, burning sensation in mouth; headache etc, High doses can cause hypothyroidism & goiter; Contraindicated in pregnancy b/c of fetal goiter
3. **Radioactive iodine ^{131}I**: for destruction of thyroid; only isotope for tx of thyrotoxicosis, while others used in dx; After oral admin, gets taken up & concentrated in thyroid follicles. **Emits gamma rays** & destroys gland by damaging DNA of thyroid cells ∴ Gland undergoes pyknosis, necrosis & fibrosis w/out damaging neighboring tissues; **used** to treat severe hyperthyroidism & thyroid cancers & post-surgically; **contraindicated in pregnancy** & lactation b/c risk of cretinism
4. **Ipodate**: contrast agent prevents peripheral conversion of T4 to T3
5. **Beta-blockers like propranolol**: prevents conversion of T4 to T3 by inhibiting iodothyronine deiodinase; ameliorate sx of thyrotoxicosis by ↓↓efx of symp adrenergic impulses on target organs

∴ Causes of Hyperthyroidism:

- **Graves' dis**: autoimmune disorder in which lymphocytes make TSH receptor-stimulating Ab that mimics TSH axns; *Tx w/Anti-thyroid drugs in young pt's, Thyroidectomy, & RAI – used after 21 yrs age, & **Beta-blockers – Propranolol to control CV complications such as tachycardia, AF & BP; but esmolol* preferred b/c shorter acting & available IV admin
- **Toxic goiters/adenomas:** tx w/surgery or prefer ^{131}I & make pt euthyroid w/anti-thyroid drugs b4 these
- Choriocarcinoma
- TSH producing Pituitary tumor
- Virus-induced subacute thyroiditis



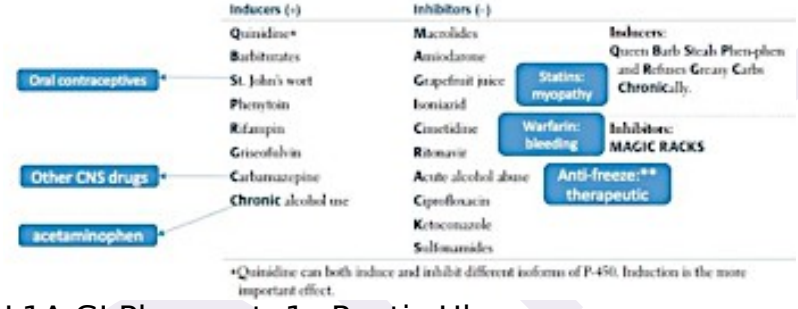
MOA of drugs of toxicological interest only:

- ***Anion inhibitors***: Competitive inhibition of iodide transport mechanism (sodium-iodide symporter); Eg: **Perchlorate, Pertechnetate & Thiocyanate**
- **Lithium** - Inhibition of hormone release & iodide organification.
- Amiodarone – inhibits peripheral monodeiodination; for hyperthyroidism, can't convert t4 to t3
- **Sulfonamides** - Inhibition of coupling rxn

Summary of hyperthyroidism & drugs:

- Relearn synthesis, release & metabolism processes of TH's. B/c most antithhyroid drugs MOA involves inhibition of these processes – Graves dis, Toxic goitres & thyroid storm are imp condition requiring this group of drugs
- Methimazole & propylthiouracil are thiomides, acts by inhibiting thyroidal perxidase & 3 steps in TH synthesis. Later one preferred in hyperthyroidism w/pregnancy
- Iodides (Lugols sol'n, potassium iodide, iodine): acts by inhibiting release of hormone. Also inhibits iodination. Used to ↓size & make less vascular toxic goitres (b4 surgery). Also used for "Thyroid Storm"
- **^{131}I used in severe cases & cancers**
- **Role of Beta blockers like propronolol in hyperthyroidism**
- **Thyroid storm: severe untreated from of thyrotoxicosis . tx'd by multiple drugs**

Enzyme Inducers & Inhibitors – Pg.273 First Aid 2012



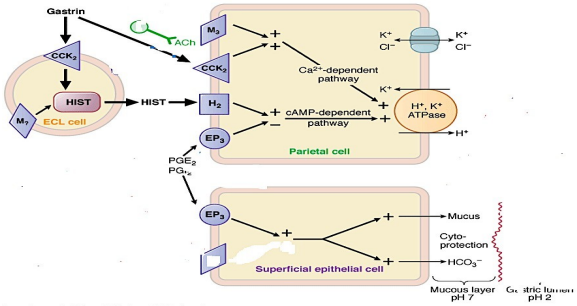
L1A GI Pharm pt. 1– Peptic Ulcers

- **Acid Peptic Dis's:** ↑acid, ↓mucus or bicarbonates, or H. pylori infection; ↑ **Acids**, ↓ **Mucous** or **H. Pylori** can all lead to peptic ulcer dis's; so can treat by drugs that neutralize acid, ↑mucus production, ↓acid secretion or antibiotics;
  - Peptic ulcers
  - Gastric ulcers
  - Duodenal ulcers
  - GERD
  - Gastritis
  - Zollinger Ellison Syndrome
  - Esophagitis

- Acid generated by carbonic anhydrase-mediated catalysis of CO_2 & H_2O to form H^+ & HCO_3^-. H^+ ions then exchanged for K^+ by H^+K^+-ATPase pump & later coupled w/Cl^- ions entering parietal cell from blood in exchange for HCO_3^-. Principal stimulants for acid secretion are histamine, gastrin & ACh released from postganglionic enteric neurons. These ↑IC cAMP, IP3, DAG & Ca^{2+} lvls ↑induce H^+K^+-ATPase rich tubulovesicles to fuse into apical plasma memb allowing H^+K^+-ATPase to secrete protons directly into lumen of canaliculus of parietal cell & then into lumen of gastric gland.
- luminal cell is on right of pictures. Can see Parietal & ECL.
- Gastrin stimulate ECL Cell & act on Parietal cell to release H^+.
- Histamine works thru Gs; Gastrin & ACh work thru IP3/DAG
- **PG's alone inhibit Acid secretion in parietal cell; not**

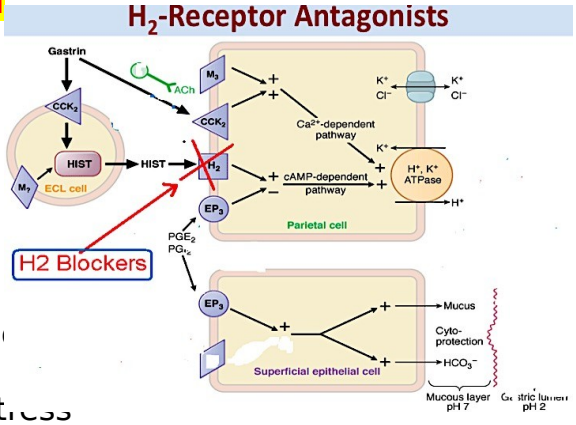
- Dyspepsia
- Indigestion

Physiology of Gastric Acid Secretion



4 category of Drugs used for APDs

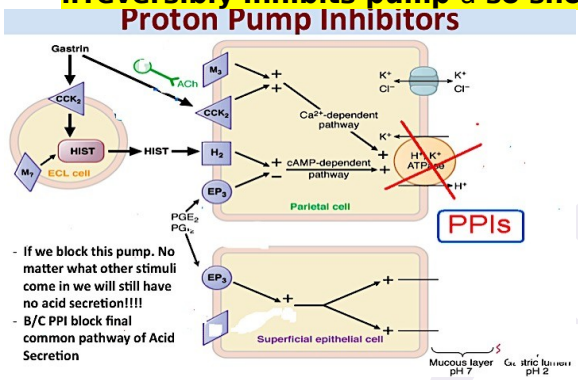
1. **Antacids**: relieve heartburn by neutralizing acids, don't interfere w/acid secretion; react w/hydrochloric acid to form chlorides, water & CO_2; combo less likely to cause constipation or diarrhea
   - ***Aluminum hydroxide***: side efx: constipation
   - ***Magnesium hydroxide***: side efx: diarrhea
   - ***Combo of Calcium Carbonate & Sodium bicarbonate***
     1. Side efx of Ca^{2+} & Na^+ bicarbonate: belching, metabolic alkalosis & milk alkali syndrome (due to Ca^{2+} carbonate ↓hypercalcemia, renal insufficiency & metabolic alkalosis due to large doses Ca^{2+} containing antacids)
2. Drugs Reducing Acid secretion
   - **Muscarinic Antagonists**: inhibit acid secretion, mostly used preop by anesthesiologists, not so imp
     1. ***Pirenzepine***: ↓HR
     2. ***Glycopyrrolate***: ↓HR
   - **H2-Receptor Antagonists**: inhibit acid secretion by blocking histamine 2 receptors on parietal cells (as histamine is major stimulus for these cells) so very powerful drugs; Given twice daily for 4-6 weeks; inhibit ~70% of 24 h acid output (not 100% b/c other stimulus also includes gastrin & ACh), ↑↑ONLY basal acid secretion (Nocturnal); doesn't reduce meal stimulated acid secretion b/c mostly used for night time – 1 dose in morning & 1 at night; adverse efx: Except Cimetidine, other **H_2 blockers** do not produce any major side efx



     1. ***Cimetidine***: banned everywhere except US (Bad Drug à never use) there are **many side efx** (so most seen in USMLE); least potent but adverse efx: Antiandrogenic efx, Gynaecomastia, Galactorrhea, CYP-450 inhibition; no good thing about this drug ↓ efx so prefer –
     2. ***Famotidine***: least expensive, IV infusion prevents stress induced ulcers for ex. in septic shock
     3. ***Ranitidine***:
     4. ***Nizatidine***:
   - **Proton Pump Inhibitors**: inhibit acid secretion; block 100% 24 hr output & block meal stimulated; if we block this pump. No matter what other stimuli come in, still have no acid secretion; block final common pathway of Acid Secretion; All prodrugs b/c converted into active metabolites in acidic secretory canaliculi of parietal cells of stomach; conversion requires acidic env; thus if admin'd w/antacids, PPIs less effective (so don't take antacids up to 30 min b4 taking PPI); irreversible, suicide inhibition of H^+/K^+-ATPase (proton pump) & thus blocks final common pathway of acid secretion; All have suffix "Prazole"; inhibit >90% of 24 h acid output; More effective than H2 blockers; ↑↑both basal acid & meal stimulated acid secretion; taken before meal, as food ↑↑bioavailability of

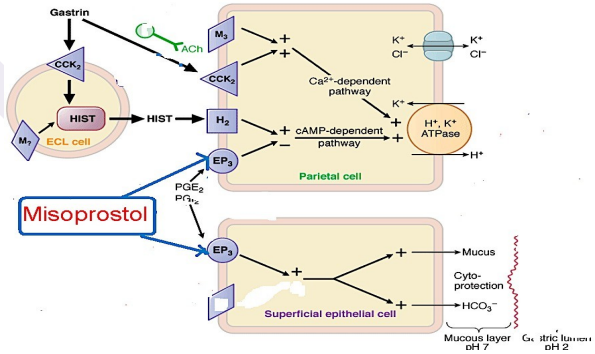
PPIs; short half life but long duration of axn. Most effective agents, DOC for both prevention & tx of NSAID induced ulcers, DOC for ZES. For H.Pylori associated APDs: PPIs given along w/2-3 antibiotics. Always **take PPI over H2 blockers;** ~~adverse efx: ↓risk of hyperplasia of ECL (seen in Animals), 3 main concerns regarding long-term safety of class – prolonged hypergastrinemia, possible gastric atrophy & chronic hypochlorhydria; long term ↓Ca2+ absorption leading to osteoporosis (esp elderly postmenopausal F's)~~

1. As result of their acid dissociation constant (pKa) lvls, accumulate in secretory canaliculus of parietal cell, achieving [higher]'s here when compared w/plasma. PPI gets protonated & converted into active sulfonamide species, that forms disulfide bonds w/cysteine residues in α-subunit of H+K+-ATPase ↓results in duration of axn that exceeds plasma half-life & inhibitory mechanism independent of H, ACh or gastrin stimulus for acid secretion. In contrast to H2RAs, in which optimal dosing at night, morning dosing of PPIs associated w/sig'ly improved acid suppression; should be admin'd b4 breakfast as amt of H+K+-ATPase in parietal cells greatest after prolonged fast & eating recruits H^+K^+-ATPase to become active & susceptible to drug axn. PPIs efx ↓w/repeated admin &, by 3rd day, steady state occurs where amt of pumps that remain inhibited over 2 h reaches ~70%. Moreover, acid suppression improves progressively as recruitment of enzyme ↓. Consequently, occasional PPI use taken on as needed basis doesn't reliably provide adequate acid inhibition & doesn't produce consistent satisfactory clinical resp. Asked to take in morning. If 2x/day, take b4 meal. Even H2 blockers should be taken before meal. **If long half life = longer duration of axn usually. This is exception. It irreversibly inhibits pump à so short life, but long duration**



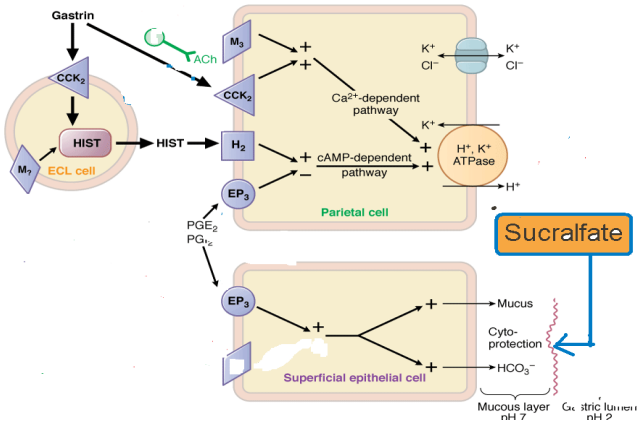
2. ***Omeprazole***:
3. ***Rabeprazole***:
4. ***Lansoprazole***:
5. ***Pantoprazole***:
6. ***Esomeprazole***:

3. **Mucosal Protective Agents**: mucosal PG's ↑mucus & bicarbonate secretion & mucosal BF by superficial epithelial cells?; **mucus protects against acid àso give mucosa protective agents to form coat over ulcer & block acid from hitting ulcer**
   - ***Misoprostol***: PGE_1 analog agonist*; ↑↓EP-3 on parietal cells & ↓mucus & bicarbonate secretion & mucosal BF; also ↓acid secretion (dual mechanism)!! 3 imp uses – prevent NSAID induced ulcers (but PPIs better), labor induction (w/oxytocin) & abortion/MTP (medical termination of pregnancy w/Mifepristone); adverse efx: diarrhea & ↑uterus contraction, so contraindicated in pregnancy



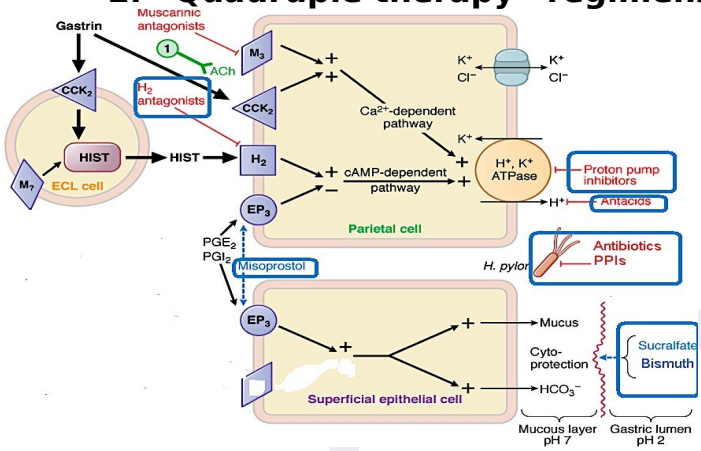
   - ***Sucralfate***: ulcer coating agent; needs acidic env so doesn't w/other acid lowering agents; **salt of sucrose** complexed to sulfated aluminum hydroxide, given 4X daily, 1 hr b4 meals, in water or acidic sol'ns of stomach, it forms viscous, tenacious paste, **sucrose sulfate** that binds selectively to base of ulcers or erosions 'crater' to form physical

barrier & coats ulcers from any further damage from HCl^-; also ↑production of PGs & HCO_3^-; used for lmtd to GI bleeding ulcers; Ques asking which coats ulcer, pick sucralfate. (already have ulcer). If asking what is most effective, still PPI



- ***Bismuth (Peptobismuth in US)***: mostly similar to sucralfate, prevents traveler's diarrhea, Bismuth-based "quadruple therapies" against H.Pylori (Not so commonly used); adverse efx: **Black discoloration** of stool & tongue but its N, not pathologic

4. **Anti H. Pylori drugs**: ***PPIs***, ***Clarithromycin***, ***Amoxicillin***, ***Metronidazole***, ***Tinidazole***, ***Tetracycline***, ***Bismuth***
   - **1. Standard "triple therapy" regimens**: PPI +Clarithromycin+ Amoxicillin or Metronidazole or Tinidazole; All drugs given twice daily for 14 days & PPIs continued for additional 4-6 weeks; Triple therapy: **PPI + Clarithromycin** (these 2 are a **must**) + **Amoxicilin/Metronidazole/Tinidazole**
   - **2. "Quadruple therapy" regimens**: PPIs+ Bismuth+ Metronidazole+ Tetracycline



L1B GI Pharm pt. 2 – Diarrhea, Constipation, IBD, IBS & Vomitting, & prokinetic agents

Antidiarrheal agents

- **Opioid derivatives- Loperamide, diphenoxylate**: stimulate Peripheral μ opioid receptor & anticholinergic axn; ⏚Tone of anal sphincter, ¬¬Propulsive movements/motility, ¬¬Intestinal secretion & enhancing absorption**;** Adv's: More potent constipating axn than morphine, less CNS efx, less abuse & longer duration of axn**;** for Non infective diarrhea, Mild traveller's diarrhea & Idiopathic diarrhea in AIDS

- **Laxatives:**
  - **1. Bulk forming laxatives:** fiber adds bulk to stools, ie. Psyllium, methylcellulose, Bran – husk, Isaphagula, Fruits, vegetable
  - **2. ***Stool softeners:** anionic surfactants that enable additional water & fats to be incorporated in stool; bloating; ie. **Docusate (oral/enema), glycerine suppository, mineral oil**
  - **3. Osmotic laxatives:** retain water in colon & exert osmotic efx; prevents water being absorbed in mucus

- Magnesium hydroxide, polyethylene glycol, lactulose, magnesium citrate. PEG
- *******Lactulose also treats Hepatic encephalopathy by same mechanism –helps trap ammonia (NH_3) in colon & bind to it by using gut flora to acidify colon, transforming freely diffusible ammonia into ammonium (NH_4^+) that can no longer diffuse back into blood

- **4. Stimulant laxatives (cathartics):** stimulate n plexus & so stimulate peristaltic axn; ie. Aloe, senna, cascara, bisacodyl
- **5. Chloride channel activator Lubiprostone:** for *IBS w/predominant constipation*; ***Activates Cl channel (ClC-2) on apical aspect of GI epithelial cells, producing chloride rich fluid secretion

Drugs for IBS (Irratable Bowel Syndrome): disorder w/episodes of abdominal discomfort (pain, bloating, distention, or cramps) + diarrhea or constipation; Tx w/following (mostly for sx)

- **Antidiarrheals** (**Loperamide**)/**laxatives (Psyllium or methylcellulose**)
- **Anticholinergics (dicyclomine)-** to relive spasm
- **Antidepressants** for pain & depression

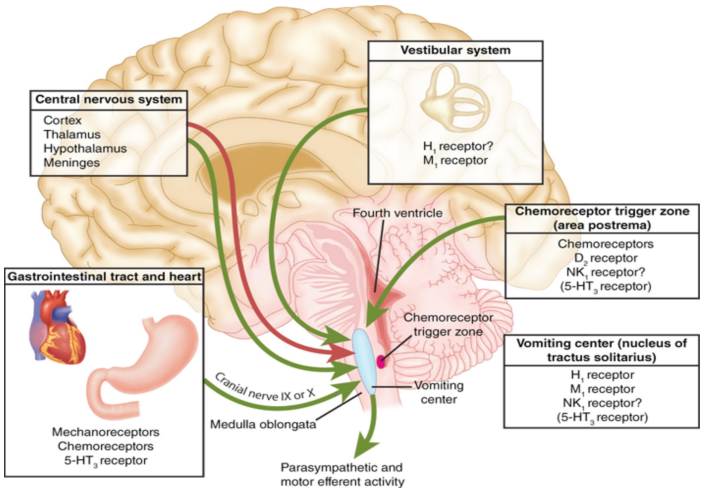
- *******Alosetron:** 5-HT3 antagonist for Diarrhea in IBD, (rel'd to Odansetron used in vomitting – also 5-HT3 antagonist); Both Ht-3 & Ht-4 produce opp efx but ⏚5-HT
- **Lubiprostone:** ⏚fluid secretion in intestine & help in passage of stools (for IBS w/constipation)
- ~~**Tegaserod:** 5-HT4 agonist (for IBS w/constipation – w/drawn)~~

Inflammatory bowel diseases

- **5-aminosalicylates: Sulfasalazine & Mesalamine**; 1st line in mild or moderate ulcerative colitis & Crohn's dis; more effective in ***maintaining*** than achieving clinical remission; MOA: inhibit PGs & LT biosynthesis
- **GC's: Budesonide** used in moderate to severe IBD; inhibits TNF-α, IL-1, PL-A2, COX-2
- **Purine analogs: Azathioprine, Mercaptopurine**: beneficial in pt's resistant to GC's. Remission after 6 mo's
- **Mtx:** rapid onset axn & effective in Crohn's dis but not so much in ulcerative colitis
- **TNF-α antagonists: Infliximab** (DOC for RA) & **Adalimumab**. Adverse efx: Reactivate Tb & other infections
- **Antiintegrins**: Natalizumab

Vomiting & Antiemetics

⏚ **Vomitting center**: loosely org'd neuronal structure in lateral medullary RF; [high] of Histamine **H_1**, DA **D_2**, Cholinergic **M**, Serotonin **$5\text{-}HT_3$** receptors, & NK_1 receptors; Inhibit Chemoreceptor trigger zone – post to 4th ventricle



4 Afferent inputs to Vomitting Center –

1. **CTZ (Area Postrema):** in floor of 4th ventricle, outside BBB; play role in any vomiting due to blood borne emetics; rich in D2, 5-HT-3 & NK receptors; acted on by – **Antiemetics: (DOAM) = Ondansetron, Metoclopramide, Domperidone & Aprepitant (NK antagonist)**

2. **Vestibular system:** play role in vomiting due to motion sickness, mediated thru CN VIII; rich in M & H1 receptors; acted on by –**Anticholinergics (Scopolamine or Hyoscine) & Antihistamines (meclizine, diphenhydramine)**
3. **GIT:** play role in vomiting due to GI irritation due to Chemotherapy, radiotherapy, enteritis, emetics from blood; mediated thru Vagus & other spinal afferent n's; rich in 5-HT_3 receptors; acted on by –**Ondansetron**
4. **CNS:** play role in vomiting due to psychiatric disorders, stress, anxiety; anticipatory vomiting prior to chemotherapy; acted on by –

- **Benzodiazepines, Dronabinol (tetrahydro canabinoid)**
- **Phenothiazines**: ***Prochlorperazine & promethazine*** that ↓vomiting by blocking M & D2 receptors b/c also block H1, causes sedation.
- **Neuroleptics**: ***Chlorpromazine, Haloperidol***

Emetics: used only to induce vomiting in case of poisoning;

- **Apomorphine** – acts on CTZ to stimulate opioid receptors
- Powdered mustard suspension
- Strong salt solution

Prokinetics: drugs that promote upper GIT Motility; ↑coordinated contraction of antrum & duodenum, ↑gastric emptying, relief gastric stasis, ↓reflux esophagitis/heartburn, ↓regurg of gastric contents & emesis; CONTRAINDICATED in bowel obstruction ******; see table –

CATEGORY	PROTOTYPE	MECHANISM OF AXN
Muscarinic agonist	Bethanachol	↑ GI motility
Anticholinestrase	Neostigmine	↑ GI motility, inhibit ACh degradation
DA D_2 blockers	Metoclopramide & domperidome	Blocks inhibitory D_2 receptor
5-HT_4 agonists	****Cisapride, Mosapride**** (not existing in market anymore, but imp for step, in PVT (Torsades des pointes - Cisapride)	Activates excitatory 5-HT_4 receptors
Motilin Agonist – peptide hormone – GI M cells	Erythromycin	Activate neural & SM motilin receptor

Dopamine D_2 blockers

- **Metoclopramide**: D_2 selective DA antagonist (anti-emetic) provides short-term benefit in tx'ing diabetic gastroparesis (delaying emptying of solids by stomach w/mechanical obstruction in DM); crosses BBB thus adverse efx: hyperprolactenemia ***& EPS***
- **Domperidone**: D_2 selective antagonist; doesn't cross BBB so no EPS but still can cause hyperprolactenemia (b/c DA inhibits PRL release)

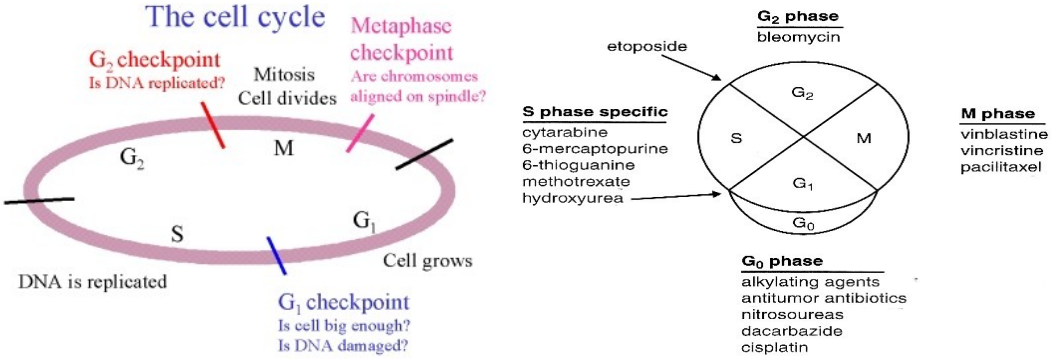
5-HT_4 agonists

- **Cisapride (PROPULSID):** serotonergic agonist, activates 5-HT_4 receptor & blocks 5-HT_3 receptor; w/drawn from market; causes upper G.I. motility, promote colonic hyper motility; no D_2 receptor activity, no CNS related side efx; no hyperprolactenemia, no anti-emetic efx; **causes ventricular arrhythmia by torsade's de pointes (when combined w/CYP450 inhibitors – KTZ, macrolides etc.)******
- **Erythromycin:** macrolide antibiotic & acts as motilin agonist; ↑gastric emptying & duodenal contraction; useful in diabetic gastric paresis

L3 Cancer - Chemotherapy

▫ Cancer chemotherapy curative in certain cancers – testicular cancer, NHL, HL, choriocarcinoma, ALL, wilms tumor, burkitts lymphoma. For many other disseminated cancers, chemo provides palliation improving QoL

▫ All cells undergo cycling can be subdivided into phase named G0 (resting phase) & into 4 cycling phases..G1, S, G2 & M. Phases for normal & neoplastic cells. There are cell cycle specific drugs & non-cell cycle drugs.



After completion of mitosis, resulting daughter cells have 2 options: (1) either enter G1 & repeat cycle or (2) go into G0 & not participate in cell cycle

- **Growth fraction**: at any particular time some cells going thru cell cycle whereas others resting; =# cells going thru cycle/# cells resting; ratio of proliferating cells to cells in G0; tissue w/large %age of proliferating cells & few cells in G0 has high growth fraction. Conversely, tissue made of mostly of cells in G0 has low growth fraction; CCS kill only cycling cells, whereas CCNS drugs kill cell that are cycling or in G0 (quiescent)
  - Rarely use 1 drug, more often combo. Combine cell cycle specific w/non-cell cycle
  - High growth fractions (leukemia, lymphoma) à use CCS drugs (more replication = can target that step)
  - Low growth faction à use CCNS drugs
  - Cycling cells are more sensitive
- Combos of agents w/differing toxicities & MOA often employed to overcome lmtd cell kill of ind anti cancer agents. Each drug selected should be effective alone
- *3 adv's of combo therapy*: suppress drug resistance (less chance of cell developing resistance), ⩧cancer cell kill (b/c admin of drugs w/diff MOA), ¬¬injury to N cells (by using combo of drugs w/out overlapping toxicities, achieve greater anticancer effect than we could by using any one agent alone)

- **Antineoplastic Drug Resistance**
  - **Primary resistance**: absence of resp on 1st exposure to currently available standard agents.
  - **Acquired resistance:** absence of resp develops in originally drug-sensitive tumor type.
- **Resistance to Cytotoxic Drugs**
  - MC anticancer mechanism: ⩧expressing MDR-1 gene (involved w/drug efflux) encodes for cell surface P-glycoprotein (12- transmemb domains w/2 ATP binding sites); drugs that reverse MDR include verapamil, quinidine & cyclosporine
  - MDR ⩧resistance to natural drug products anthracyclines, *vinca* alkaloids & epipodophyllotoxins

Modes of Resistance to Anticancer Drugs

Drugs or Drug Groups	Mechanism of Resistance against them
Etoposide, mtx, vinca alkaloids, estrogen & androgen receptors	Change sensitivity (or ↑lvl) or ↓binding affinity of target enzymes/ receptors
Mtx, alkylating agents, dactinomycin	⊏⊏ drug accumulation via ↑glycoprotein transporters, or ↓ permeability
Purine & pyrimidine antimetabolites	Formation of drug-inactivating enzymes
Alkylators, bleomycin, cisplatin, doxorubicin	reactive chemicals that "trap" anticancer drug
Alkylating agents, cisplatin	⁊⁊ nucleic acid repair mechanisms
Purine & pyrimidine antimetabolites	⊏⊏ activation of pro-drugs

▭ Adverse efx of Anticancer drugs: bone marrow suppressive (Toxic) à loss hair. Mucocytes. MALT ulcers. Combo can minimize toxicity (less dose of each); most antiproliferative so damage DNA & initiate apoptosis ▭ also affect rapidly dividing *normal* cells leading to severe toxicity. Following toxicities exhibited –

- Bone marrow: leukopenia & resulting infections, immunosuppression, thrombocytopenia, anemia ▭ Suppression can cause **aplastic anemia**; few drugs are marrow sparing (know exceptions)
- Neutropenia is a common toxicity. à Give G-CSF & GM-CSF.
- Treat anemia w/Erythropoietin.
- GI tract: oral or intestinal ulcerations, diarrhea
- Hair follicles: alopecia
- Gonads: menstrual irregularities, including premature menarche; impaired spermatogenesis
- Wounds: impaired healing
- Fetus: teratogenesis (esp during 1st trimester)
- Oral ulcers: Mucocytis, diarrhea, hair loss, teratogenesis.

Distinctive Toxicities of Some Anticancer Drugs:******

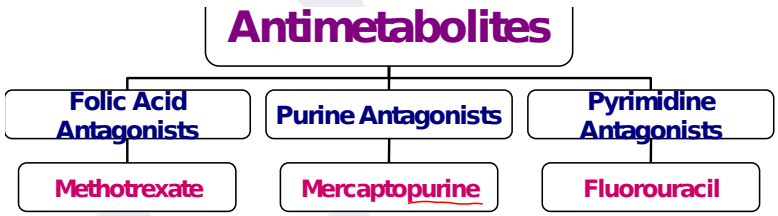
Toxicity	Drug(s)
Renal	Cisplatin*, methotrexate
Hepatic	6-MP, busulfan, cyclophosphamide
Pulmonary	Bleomycin*, busulfan, procarbazine
Cardiac	Doxorubicin, daunorubicin
Neurologic	Vincristine*, cytarabine, cisplatin, paclitaxel
Immunosuppressive	Cyclophosphamide, cytarabine, dactinomycin, methotrexate
Other	Cyclophosphamide (hemorrhagic cystitis); procarbazine (leukemia); asparaginase* (pancreatitis)

*Less Bone marrow suppression – 'marrow sparing'; Know everything on this table.

Prevention or Management of Drug Induced toxicities:

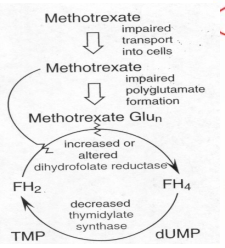
- toxicities of some anticancer drugs well anticipated & hence prevented by giving proper meds; ie. mesna given to prevent hemorrhagic cystitis (hematuria) by cyclophosphamide
- Dexrazoxane: ▭risk of anthracycline chemo-induced cardiomyopathy/cardiac complications

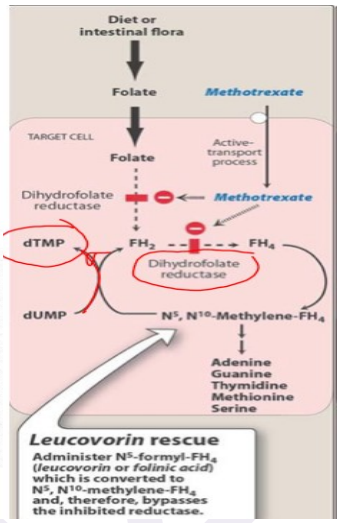
▭ CCS (***Cell Cycle Specific) Agents***: useful in tumors w/large proportions of proliferating cells (in growth fraction); includes *Antimetabolites* & *Plant Alkaloids*



➢ ***Antimetabolites***: Folic Acid Antagonist Mtx, Purine antagonist 6-MP, & Pyrimidine antagonist 5-FU

- **Methotrexate**: folic acid antagonists; S phase specific; inhibits DHFR ⊔prevents formation of THF (**FH_4 = tetrahydrofolate**, key 1-carbon carrier for enzymatic processes in de novo synthesis of thymidylate, purine nucleotides & AA's serine & methionine); used for acute leukemia, choriocarcinoma, osteosarcoma, Burkitt's & NHL's, Ca breast, psoriasis, RA (as immunosuppressant pt of DMARDS), Abortifacient (like mifiprestone w/misoprestol PG)**;** can be used w/tamoxifen or others, rarely used alone; toxicity: Mucositis, nephrotoxic, marrow suppression, folic acid def so use Rescue w/leucovorin (folinic acid/THF) ⊓toxic efx of MTX on normal cells by bypassing inhibited reductase aka leucovorin rescue ****; mechanism of resistance: ⊓drug transport, Altered DHFR, ⊓polyglutamate formation or ⊒DHFR lvls



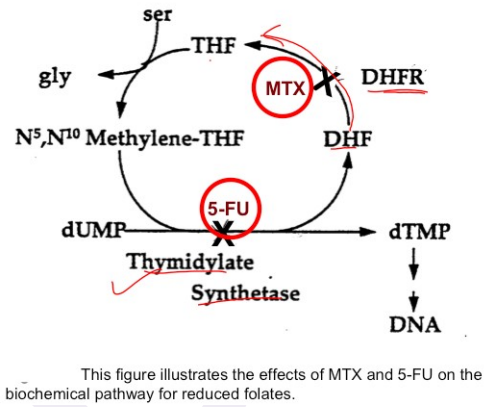


⊔ **Purine antagonists**: S phase specific so afx DNA synthesis – either –6MP or 6-TG

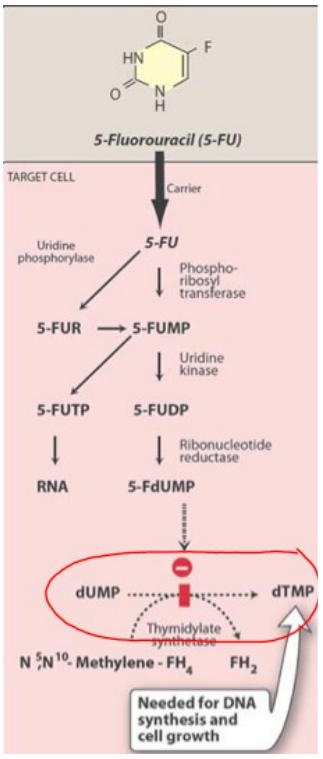
- **Mercaptopurine (6-MP):** purine antagonist prodrug S phase specific afx DNA synthesis, must be activated by HGPRT to nucleotide form that inhibits enzymes of purine nucleotide interconversion; metabolised by xanthine oxidase thus ⊒toxicity w/allopurinol so ⊓dose in such pt's; for ALL, AML & as immunosuppressant; BM depression & hepatic toxicity
- **Thioguanine (6-TG):** purine antagonist, S phase specific afx DNA synthesis

⊔ **Pyrimidine antagonists**: act on S phase so afx DNA synthesis; *5-FU, Cytarabine, Gemcitabine, Capecitabine*

- **5-FU (Fluorouracil):** incorporated into DNA; converted to 5-FdUMP ⊔competes w/dUMP for thymidylate synthetase ⊔ inhibits thymidylate synthase causing depletion of Thymidylate ⊔Thymineless death of cells; for Colorectal cancer- FOLFOX (5-FU+ oxaliplatin+leucovorin), Ca breast & ovary, Head & neck cancer, & topical for basal cell cancer & keratosis; resistance via altered thymidylate synthase

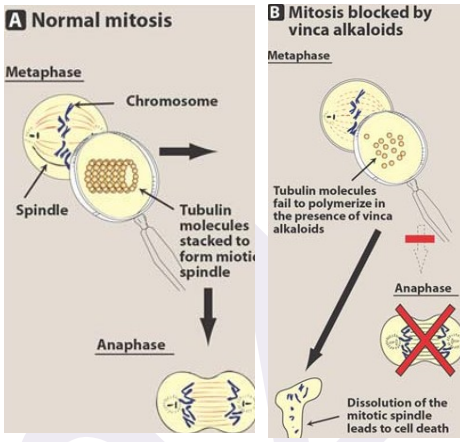


This figure illustrates the effects of MTX and 5-FU on the biochemical pathway for reduced folates.

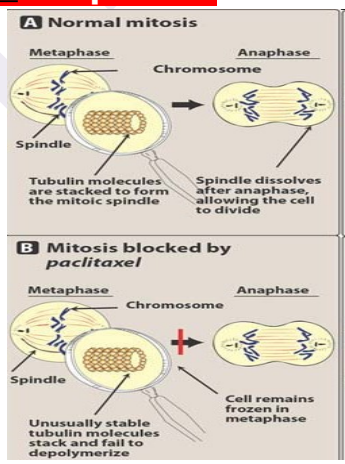


- **Cytarabine**: S phase specific; for induction of remissions in AML**; adverse efx: Neurotoxicity (cerebellar dysfunc, peripheral neuritis) & immunosuppressive**
- **Gemcitabine**: S phase specific; for pancreatic cancer, small cell lung cancer; adverse efx: myelosuppression
- **Cytarabine & Gemcitabine**: **S-phase specific;** activated by deoxycytidine kinase to monophosphate, diphosphate & triphosphate forms that inhibit DNA synthesis by competitive inhibition of DNA pol's & interference of chain elongation

- **Plant Alkaloids**: Vinca Alkaloids (Vinblastine, Vincristine, Vinorelbine), Podophyllotoxins (Etoposide, Teniposide), Camptothecins (Topotecan, Irinotecan) & Taxanes (Paclitaxel, Docetaxel); **all** derived from plant extracts. **Vinca** & **Taxanes** have same axn so we can categorize: Both inhibit **M phase** (**mitosis**)

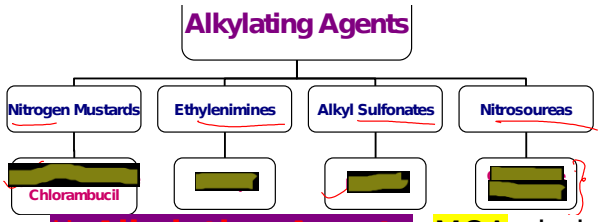


  - **Vinca alkaloids:** CCS agents- afx M phase**;** binds to microtubular tubulin in dimeric form ␣drug-tubulin complex adds to forming end of MT's to terminate assembly ␣MT's depolymerization resulting in mitotic arrest at metaphase, dissol'n of mitotic spindle & interference w/chr segregation; derived from vinca rosea, periwinkle plant, "Spindle Poison" [MT's imp pt of cytoskeleton & mitotic spindle]
    - **VinBlastine:** Uses: ABVD (adriamycin, Bleomycin, Vinblastine, Dacarbazine) regimen HL's, Ca Breast, testicular cancer, head & neck Ca, non-small cell lung cancer**; Toxicity: Bone marrow suppression, Alopecia**
    - **VinCristine:** Uses: MOPP regimen (HL), Childhood tumors- Wilms' tumor, Choriocarcinoma, Childhood leukemias- acute leukemias**; Toxicity: Peripheral neuropathy**** (bilateral foot drop, loss DTR's, ↓vibratory sensations), areflexia, m weakness, paralytic ileus,** but mild/marrow sparing efx
    - **Vinorelbine:** for non-small cell lung cancer**; Toxicity: myelosuppression**



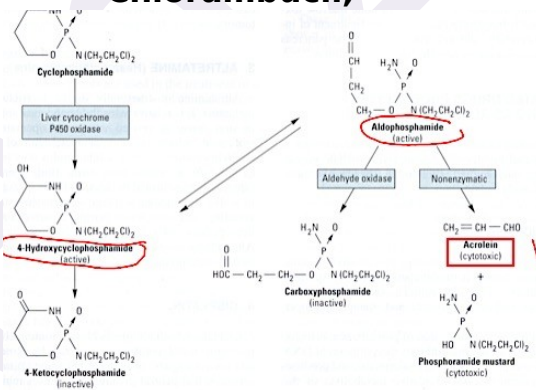
  - **Taxanes (pic):** afx M phase; alkaloid esters derived from Western & European Yew; mitotic "spindle poison" thru enhancement of tubulin polymerization ␣prevent MT disassembly into tubulin monomers; includes paclitaxel (**Taxol**) & docetaxel (Taxotere) mainly to treat **breast cancer; toxicity: Neurotoxicity**
    - **Paclitaxel:** taxane for ovarian & breast cancer
    - **Docetaxel:** taxane for advanced breast cancer
  - **Podophyllotoxins**: **Etoposide, Teniposide**; semi-synthetic podophyllotoxin derivatives from root of mayapple; block cells in late S-G_2 phase of cell cycle thru inhibiting *topoisomerase II* resulting in ds-DNA strand breakage during replication; for Testicular cancer, Small cell carcinoma of lung- Cisplatin + Etoposide/irinotecan
    - **Top II** binds tightly to DNA double helix & make transient breaks in both strands so enzyme then causes 2nd stretch of DNA double helix to pass thru break, & finally **reseals** break
    - **Etoposide** & **teniposide** both block **cell cycle** in 2 specific places: phase btwn last division & start of DNA replication (G1 phase) & block replication of DNA (S phase). But researchers don't have good understanding of how they do this; water **in**soluble & require solubilizing vehicle for clinical formulation; After IV admin, they're protein bound & distributed thru **except** brain & excreted in urine
  - **Camptothecins**: ***topotecan*, *irinotecan***; **interfere w/*Topoisomerase I* (**breaks & reseals ss-DNA) ␣ **DNA damage; {TOP I** reversibly cuts *ss* of double helix; have both nuclease (strand-cutting) & ligase (strand-resealing) activities. Create **nick** in strand & then reseal to relieve supercoils}
    - **Topotecan:** metastatic ovarian cancer (cisplatin-resistant)
    - **Irinotecan:** colon & rectal cancer; also w/etoposide for small cell cancer lung; toxicity: severe diarrhea

␣ CCNS (***Cell Cycle NON-Specific) Agents***: bind to DNA & damage it; useful in low growth fraction solid tumors & high growth fraction tumors; includes Alkylating Agents,



Alkylating Agents: MOA via intramolecular cyclization to form either ethyleneimonium or carbonium ion (strongly electrophile); Alkylation w/in DNA at N7 pos of guanine resulting in miscoding thru abnormal bp'ing w/thymine or in depurination by excision of guanine residues, leading to strand breakage ⎵cross-linking DNA; 4 groups of alkylating agents: know drug names, even if you forget drug class; chem'al structure same for all; all have toxicity of marrow suppression w/leukopenia & thrombocytopenia; if Ending in **mustine** à effective for **brain tumors;** 1 forms cycle & form 2 ions (**toxic intermediates cause alkylation)**

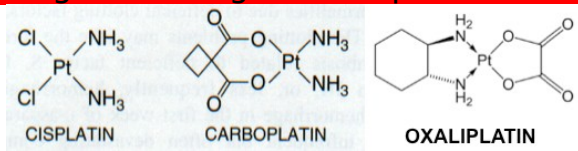
- **Nitrogen mustards:** *******Cyclophosphamide, Chlorambucil, Melphalan, Ifosfamide, mechlorethamine**
  - ***Cyclophosphamide/Ifosfamide:*** *for* NHL, ovarian & Breast Ca (lymphomas, some leukemias & solid tumors)**; advsere efx/ toxicity: hepatic toxicity, immunosuppressive, hemorrhagic cystitis** (results from toxic metabolite acrolein**)** & **CC by coadmin w/MESNA (**Mercaptoethane sulfonate, provides e-'s from sulfhydryl group**)**; to prevent DNA repair by guanosine-O6-alkyl-a-transferase (GOAT), O6-benzyl guanine is given; Hepatic metabolism à P450; convert to hydroxycyclophosphamide to aldophosphamide (active still) to carboxyphosphamide – non-active



  - ***Mechlorethamine, Procarbazine* –** for HL's (MOPP regimen)
- **Ethylenimines: Thiotepa** for ovarian cancer
- **Alkyl Sulfonates: Busulfan:** alkylating agent for CML tx; adverse efx: pulm toxicity, hepatic toxicity
- **Nitrosoureas: Carmustine, Lomustine, Semustine & Streptomycin;** for brain tumors; Highly lipophilic & all cross BBB for brain tumors; Non-cross reactive w/other alkylating agents; all require biotransformation by nonenzymatic decomposition; -**mustine**
  - ***Streptozocin* –** naturally occuring sugar containing**;** Tx insulin secreting islet cell carcinoma of pancreas; used in animal models to destroy beta cells to cause diabetes (not clinically used)

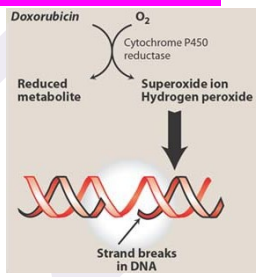
⎵ **Alkylating rel'd agents**: CCOPD! = Procarbazine, Dacarbazine, Cis*platin*, Carbo*platin*, Oxali*platin*; MOA by alkylation of guanyl residue at N7 pos

- Dacarbazine: treat cancers – malignant melanoma, HL, Sarcoma, & islet cell carcinoma pancreas; causes N/V, bone marrow suppression, & rarely hatal hepatotoxicity
- ***Procarbazine* –** *for HL (MOPP), adverse efx:* leukemogenic (leukemia), & pulm toxicity
- ***Cisplatin, (Carboplatin, Oxaliplatin)* –** treats non-small cell & small cell lung cancer, testicular, ovarian carcinoma, Ca bladder**;** inorganic metal complex, kills cells in all phases of cell cycle thru cross-linking; **platin** suffix = **platinum containing**: alkylate N7 of guanine – cross link DNA strands; cause nephro- & ototoxicity; nephrotoxicity **tx w/**give mannitol osmotic diuretic, or amifostine**;** only nephrotoxic drug. Also ototoxic. highly nephrotoxic, so don't give w/things like amphotericin B, Vancomycin, Cephalosporins;

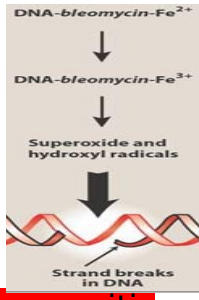


Antibiotics: work by binding to DNA thru 1) intercalation btwn bp's & (-) of new RNA or DNA 2) cause DNA strand scission 3) & interference w/cell replication; products of various strains of soil fungus *Streptomyces*; ***includes Anthracyclines (Dox, Daun), Dactinomycin, Plicamycin, Mitomycin, Bleomycin***

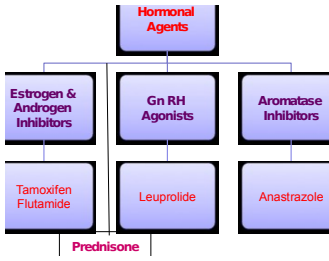
- **Anthracyclines: Doxorubicin***** & Daunorubicin****; Toxicity:** bone marrow depression, total alopecia, Cardiac toxicity- dilated cardiomyopathy can cause arrhythmias & HF due to oxygen free radicals; prevent w/dexrazoxane iron chelating agent –bind heavy metals to prevent forming free radicals – protect against cardiotoxicity; & antioxidants like vit E
  - **Doxorubicin/Adriamycin:** does intercalation btwn DNA ⊟block DNA & RNA synthesis; inhibits Topoisomerase II, but generate oxygen radicals; *CCNS; **ABVD regimen for HL, carcinomas of breast, endometrium, ovary, testicle, thyroid, lung & osteosarcoma; toxicity:** generate free radicals ⊟ **cardiac toxicity** thru oxygen radical mediated damage to memb's, alopecia, stomatitis



  - **Daunorubicin**: treats acute leukemia; toxicity: cardiac toxicity
- **Dactinomycin:** intercalates into ds-DNA btwn adj guanine-cytosine bp's & inhibits DNA-dependent RNA polymerase; for Wilms' tumors, Melanoma; 3 D's intercalate btwn bp's, rRNA formation being most sensitive to drug axn, DNA replication less effected, while protein is blocked; degree of cytotoxic efx determined by cells ability to accumulate & retain antibiotic; mainly excreted in bile; toxicity: immunosuppressive
- **Bleomycin****: CCS drug that afx G2 phase; combines w/iron forming complex that generates free radicals in presence of oxygen [complexes w/Fe & $O_2 \rightarrow$ DNA strand scission via superoxide & hydroxyl radicals]; mixture of 11 diff glycoproteins used in therapy, major components being A_2 & B_2; for Testicular cancer, HL (ABVD regimen), SCC of Head & neck, penis, cervix & vulva; toxicity: Pneumonitis ⊟Pulm fibrosis*** , edema of hands, stomatitis, alopecia



Hormonal Agents: b/c sex hormones concerned w/stimulation & control of proliferation & func of certain tissues, like mammary & prostate glands, cancers arising from these tissues inhibited or stimulated by appropriate changes in hormone balance; sex hormones used in cancer of female & male breast, prostate & cancer of endometrium of uterus; **aka estrogen & androgen inhibitors, Prednisone, GnRH Agonist Leuprolide & Aromatase inhibitors (Anastrazole)**; in prostate cancer, estrogens lead to suppression of androgen production; produce fluid retention thru their sodium-retaining efx; prolonged use of androgens & estrogens causes masculinization & feminization, respectively; extended use of adrenocortical steroids can cause HTN, diabetes & cushingoid appearance



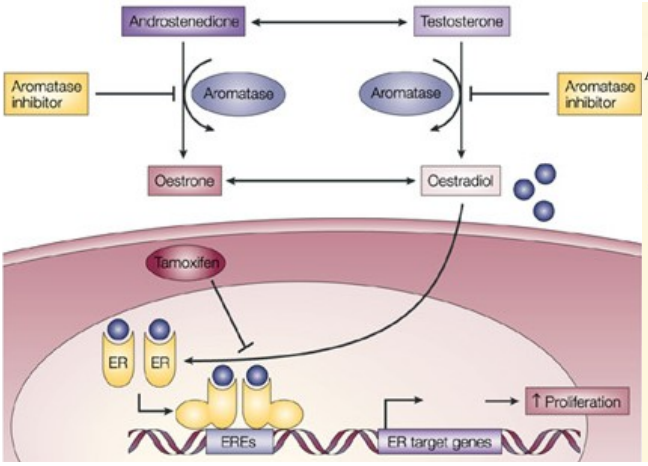
⊟ **Estrogen & Androgen Inhibitors**

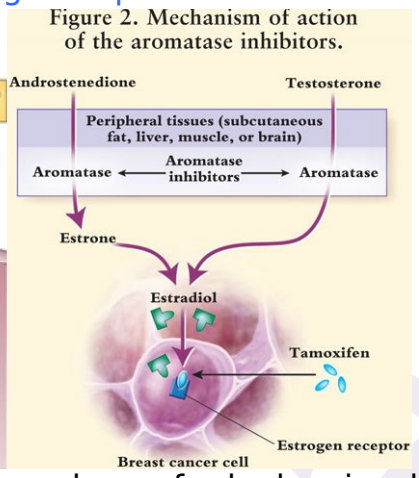
- **Tamoxifen**: SERM (selective estrogen receptor modulator) w/antiestrogenic efx on breast tissue; blocks estrogen receptors (ER) in breast & induces conformational changes in receptor ⊟ ⊓estrogen resp; primary therapy *for metastatic breast cancer*; estrogen-receptor (ER) +ve tumors more likely to respond
- **Flutamide**: Androgen/testosterone receptor blocker for Carcinoma prostate w/GnRH agonist (*leuprolide*)

⊟ **GnRH Agonists: Leuprolide, Goserelin, Nafarelin**: initially ⊜LH & FSH w/'flare' of sx then downreg/inhibit FSH & LH release ⊟ ⊓testicular androgen synthesis; for prostate Cancer; analogs

more potent than natural hormone & fxn as GnRH agonist, w/paradoxic efx on pituitary (initially ⇧, but then ⇩ by continuous admin)

- **Aromatase Inhibitors**:
  - **Aminogluthethimide:** inhibit adrenal steroid synthesis at 1st step, conversion of cholesterol to pregnenolone
  - **Anastrozole, letrozole:** inhibits aromatase that converts androstenedione to estrone; used for Advanced Ca breast that's no longer responsive to tamoxifen





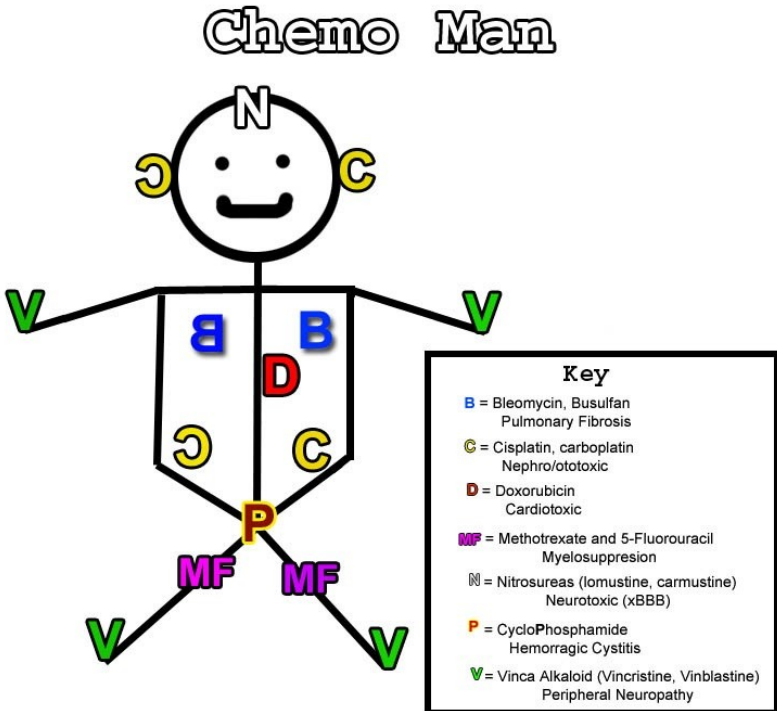
  - **Prednisone**: widely used GC in cancer chemo for leukemias, lymphomas (MOPP. Other P is procarbazine)

- **Miscellaneous AntiCancer Agents**
  - ***L*-Asparaginase:** enzyme isolated from bacteria; catalyzes deamination of asparagine to aspartic acid & ammonia; neoplastic cells require external source of asparagine b/c their lmtd capacity to made sufficient AA's to support growth & func; hydrolyzes blood asparagine & thus, deprives tumor cells of this AA, which is needed for protein synthesis; used for childhood acute *L*eukemia*****; toxicity: Anaphylactic shock, Acute pancreatitis***** (used to use for leukemia. But now don't use as much b/c of anaphylaxis & pancreatitis)
  - **Hydroxurea******:** inhibits ribonucleotide reductase resulting in depletion of deoxynucleoside triphosphate pools thereby inhibiting DNA pyrimidine synthesis; *S-phase specific agent* used for CML*
  - **Mitoxantrone:**
  - **Imatinib******: Gleevac used for CML;** inhibits tyrosine kinase of protein product of Bcr-Abl oncogene commonly expressed in CML; for Ph + CML******; also for kit=+ve GIST's
  - Erlotinib/Tarceva: treats non-small cell lung cancer, pancreatic cancer & other cancers that failed prior trial of chemo; tyrosine kinase inhibitor that inhibits EGFR (highly expressed & sometimes mutated in those cancers)
  - **Interferons: α interferon:** used for hairy cell leukemia, T cell lymphoma
  - **Monoclonal Ab's*****:**
    - **Rituximab:** chimeric Monoclonal Ab against CD20 Ag (cell receptor on surface of/specific for B lymphocytes); for CD20+ NHL's & other dis's rel'd to excess B cell func; depletes B cells (& abnormal Ab production) thru multiple pathways, including complement-mediated lysis, Ab-dependent cytotoxicity (via NK cells) & induction of lymphocyte apoptosis, also for RA
    - **Trastuzumab:** Monoclonal Ab against HER-2 Ag for HER2 +ve Breast cancer; binds to portion of EC domain of HER2 & prevents activation of transmemb tyrosine kinase ⇩ down regulates proliferation & promotes apoptosis
    - **Certolizumab pegol:** pegylated (pegol) humanized monoclonal Ab that targets TNF-α; lacks Fc region (preventing complement activation & mediated cytotoxicity) & used in tx'ing autoimmune disorders associated w/TNF-α;

Tx of Specific Cancers*****

- **HL/Hodgkin's dis: (**Patient with Hodgkin's develops cardiac failure à Adriamycin (Doxorubicin)
  - **ABVD regimen (Adriamycin, bleomycin, vinblastine, dacarbazine)**
  - **MOPP regimen (mechlorethamine, vincristine/oncovin, procarbazine, prednisone)**
- **NHL: tx w/C-DROP regimen (cyclophosphamide, doxorubicin, Rituximab, vincristine, prednisone)**
- **Multiple myeloma: tx w/MP protocol (melphalan & prednisone); also can use**
  - **Bortezomib:** binds & inhibits 26S proteasome to facilitate apoptosis of neoplastic cells by preventing degdration of pro-apoptotic factors in MM
- **Ca Breast:**
  - **CAF regimen (Cyclophosphamide (w/MENSA) + Adriamycin + 5-FU)**
  - **CMF protocol (cyclophosphamide (w/MENSA) + MTX (w/leucovorin) + fluorouracil)**
  - **Tamoxifen**
  - **Anastrozole, letrozole**
- **Small cell lung cancer: tx w/Cisplatin + Etoposide/Irinotecan**
- **Testicular cancer**
  - **BEP (Bleomycin, etoposide, cisplatin) [**Bleomycin & platinum compound]; develops dry cough & pulm fibrosis à drug is belomycin
  - **CVB (Cisplatin, vinblastine, bleomycin)**
- **Prostate Ca: tx w/Leuprolide (LH Releasing Hormone agonist)+ Flutamide (antiandrogen)**
- **Ca Bladder: tx w/M-VAC (Mtx, vinblastine, adriamycin, cisplatin)**
- **Colorectal cancer: tx w/FOL (5-FU+ oxaliplatin + leucovorin)**
- **Choriocarcinoma: tx w/Methotrexate + leucovorin**
- **Brain cancer, tx w/Carmustine/ lomustine/semustine**
- **CML tx w/Imatinib / Hydroxyurea/busulfan/Bone marrow transplantation**
- **AML: tx w/Cytarabine+ idarubicin**
- **ALL: For induction: Vincristine+prednisone, Maintainance: Mtx, 6-MP**

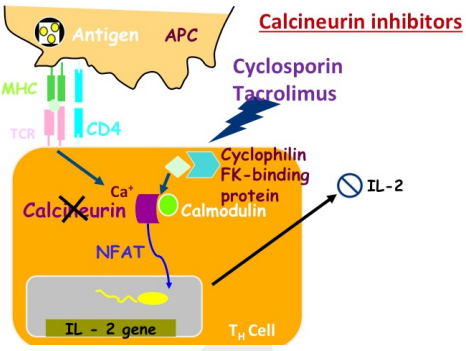
- Prevention/management of Cancer Chemo induced toxicity*****
  - N/V tx'd/prevented w/5-HT3 antagonist ondansetron à 5-HT3 b/c when we kill cancer cells there's a serotonin release (we block axn of this)
  - Bone marrow suppression tx'd or prevented w/Filgrastim, Sargromastim (colony stimulating factors)
  - MTX toxicity tx'd or prevented w/Leucovorin
  - Cyclophosphamide induced toxicity tx'd or prevented w/MESNA
  - Cisplatin induced nephrotoxicity tx'd or prevented w/Mannitol/Amifostine
  - Anthracycline induced cardiotoxicity tx'd or prevented w/Dexrazoxane



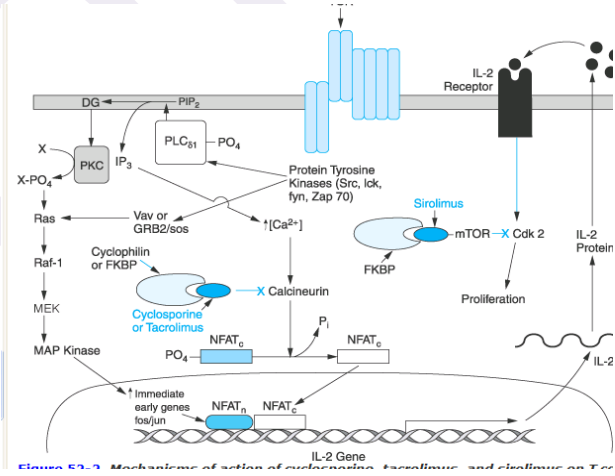
L4 Immunopharm

- **Corticosteroids**: inhibit MHC expression, block cytokine gene expression, inhibit proliferation of T lymphocytes, either used alone or in combo w/other drugs; uses of steroids as immunosuppressants: commonly combined w/other immunosuppressive agents to prevent & treat transplant rejection, high dose pulses of IV *methylprednisolone* used to reverse acute transplant rejection & acute exacerbations of selected autoimmune disorders; pulse therapy à minimize long term side efx; Limitation: Long term complications, ** inhibits MHC expression. If we give GC's for long term for things like RA, expect Cushing's – diabetes, cataracts, osteoporosis. ADR: GR in kids, Osteomalacia, ↓risk infection, Poor wound healing, HTN
- **Calcineurin inhibitors: cyclosporine, tacrolimus**; available anti-IL2-receptor Ab's are monoclonal agents that are not lymphocyte depleting, but instead cause func'al arrest of lymphocyte func by blocking efx of IL-2 on its receptor, thus –vely influencing signal 3;
  Specific T cell inhibitors à suppress CMI resp more than humoral (suppress IL's)
  - **Cyclosporine:** binds cyclophilin; immunosuppressive for human organ transplantation in tx of graft vs host dis after bone marrow transplantation & in therapy of certain autoimmune disorders; MOA: specific & reversibly inhibits immunocompetent lymphocytes in G0 & G1 phase of cell cycle (esp T-helper cells); +inhibits lymphokine production & release; for Ulcerative colitis doses, considered an immunomodulators; usually combined w/other agents, esp GC's & azathioprine - Transplantation & autoimmune dis's; side efx: renal dysfunc, tremor, hirsutism, HTN & gingival/ gum hyperplasia; Highly nephrotoxic à watch Cr clearance. Use w/other drugs; DI: Substances that inhibit CYP enzymes ↑↑cyclosporine metabolism & ↓[blood]'s; include: Antifungals (*ie. KTZ*), Antibiotics (*erythromycin*), GC's (methylprednisolone), HIV-PI's (*indinavir*)
  - Drugs that ↑CYP3A, ↓cyclosporine metabolism & ↑↑[blood]'s. Inducer à ↑↑effectiveness of other drugs. Ie. Antibiotic *rifampin*, Anticonvulsants *phenobarbital, phenytoin*; Cyclosporine + Sirolimus/Rapamycin = Enhanced renal toxicity
  - **To avoid renal toxicity separate by time**

- **Tacrolimus:** binds FKBP (FK-binding protein) & cyclophilin ⇂ complex à inhibits calcineurin à ↓IL-2, IL-3 & IFN production; prefer for Kidney, liver, heart, & other organ transplantation, RA, Psoriasis; ADR: Nephrotoxicity (w/both cyclosporin & tacrolimus);



- Normal: Ag presented by APC (mac or fibroblast) à presented to T cell. Once T cell receptor activated à influx Calcium & binds Calmodulin (activates **calcineurin**) ⇂ Calcineurin causes transcription of IL-2 & other genes (needed for CMI resp) ⇂Cause transcription of IL's as Calcineurin is needed for NFAT.Know 2 drugs: Cyclosporin – binds cyclophilin; Tacrolimus – binds FK binding protein. Once bound they form drug-protein complex that inhibits calcineurin. No calcineurin activation à no activation of NFAT (Nuclear factor that cause transcription of interlukins like IL-2)
- **Sirolimus**: inhibits T-lymphocyte activation & proliferation ⇂ ↓IL-2 made; like cyclosporine & tacrolimus, therapeutic axn requires formation of complex w/immunophilin FKBP-12. However, sirolimus-FKBP-12 complex doesn't affect calcineurin activity directly; binds to & inhibits protein kinase, designated *mammalian target of rapamycin* (mTOR) – key enzyme in cell-cycle progression; inhibits mTOR blocks cell-cycle progression at G1 ⇒ S phase transition; for prophylaxis of organ transplant rejection in combo w/calcineurin inhibitor & GC's; binds diff subtype of FK binding protein. à no affect on calcineurin. (**inhibits protein kinase mTOR**) [stops cell cycle progression from G1àS phase]; ADR: Dose-dependent ↓in serum cholesterol & TG's/TAGs, Anemia, Leukopenia, Thrombocytopenia , Cause bone marrow suppression.[Similar to tecrolimus. à enhance toxicity. **Tacrolimus** is **calcineurin inhibitor**. binds **FK binding protein**]. Both cyclosporine & tacrolimus bind to immunophilins (cyclophilin & FK506-binding protein [FKBP], respectively), form complex that binds phosphatase calcineurin & inhibit calcineurin-catalyzed dephosphorylation essential to permit movement of NFAT (nuclear factor of activated T cells) into nuc (need NFAT for transcription of IL-2 & other growth & differentiation-associated cytokines/lymphokines). Sirolimus (rapamycin) works at l8r stage in T-cell activation, downstream of IL-2 receptor. Sirolimus also binds FKBP, but FKBP-sirolimus complex binds to & inhibits mammalian target of rapamycin (mTOR), kinase involved in cell-cycle progression (proliferation – inhibited by Sirolimus)



- **Enzyme inhibitor: Mycophenolate mofetil, leflunomide**
  - **Mycophenolate Mofetil**: inhibits inosine monophosphate DH involved in denovo purine synthesis in T lymphocytes; used for transplant rejection – used in combo w/GC's & calcineurin inhibitor
  - **Leflunomide**: inhibits enzyme required for ribonucleotide synthesis in RA
- **Anti-proliferative agents: azathioprine, cyclophosphamide;** cytotoxic to proliferating lymphoid cells
  - **Azathioprine**: converts to 6-MP- inhibits purine metabolism; immunosuppressive as adjunct therapy for preventing rejection in renal transplantation & managing severe RA unresponsive to other tx's; chief toxic efx: bone marrow suppression (severe leukopenia &/or thrombocytopenia), skin rashes, N/V, +^risk neoplasia
  - **Cyclophosphamide**
  - **Mtx**: DMARD, anti-inflammatory; afx adenosine (naturally anti-inflammatory, so ↓ immunosuppress)
  - Among anticancers à these are also anti-inflammatory
- Suffix cept = receptor molecule, mab = monoclonal Ab; nib = kinase inhibitor
- **Anti TNF drugs: etanercept, infliximab, adalimumab**
  - *Infliximab*- anti-TNF-α monoclonal Ab currently used for Rx of RA & Crohn's dis

- *Etanercept*: TNF-α inhibitor added to Mtx to treat moderate-severe RA in pt's who've failed mtx alone; fusion protein linking soluble TNF-α receptor to Fc component of human IgG1; ¬¬biological activity of TNF-α by acting as decoy receptor

- **Ab's: monoclonal Abs (muromonab)***, anti-D Ig**
  - **Human IgG against Rh(D) Ag**: administer to Rh–ve mother w/Rh+ve fetus; given w/in 72 hrs of delivery/abortion – prevent haemolytic dis in subsequent pregnancy; Ig against D Ag; RH- mother w/RH+ baby. à future babies w/Erythroblastosis fetalis
- Monoclonal Ab's & Clinical Uses
  - ******Muromonab** CD3: binds CD3 Ag GP (epsilon chain) to prevent organ transplant rejection rxn; CD3 binds to CD3; Ab tx induces rapid internalization of T-cell receptor – prevents subsequent Ag recog aka kills CD-3 +ve cells by inducing Fc mediated apoptosis, Ab mediated cytotoxicity & complement-dependent cytotoxicity; indicated for tx of acute organ transplant rejection; targets CD3 à CD3 helps w/MHC in recog of molecule to help activate T cell receptor; cause anaphylaxis/anaphylactoid rxns, seizures & encephalopathy as cytokine release syndrome
  - **Daclizumab**: blocks IL-2 receptors for preventing organ transplant rejection rxn
  - *******Infliximab** : TNF-α antagonist used for RA, crohn's
  - *******Abciximab**: antagonist at gpIIb/IIIa receptor as antiplatelet
  - ******Rituximab**: bind to CD20 Ag on B lymphocytes for NHL
  - ******Traztuzumab**: Bind to HER2 protein to treat Carcinoma breast
  - **Palivizumab**: use- respiratory syncytial virus (RSV) infection used in place of ribavarin
  - **Denosumab**: monoclonal Ab against RANKL, used to ¬¬skeletal-rel'd events if metastasis to bone occurs; ⎓density bone & commonly used for tx of osteoporosis
  - **Bevacizumab**: VEGF inhibitor, tx of some metastatic cancers ie. colon, lung; inhibit VEGF binding to tyrosine kinase receptor, inhibiting angiogenesis
  - **Gemtuzumab**: inhibit/block CD33 – in T cell & CML leukemias

Use and Toxicities

Immuno suppressant	Transplant rejection	Immunological disorders	Toxicity
Prednisone	√	√ SLE, RA, uveitis, psoriasis	Osteoporosis Adrenal suppression
Calcineurin inhibitors Cyclosporin Tacrolimus	√	√ SLE, RA, uveitis, psoriasis	Nephrotoxicity * Drug interactions
Mycophenolate Mofetil	√		Neutropenia
Cytotoxic drugs: Azathioprine Cyclophosphamide Methotrexate	√	√	BM suppression Haemorragic cystitis

Uses

Immunosuppresant	Immunological disorders	Transplant rejection
Etanercept	RA	----------
Leflunomide	RA	
Thalidomide	Leprosy (ENL)	
Muromonab, Daclizumab	Renal transplant	
Infliximab	Crohn's disease, RA	
Abciximab	Coronary angioplasty	
Rituximab	B-cell lymphoma	
Traztuzumab	Ca breast- overexpressing HER-2	
Palivizumab	respiratory syncytial virus (RSV)	
Rh-D Immunoglobulin	Prevention of haemolytic disease of new born	

⎓ **Immunomodulators**: agents that stimulate immune resp's w/potential for imp therapeutic uses like tx of immunodef dis's, chronic infectious dis's

- **Thalidomide**: available only under restricted distribution program; inhibits TNF-α (like infliximab), ¬¬phagocytosis, used for Erythema nodosum leprosum (ENL of Lepra rxn) & in multiple myeloma
- **Aldesleukin**: recombinant interleukin-2 used in RCC, malignant melanoma
- **Interferons**:
  - α-2a – used in hairy cell leukemia, CML, kaposi's sarcoma & hep B
  - Beta -1b – used in MS (multiple sclerosis)
  - Gamma -1b – used in CGD

L5 Drugs of Abuse

- DA Hypothesis of Addiction: DA in mesolimbic system appears to play primary role in expression of "reward," but excessive DA'ergic stimulation may lead to pathologic reinforcement such that behavior may become compulsive & no longer under control—common features of addiction. Tho not necessarily only neurochem'al charac of drugs of abuse, appears most addictive drugs have axns including facilitating efx of DA in CNS. DA reward system in mesolimbic system cause addiction.

Drug	Class	CF's	Molecular target	Pharm	Efx of DA Neurons
Drugs that activate G Protein coupled receptors					
Opioids, ie. Heroin	opioid	Euphoria, depressed mental status, miosis, respiratory depression, constipation, low lethargic behavior	**-OR (G_{io})**	Agonist	Disinhibition; w/drawal efx can last weeks!!! Seen by lacrimation & yawning
Cannabinoids (marijuana: THC, cannabis)	psychoactive	↓appetite, euphoria, dysphoria/panic, impaired time perception, dry mouth, conjunctival injection	**CB_1R (G_{io})**	Agonist	disinhibition
-Hydroxybutyric acid (GHB)			**$GABA_BR$ (G_{io})**	Weak agonist	Disinhibition
LSD, Mescaline, Psilocybin	hallucinogen	Visual hallucinations, euphoria, dysphoric/panic, tachycardia, HTN	**5-HT_{2A} R (G_q)**	Partial agonist	…
Drugs That Bind to Ionotropic Receptors and Ion Channels					
Nicotine			**nAChR ($_{22}$)**	**Agonist**	**Excitation**
Alcohol			**$GABA_AR$, 5-HT_3R, nAChR, NMDAR, Kir3 channels**		**Excitation, disinhibition (?)**
Benzodiazepines			**$GABA_AR$**	**Positive modulator**	**Disinhibition**
Phencyclidine (PCP), ketamine	hallucinogen	Violent behaviour, disassociation, hallucinations, amnesia, nystagmus (horizontal), ataxia	**NMDA R**	**Antagonist**	**…**
Drugs That Bind to Transporters of Biogenic Amines					
Cocaine	Stimulant Smoked or snorted	Euphoria, agitation, chest pain, seizures, tachycardia/HTN, mydriasis, signs of abuse: rhinitis, insomnia	**DAT, SERT, NET; metabolite Benzoylecgonine**	**Inhibitor**	**Blocks DA uptake**

Amphetamine	stimulant	Violent behavior, psychosis, diaphoresis, tachycardia/HTN, choreiform movements, tooth decay	**DAT, NET, SERT, VMAT**	**Reverses transport**	**Blocks DA uptake, synaptic depletion**
Ecstacy/MDMA/MDA/ MDEA			**SERT > DAT, NET**	**Reverses transport**	**Blocks DA uptake, synaptic depletion**
Barbiturate		Intoxication =			

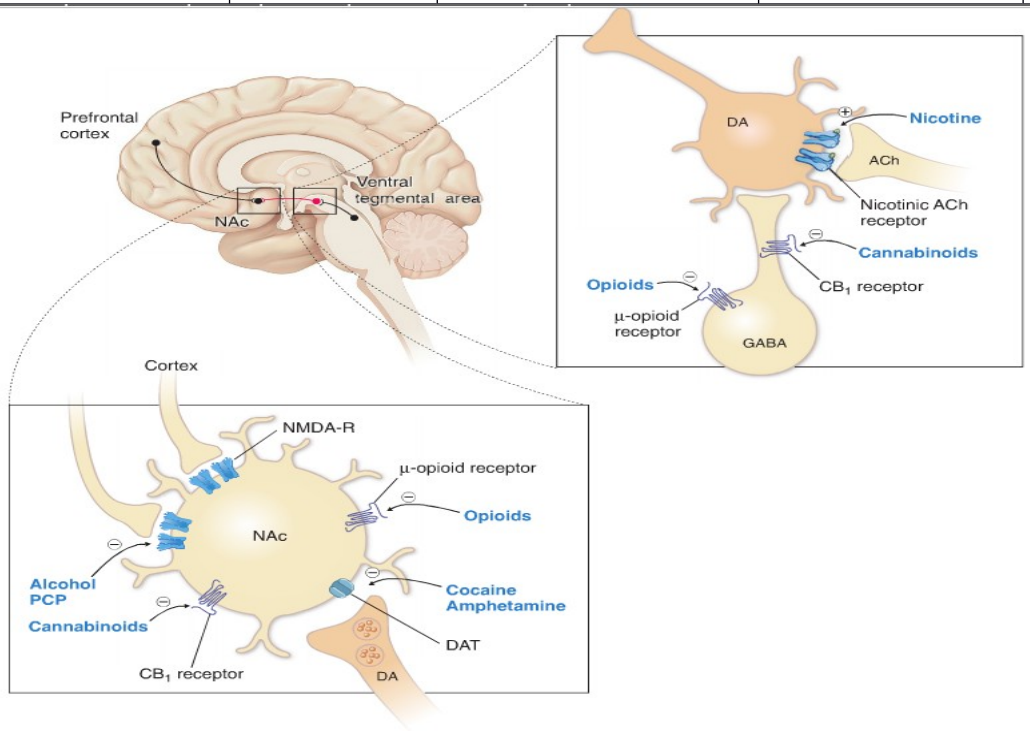


FIGURE 18–4. The mesolimbic dopamine pathway: a final common substrate for the rewarding actions of drugs. All drugs of abuse activate the mesolimbic dopamine pathway, which comprises ventral tegmental area (VTA) dopamine neurons that project to the nucleus accumbens (NAc). Different interneurons interact with VTA neurons and NAc neurons to modulate mesolimbic neurotransmission. **Nicotine** interacts with excitatory nicotinic cholinergic receptors located on VTA dopamine neuron cell bodies to enhance dopamine release in the nucleus accumbens (NAc). **Cocaine** acts predominantly at the dopamine nerve terminal to inhibit reuptake of dopamine via the dopamine transporter (DAT), thus increasing synaptic levels of dopamine that can impinge on NAc. **Amphetamine** also acts at the dopamine nerve terminal to facilitate release of dopamine-containing vesicles, and possibly to enhance reverse transport of dopamine through DAT (*not shown*). Both **cannabinoids** and **opioids** decrease GABA release from local inhibitory interneurons in the VTA, resulting in disinhibition of dopamine neuron activity and increased dopaminergic neurotransmission. Cannabinoids and opioids can also act within the NAc. **Alcohol** and other **CNS depressants** act on NMDA receptors (NMDA-R) to reduce glutamatergic neurotransmission in the NAc. The effects of alcohol on dopaminergic neurons in the VTA appear to be both excitatory and inhibitory, and are the subject of active investigation (*not shown*).

- Dopamine reward system in mesolimbic is always final pathway.
- VTA to nucleus accumbens
- Cannibus à CBT1 and CBT2 receptors. (affect release of DA)

- **Opioids** commonly abused: heroin, morphine, codiene, oxycodone & meperidine (common among health care professionals)
  - **IV heroin**: feeling of "rush" followed by euphoria, tranquility & sleepiness ("the nod"), pinpoint pupil, respiratory depression, coma; treat by Methadone; w/drawal efx: intense dysphoria, nausea vomiting, m aches, Lacrimation, rhinorrhea, yawning & sweating, chills, goose flesh ("cold turkey"), tremors, m jerks ("kicking the habit"); tx w/drawal w/substituting w/Methadone or buprenorphine followed by its slow dose ↓, Clonidine also effective for w/drawal; using opioid antagonist (naloxone, naltrexone) in abuser may precipitate w/drawal (precipitated w/drawal)
- **Marijuana or Cannabinoids**: "grass" obtained from cannabis sativa; Tetrahydrocanabinol (THC) is active ingredient; "Hashish" is partial purified material which is more potent; feeling of being "High", euphoria, uncontrollable laughter, ↓appetite, altered sense of time, difficulty concentrating, ↓memory; vasodilation & tachycardia; Habitual users show

Reddened conjunctiva. 2 type of receptor in VTA. THC is agonist at CB1 & CB2 (cannabinoid) receptors & they are in many areas of CNS. Therapeutic THC analog is Dronabinol, used to treat – Nausea vomiting in pt's receiving cancer chemo

- **g-HydroxyButyrate (GHB)/**Club/date rape drug**:** weak agonist on $GABA_B$ receptor; Lactone (GBL) found in nail polish remover; used as hypnotic: Euphoria, Enhanced sensory perception, feeling social closeness, Amnesia, general anesthesia, coma, death; rapid onset, short half-life, t_{max} = 20-30 min; $t_{1/2}$ = 60 min; odorless liquid;

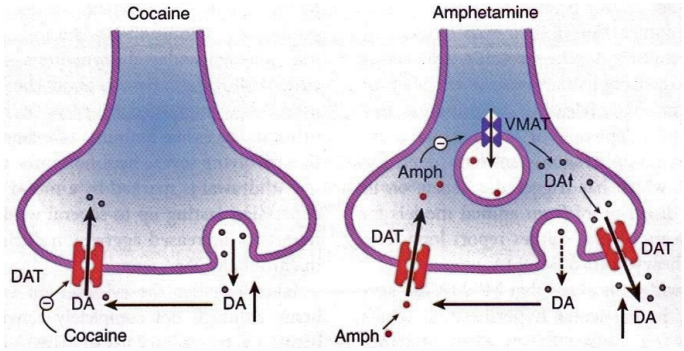
Hallucinogens: LSD, Mescalin, psilocybin ergot derivatives; Known hallucinogens

- **LSD:** 5-HT2A receptor agonist; CNS efx "psychedelic" & "mind revealing", blurring vision, perspective distortions, distorted time perception, hallucinations; ↑ signs of central stimulation & overactive SNS (dilated pupils, ↑HR, mild ↑BP, tremor); afx serotonin & causes DA release

- **Nicotine**: all forms of use cause cancer. Risk certain dis's – COPD (90%) & CV dis (25% MI) also substantially ↑; smoking has deleterious efx on pregnancy: ↑abortions, ↓birth weight, ↑neonatal morbidity & mortality; delayed physical & mental dev't in children; MOA: nACh-R. Activation in VTA→ release of DA; tx w/
  - Replacement therapy – by chewing gum or transdermal patch. Also electronic delivery (smokeless). Abstinence rates ≈ 20% (<success rates for any other addiction), but higher than w/placebo.
  - *Clonidine (off label)* – a_2 adrenergic agonist; ↓anxiety, irritability & craving during w/drawal
  - Varenicline – partial agonist at a_4b_2 nACh-R for smoking cessation
  - Bupropion – antidepressant & nACh-R antagonist
- **Ketamine & PCP (Phencyclidine) "Angel dust/Hog/Special K":** NMDA antagonist; most dangerous hallucinogen; Ketamine (dissociative anesthetic) structurally rel'd to PCP & abused; pyschomimetic; may be smoked (by mixing powder w/tobacco), "snorted", taken orally or injected IV'ly; Efx of euphoria (can be addictive) & physio'al efx (dx'ic) – hyperreflexia, hypersalivation, horizontal & vertical nystagmus, marked HTN, seizures (fatal), Dissociation [loss of contact w/reality (self, senses), inability to communicate, aggression, panic, violence); Ketamine à Acts on NMDA à glutamate.

Stimulants w/pre-synaptic axn:

- Efx of cocaine & amphetamines: elevate mood, induce euphoria, ↑alertness & ↓fatigue
  - **Coke/Cocaine** high lasts 30-60 min; blocks presynaptic DA transporter (DAT) (Also NET & SERT). Look for nasoseptal hemorrhage.
  - **Methamphetamine** lasts 12-24 hr. blocks DAT, but also causes DAT to run backwards, releasing DA from terminal cytoplasm; sx: excitement, paranoida, random behavior, moist skin & dry mouth;
  - Smoked or injected, "rush" intensely pleasurable for period of sec to min, followed by longer period of milder euphoria mixed w/↑anxiety & strong desire to obtain more of drug
  - Repeated use over short times → toxic paranoid psychosis clinically indistinguishable from florid early signs of schizophrenia
  - MOA may also involve NET & SERT. Mice lacking DAT can still be made addicted to these drugs.

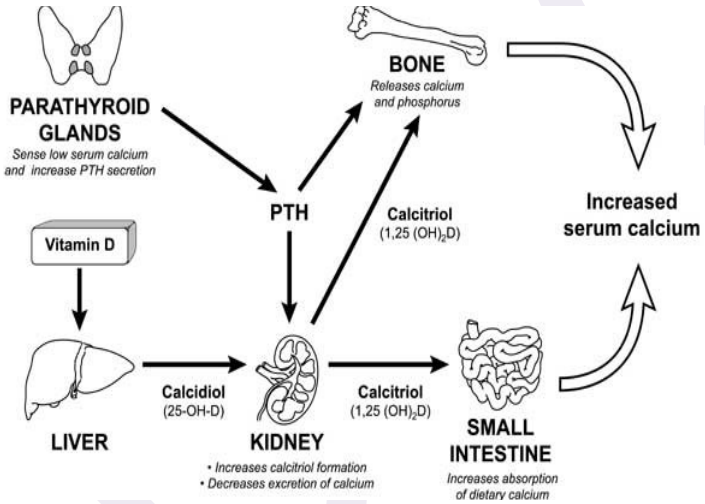


- Site of Axn
  - Reward center: set of DAergic cells from VTA (ventral tegmental area) to nucleus accumbens.
  - Overdose
  - **Cocaine**: cardiac toxicity, irregular breathing & apnea, itching (cocaine 'bugs'), tachycardia, impotence, paranoid delusions & severe HTN → stroke or MI; during pregnancy, can cause via vasoconstrictive efx – insufficient BF to developing fetus resulting in spontaneous abortion, intrauterine GR, placental abruption &/or prematurity
  - **MethAmphetamine**: tachycardia, HTN, mydriasis, loss of appetite

➢ W/drawal signs of both amphetamine & cocaine: ↓appetite, exhaution, ↓sleep time & mental depression

➢ **MDMA (Ecstacy) toxicity**: common "club drug" used for ↓energy & pleasurable feelings such as peacefulness & empathy; **causes massive release of serotonin; preferential affinity for SERT ⊟ thus SERT inhibitor ⊟** euphoria, facilitate interpersonal comm, heightens sexuality; **Hyperthermia potentially fatal side efx of use of high doses of ecstasy – serotonin syndrome (or toxidrome).**

Bone Drugs



Hormones affecting Ca2+ metabolism: PTH, Vit D3, Calcitonin

1. **PTH:**
   1.
2. **Vit D3 (IV):** fat soluble; aids in Ca2+ & phosphorus reg; for tx of tetany, m weakness, rickets & OP;
3. **Calcitonin (oral):** bone metabolism regulator resists efx of PTH on kidneys & bone, ↓Ca2+ by binding certain receptor sites on osteoclast cell memb & changing transmemb passage of phosphorus & ca2+; used for postmenopausal OP & asymptomatic Paget dis of bone

- **Calcium gluconate (IV):** electrolyte & water balance agent – vital regulator of excitation threshold of m's & n's, cardiac func, blood clotting mechanisms, body skeletal & teeth, & maintenance of renal func; used for –ve Ca^{2+} balance & overcoming cardiopulm resuscitation, cardiac toxicity of hyperkalemia, & to avoid hypocalcemia during transfusion of citrated blood

Bisphosphonates: Etidronate, Alendronate, Pamidronate, Residronate, Zolendronate; retard formation & dissolution of hydroapatite crystals in bone – inhibit osteoclast mediated bone resorption; used – postmenopausal Osteoperosis, Hypercalcemia associated w/malignancy, Paget's dis; adverse efx: gastric irritation (except etidronate) & esophageal ulceration

- **Alendronate:** synthetic bisphosphonate; bone resorption inhibitor, prevents & treats osteoporosis in postmenopausal women; don't protect against breast cancer (like Raloxifene)
- **Etidronate:** bone metabolism regulator; for heterotropic ossification caused by spinal cord injury or after total hip replacement & in tx of symptomatic Paget dis

- **Plicamycin/Mitramycin:** cytotoxic antibiotic, ↓↓serum Ca2+ & bone resoprtion; for Paget's dis & hypercalcemia

- **Thiazide diuretics**: ***hydrochlorothiazide, chlorthalidone & indapamide***; ↓Ca2+ reabsorption from renal tubules; for idiopathic hypercalciuria

- **Osteoperosis**: abnormal loss of bone predisposing to fx; due to postmenopausal, long term GC's, thyrotoxicosis, hyperparathyroidism; tx w/HRT (estrogen + progesterone), SERMs – Raloxifene agonist*, Teriparatide, Bisphosphanates (alendronate, residronate), calcitonin, Vit D, Calcium, Leuprolife agonist (↓estrogen & so preventatively protects)

DLE (Drug induced Lupus): precipitated by Procainamide, Hydralazine, Isoniazid, Minocycline, TNF-a inhibitors (etanercept); CF's: abrupt-onset sx: fever/fatigue, arthralgias/arthritis, rash, serositis, pleuritic chest pain; lacks unusual cutaneous manifestations & rarely neurologic or renal complications; predilection for slow acetylators; Lab w/Anti-histone Ab's in >95%, anti-dsDNA Ab's rarely (specific for SLE); clinical improvement is rapid on discontinuation of causative agent

- Procainamide, hydralazine & INH metabolized by phase II acetylation in liver; hepatic expression of N-acetyltransferance genetically determined & pt's w/slow acetylator phenotype @greater risk DLE +also predisposed to INH-induced peripheral neuropathy due to ↓[drug]'s
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