# Final Exam Review – March 2005

## New Topics Since Midterm

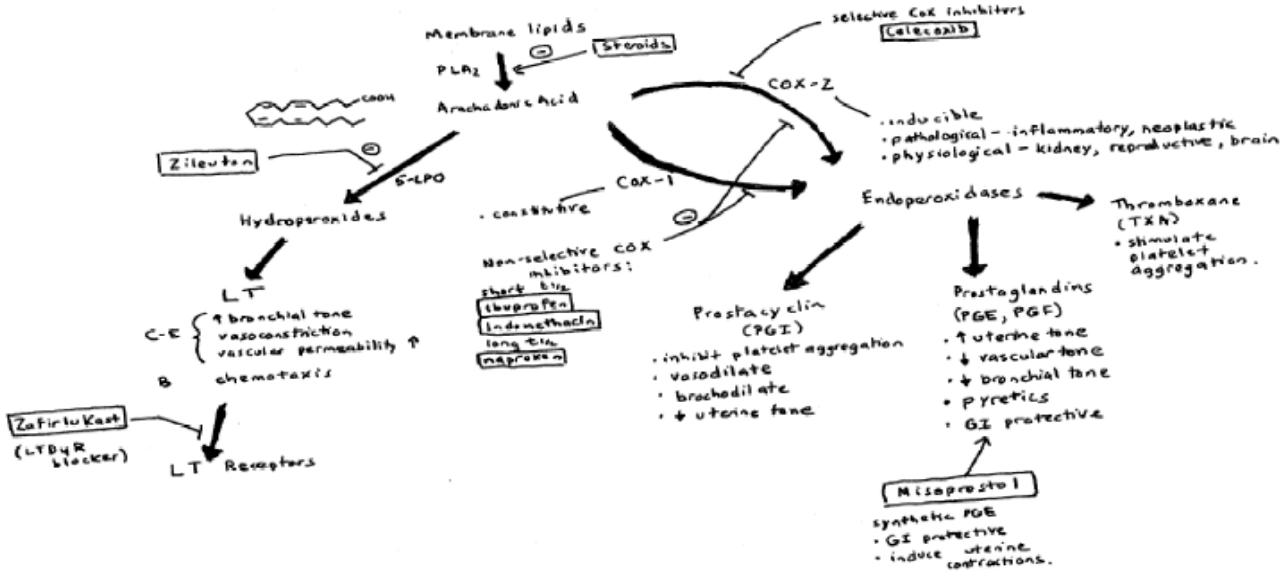
Antiinflammartory Drugs
Antihistamines
Immunosuppressive therapy
Drug Development
Drugs Fro Movement Disorders
Anxiolytics/Antidepressants
Anti-Convulsants
Antimicrobials
Chemotherapy
Opioids

## Cases

Placebo
Geriatric Pharmacology
Antiemetics
Renal failure
Placental Transfer
Alcohol
Drug Allergy
Migraines
Folate
Oral Hypoglycemics
Cancer Analgesia

***Drugs on Dr. Rosow's Final Drug List are either italicized and bolded and/or boxed.***

**Anti-inflammatory Drugs (Weinblatt):**




Anti-inflammatory drugs try to inhibit cyclooxygenase produced prostaglandins and other pro-inflammatory mediators. 1

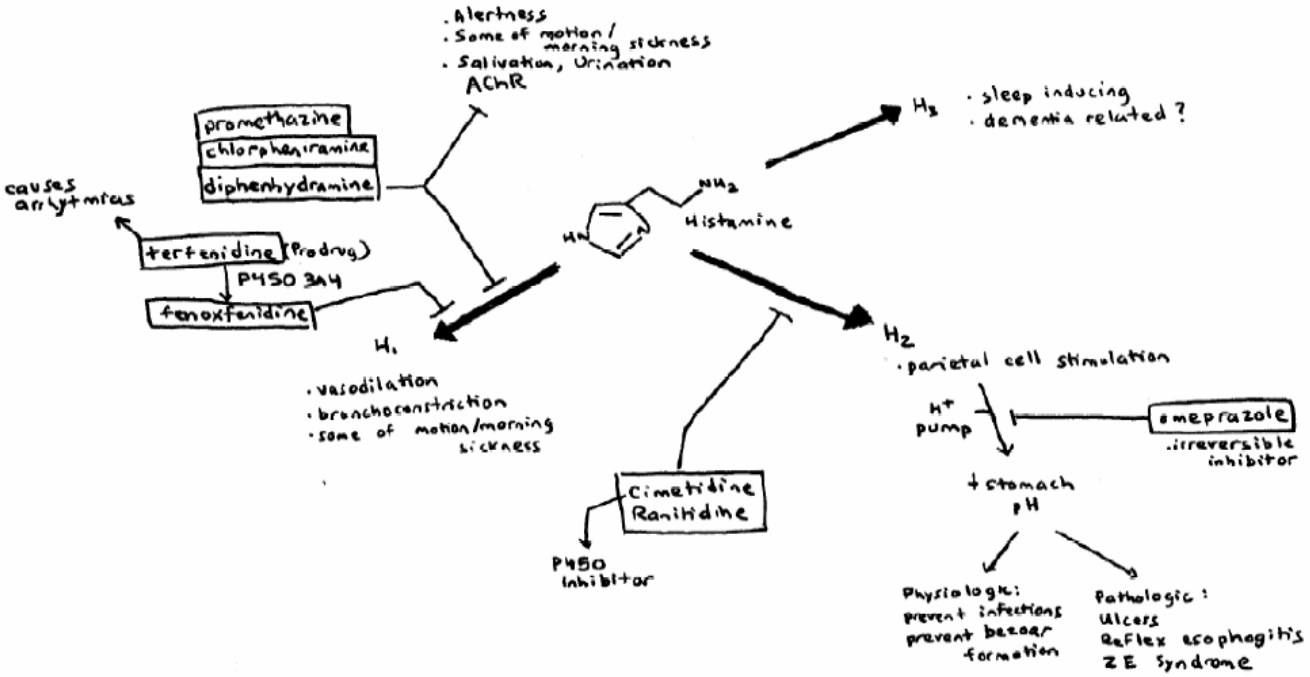
1. Corticosteroids may inhibit production of cyclooxygenase enzyme.

2. ***NSAIDs*** inhibit COX-1. ***NSAIDs*** are designed to function as **analgesics**, **anti-inflammatories**, and **anti-pyretics**. Inhibition of COX-1 leads to other effects like gastric mucosal damage, nephrotoxicity, CNS effects, and platelet inhibition.
    - ***Aspirin*** irreversibly inhibits COX-1. Aspirin is used to inhibit thromboxane synthase in platelets. Without thromboxane synthase, $TXA_2$ levels decline, and the patient's ability to activate and aggregate platelets is diminished, so aspirin functions as an anticoagulant (i.e. post MI or MI prophylaxis).
    - Other ***NSAIDs*** reversibly inhibit COX-1:
        - ***Ibuprofen, Indomethacin, Naproxen.*** Ibuprofen and Indomethacin have short half lives vs. naproxen has a longer half life. This is important for rapid onset or longer duration of action. Uses of these drugs include rheumatoid arthritis, osteoarthritis, gouty arthritis, dysmenorrhea, surgical pain, and other muscular pain.
        - ***Sulfasalazine*** a molecule of sulfapyridine linked to 5-aminosalicylic acid. Sulfasalazine travels to intestine where it is broken down by bacteria, releasing the anti-inflammatory 5-aminosalicylic acid. Sulfasalazine is used in ulcerative colitis
    - NSAIDs cause gastropathic side effects by reducing levels of cytoprotective prostaglandins like $PGE_1$. ***Misoprostol*** is a $PGE_1$ analog which restores the cytoprotective effect to GI mucosa.
    - To avoid some of the side effects caused by COX-1 inhibition, there is a new class of drugs called ***coxibs*** or ***COX-2 selective inhibitors***. These drugs include ***celecoxib*** and ***rofecoxib***, which are used for rheumatoid arthritis, osteoarthritis, gouty arthritis, dysmenorrhea, surgical pain, other muscular pain, and for familial adenomatous polyposis (***celecoxib***). Theoretically the *coxibs* should decrease gastropathic side effects. However, they may have deleterious cardiovascular effects.
3. Newer methods of anti-inflammatory therapy: ***anti-cytokine therapies*** which limit TNF levels.
    - ***Etanercept:*** soluble TNF receptor. Used in rheumatoid arthritis as a monotherapy.
    - ***Infliximab:*** anti-TNF IgG. Used in Crohn's disease, and in rheumatoid arthritis in combination with ***methotrexate***.

**Anti-Histamine Drugs (Dershwitz):**

1. $H_1$ blockers: ***diphenhydramine, chlorpheniramine, promethazine, terfenadine, fexofenadine***.
    a. Used to control hypersensitivity reactions (antagonize bronchoconstriction, vasodilatation, itch), lessen rhinorrhea and coughing, causing sedation (also a general side effect).
    b. Anti-cholinergic side effects: xerostomia, blurred vision, urinary retention, tachycardia, mydriasis
    c. ***Terfenadine*** can cause arrythmias. ***Terfenadine*** is a prodrug converted into ***fexofenadine***.

2. $H_2$ blockers: ***cimetidine, ranitidine***
    a. Used for gastric ulcers, peptic ulcers, etc.
    b. ***Cimetidine*** is a P450 inhibitor.
    c. Instead of $H_2$ blockers, can use ***proton pump inhibitors*** like ***omeprazole*** which have a longer lasting effect (because they covalently inhibit the gastric H+ K+ ATPase.

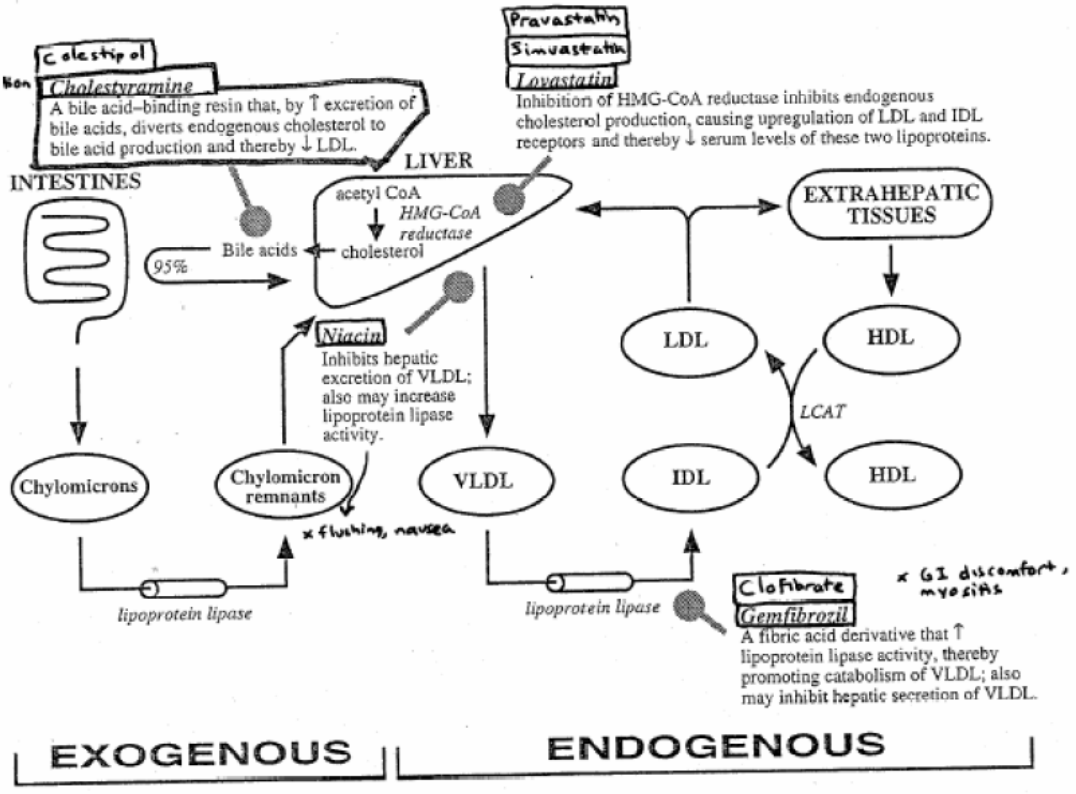



**Drug Discovery**

1. Pre-clinical research: Need to find great number of possible compounds which may have some biological effect (natural products, combinatorial chemistry, rational drug design, etc.).
2. Pre-clinical screening: biochemical and research, screening, animal tests. File Notice of Claimed Investigational Exemption for a New Drug (*IND*) with the FDA to begin human trials.
3. Human Clinical Trials:
   Phase One: *safety* and *pharmacokinetics*
   Phase Two: *Efficacy* and *establish clinical doses*
   Phase Three: large multi-center trial, *establish efficacy*, find rare side effects
4. File New Drug Application (*NDA*) with FDA.
5. Phase Four: Post-Marketing Surveillance. Monitor safety of drug as it is in use.

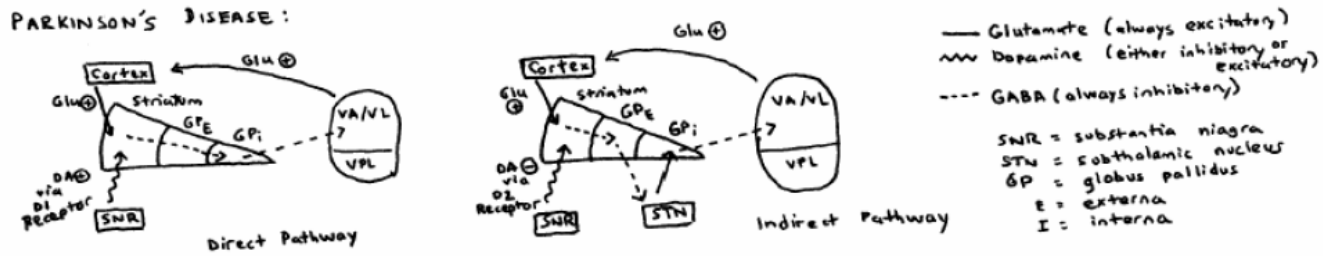
**Lipid Lowering Drugs (Lees):**

| Class | Drug | Mechanism | Effect on LDL | Effect on HDL | Effect on TG | Side Effects |
|---|---|---|---|---|---|---|
| Bile Acid Resins | ***Cholestyramine, Colestipol*** | Inhibit enterohepatic cycle; more bile excreted so more cholesterol converted into bile | ↓↓ | — | slight | Compliance: bad taste, severe GI discomfort |
| | ***Niacin*** | Inhibit lipolysis, lower LDL and VLDL, raise HDL | ↓↓ | ↑↑ | ↓ | Red flushed and itchy face / dermatitis (compliance) |
| Lipoprotein Lipase Inhibitors | ***Clofibrate, Gemfibrozil*** | Inhibit lipoprotein lipase. May also upregulate PPARs | ↓ | ↑ | ↓↓↓ | Myositis, liver effects (increased liver enzymes) |
| HMG-CoA Reductase Inhibitor | Statins = ***lovastatin***, **pravastatin** etc. | Inhibit HMG-CoA reductase, rate determining step of endogenous cholesterol synthesis | ↓↓↓ | ↑ | ↓ | Myositis, increased liver enzymes |
| | ***Sitostanol*** | Inhibit dietary cholesterol absorption | ↓ | | | |

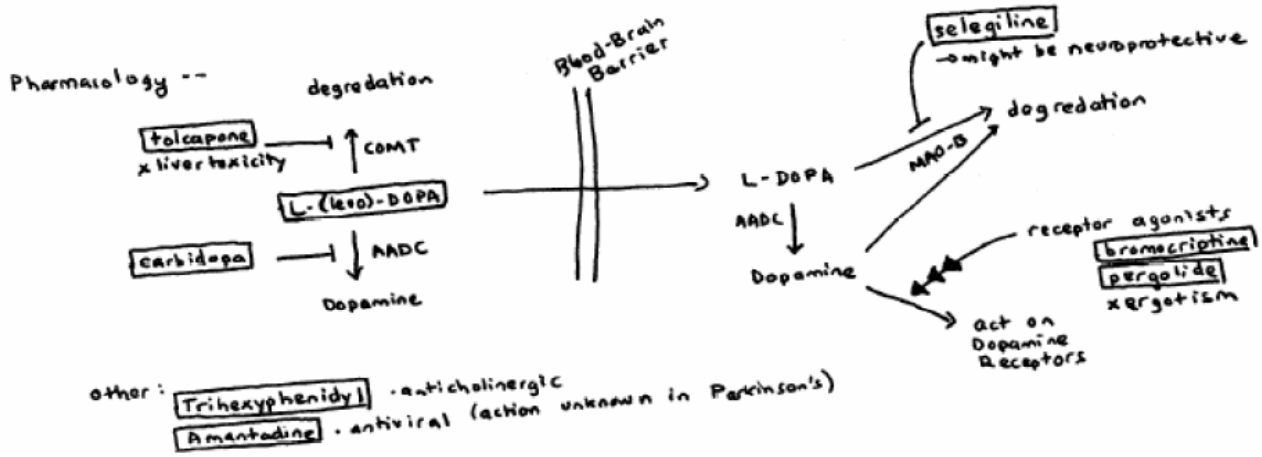


**Movement Disorders (Standaert):**

Parkinson's Disease involves loss of dopaminergic neurons in substantia nigra. Chief symptoms are rigidity, bradykinesia, and tremor. There are also many other classic symptoms.




Pharmacologic treatment of Parkinson's involves methods to increase CNS dopamine.

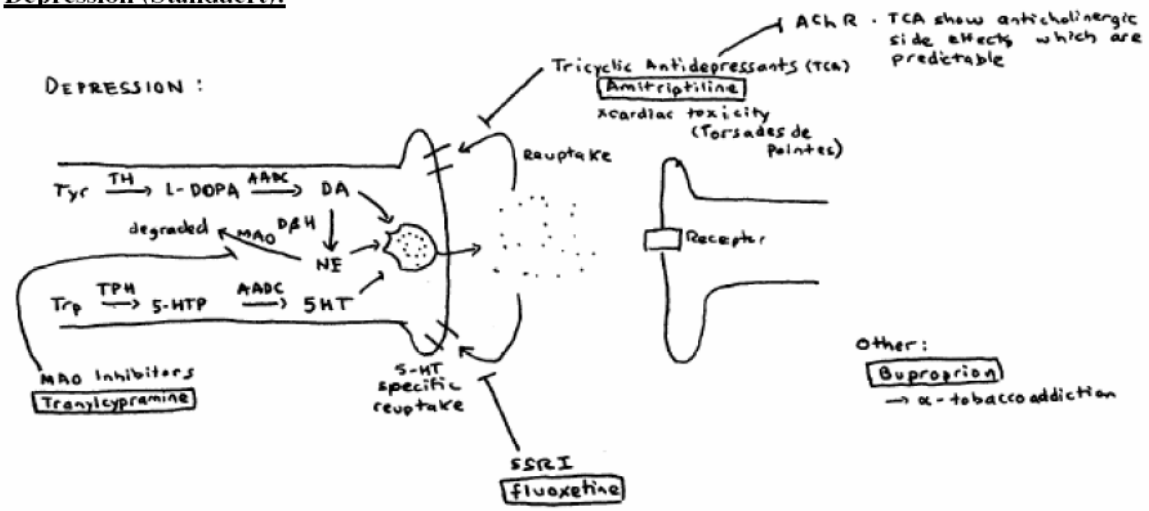



1. Restore dopamine levels in CNS: ***Levodopa*** (L-DOPA) is used because dopamine does not cross BBB. L-DOPA is converted to dopamine by DOPA decarboxylase in CNS.
    a. Recall how tolerance develops. Requires either elaborate dosing schemes or drug holidays (not very successful).
2. Helping to maintain levels of levodopa:
    a. ***Carbidopa:*** inhibits peripheral decarboxylation of DOPA
        i. Combination of levodopa/carbidopa = Sinemet
    b. ***Entacapone:*** inhibits catechol O-methyltransferase (increase $t_{1/2}$)
    c. ***Selegiline:*** inhibits central MAO-B
3. Dopamine agonists / mimetics: ***Bromocriptine, Pergolide***
    a. ***Trihexylphenidyl:*** anti muscarinic side effects
    b. ***Amantadine:*** also anti-viral, has anti-cholinergic effects

**Anti-psychotics:** all antagonize dopamine receptors for psychotic illnesses and schizophrenia. As dopamine blockers, can cause Parkinsonian side extrapyramidal effects (dystonia). Two major side effects: *tardive dyskinesia* (choreiform disorder affecting mouth and face which persists after treatment stopped) and *neuroleptic malignant syndrome* (muscle rigidity, hyperthermia, increased creatinine kinase; treat with dantrolene, cool patient).

- Typical anti-psychotics: block $D_2$ receptors but also have significant anti-cholinergic effects. These three listed in increasing order of $D_2$ blockade and decreasing order of anti-cholinergic effect.
    - ***Chlorpromazine, Thioridazine, Haloperidol***
- Atypical anti-psychotics: do not block $D_2$ receptors, but $D_4$ and other subtypes.
    - ***Clozapine***: causes agranulocytosis and requires regular blood checks
    - Rispderal, olazenapine, quietapine, etc.

**Depression (Standaert):**




Depression Pharmacotherapy: based on amine hypothesis ➔ increase levels of dopamine, norepinephrine, serotonin

- Tricyclics and heterocyclics: block reuptake of serotonin and norepinephrine. Have anti-cholinergic side effects
    - ***Amitriptiline,*** nortriptyline, *trazodone*(sedation)
- SSRIs: less anticholingeric side effects, but can inhibit P450
    - ***Fluoxetine,*** *sertraline, citalopram, escitalopram, paroxetine*
- Non-selective MAOI: used for atypical depression
- Buproprion: structurally similar to tricyclics, but may actually help release norepinephrine. Also used in smoking cessation.

**Anxiolytics/Anticonvulsants (Standaert):**

**Sedative / Hypnotics:**

- Two major classes: *benzodiazepines* and *barbiturates*
- Both bind to $GABA_A$ receptor (which regulates inhibitory transmitter GABA).
  Benzodiazepines increase frequency of channel opening.
  Barbiturates prolong duration of opening.

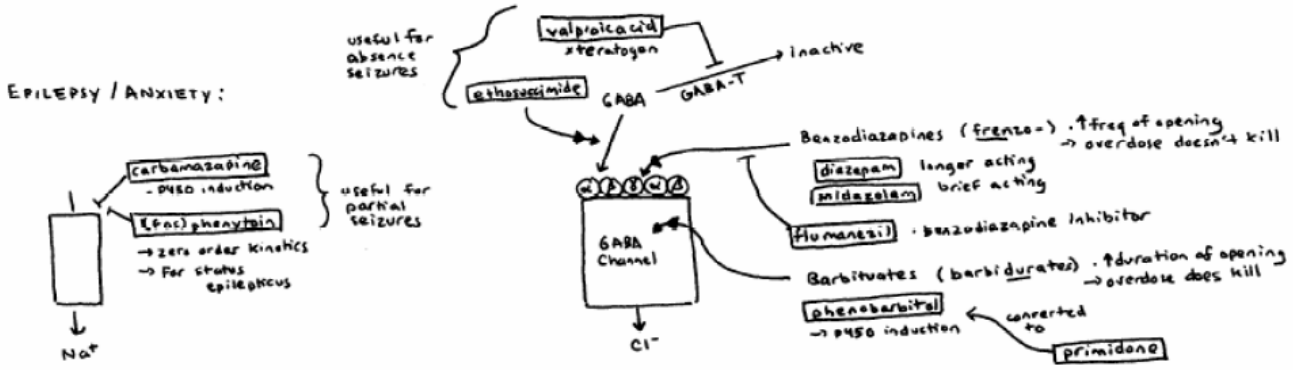
- Benzodiazepines
  Used as anti-anxiety and for sedation (also anesthesia)

Differentiated based on half lives:
Short: ***midazolam,*** triazolam
Medium: temazepam, lorazepam
Long: ***diazepam***, flurazepam
Benzodiazepine antagonist: ***Flumazenil***

- Barbiturates
  Major toxicities are sedation and respiratory depression.

- Tolerance and cross tolerance
  Chronic use of either class results in tolerance to all members of that class and cross-tolerance to other class.
  Both produce dependence; withdrawal may create anxiety, agitation, seizures.

**Anti-convulsants:**
Some mechanisms include blocking sodium channel conductance and increasing GABA channel conductance.

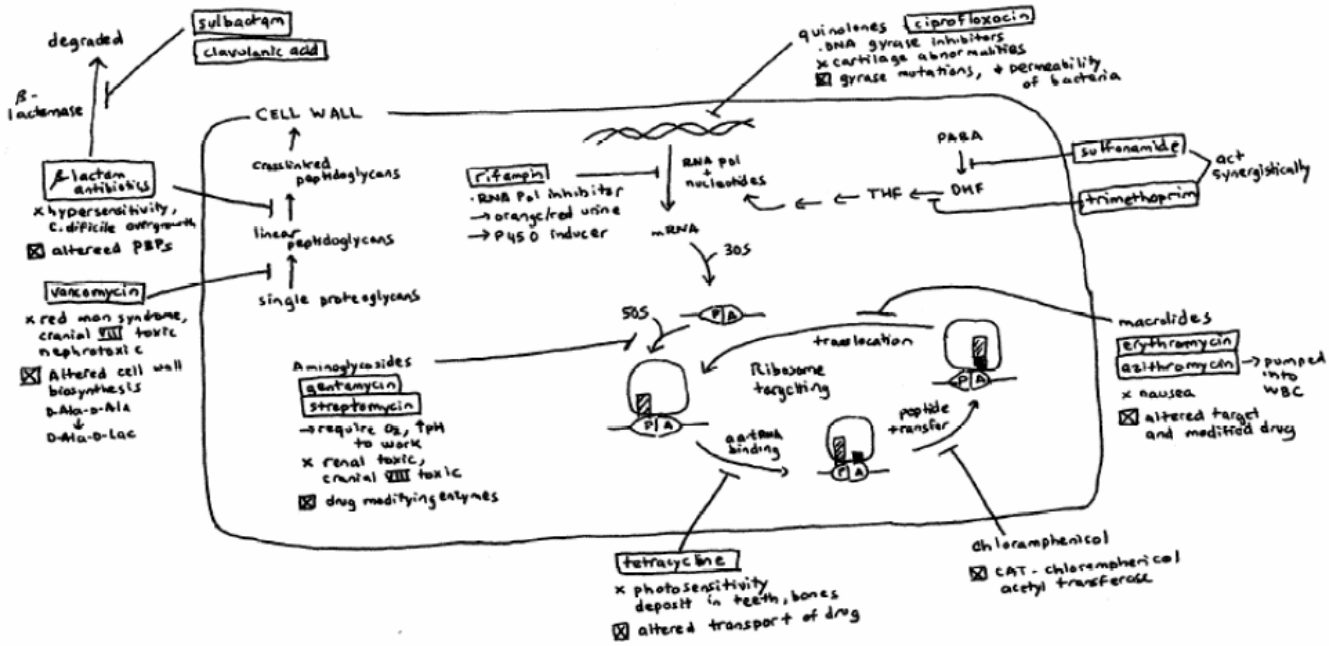


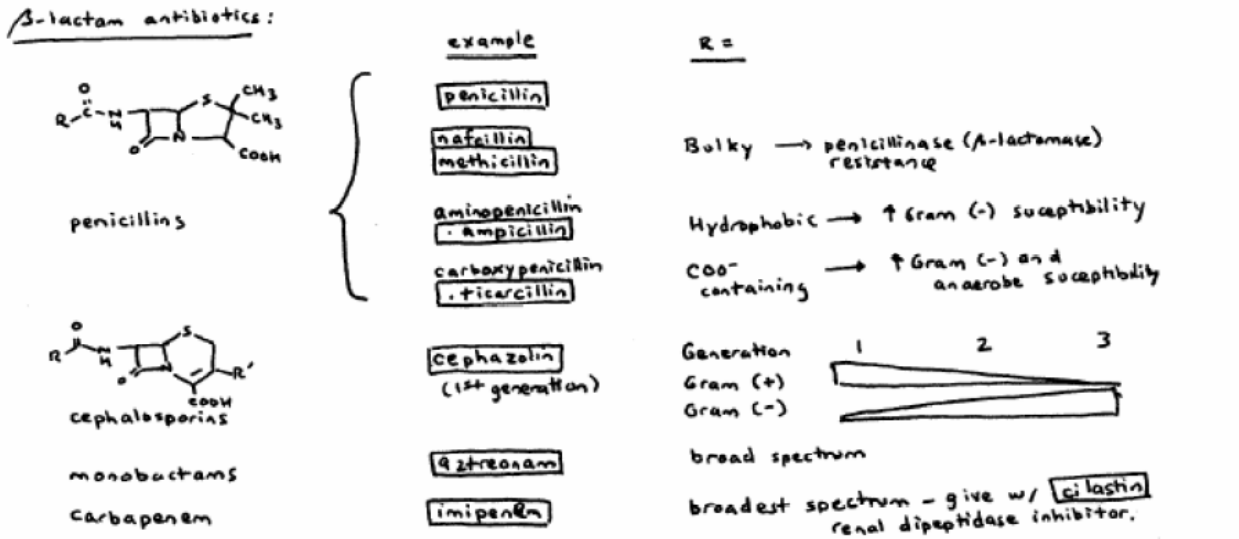

Na Channel blockers: ***phenytoin***, ***fosphenytoin***, and ***carbamazepine***
***Phenytoin:*** used for partial, tonic clonic seizures, and status epilepticus. Side effects: gingival hyperplasia, hirsutism, sedation, fetal hydantoin syndrome. Zero order kinetics.
***Fosphenytoin***: water soluble prodrug metabolized to phenytoin in blood.
***Carbamazepine***: used for partial and tonic-clonic seizures. Side effects include agranulocytosis and P450 inhibition.

Barbiturates: ***Phenobarbital*** and ***Primidone***: used for tonic clonic seizures
Benzodiazepines: ***Diazepam***, ***Lorazepam***: used for status epilepticus

***Valproic acid*** and ***Ethosuccimide:*** for absence seizures. Side effects include birth defects / spina bifida and GI distress respectively.

**Anti-microbials (Rubin):** You do not need to focus on principles of therapeutics, but you should know the major classes and their mechanism.

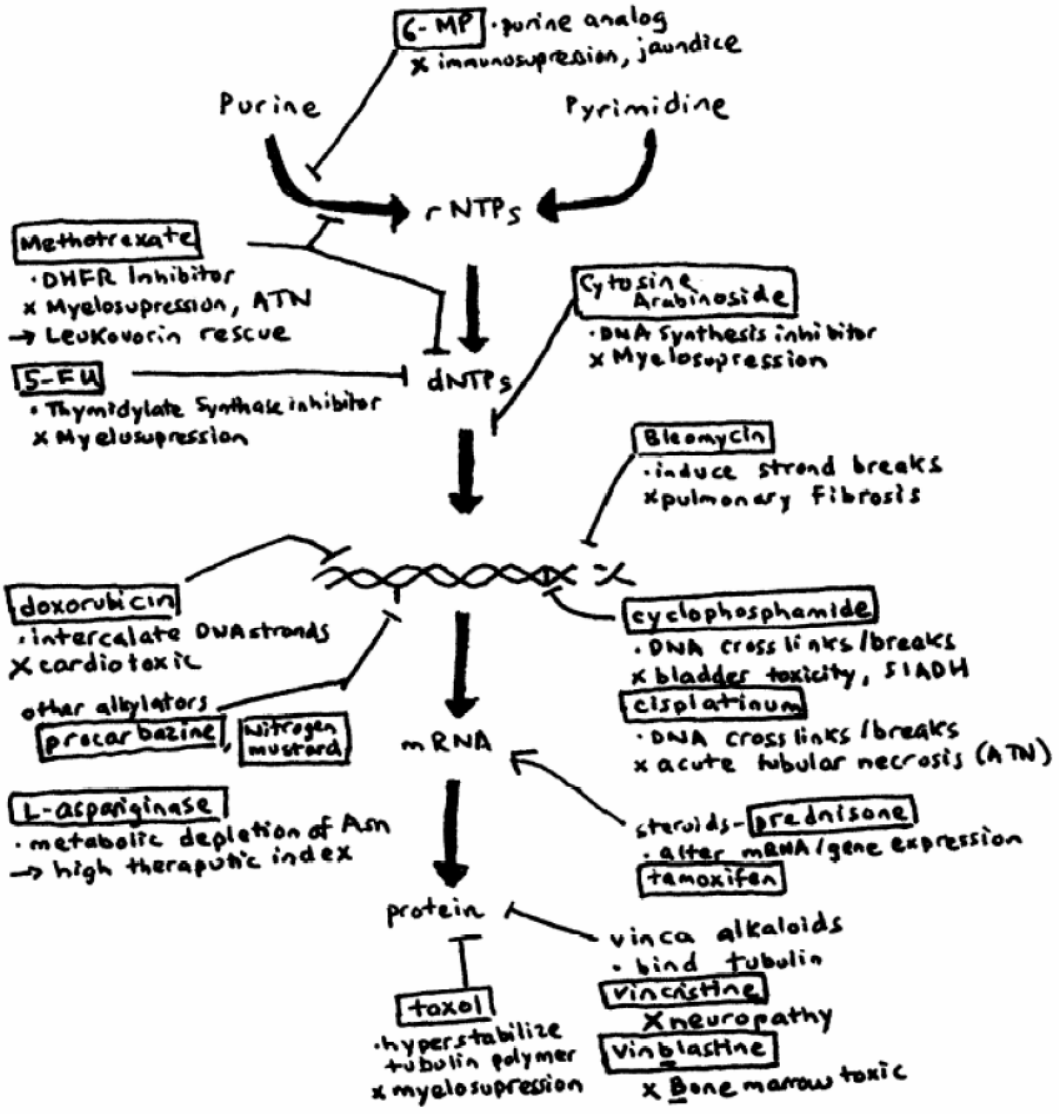



Tuberculosis regimen: RIPES = ***rifampin***, ***isoniazid***, pyrazinamide, Ethambutol, Spectinomycin

***Isoniazid:*** decrease synthesis of mycolic acids required for waxy cell wall of TB. Can cause hemolysis in G6PD and neurotoxicity.

**Anti-neoplastics (Kufe):**

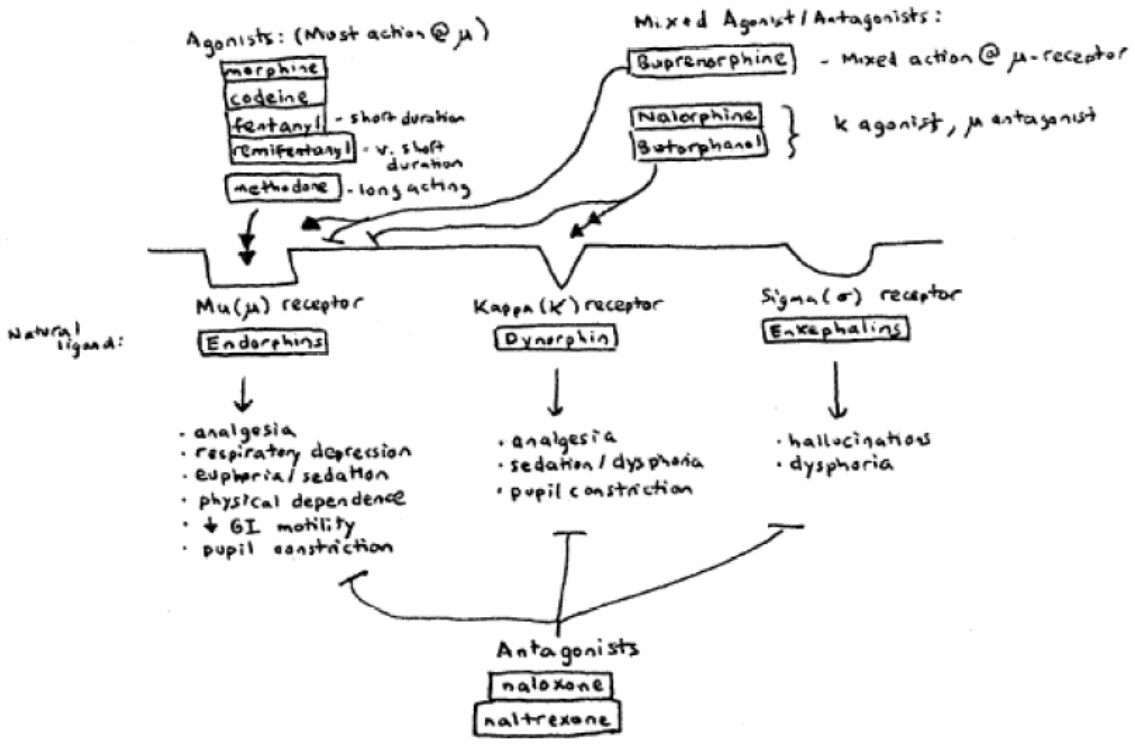



- Recognize how various anti-neoplastics act at every step of the way from nucleotide, to DNA synthesis, transcription, translation, and the cell cycle (with vinca alkaloids blocking M phase).
- Principle of combination chemotherapy: for chemotherapy using multiple drugs with distinct mechanisms, to achieve maximum effect subject to each drug's dose limiting toxicity
    - Compare to hypertension: use multiple drugs to minimize side effects and doses
- Resistance: compare and contrast to microbial resistance mechanisms
    - Decreased expression of gene → decrease uptake: ***Methotrexate, CytArabinoside***

- Increased expression of gene: resistance to *methotrexate* by increasing the copy number of the DHFR gene. (double minute chromosomes, and HSR)
- Altered gene product: ***methotrexate, 5-FU, vinca alkaloids***

**Opioids (Rosow):**

- Mechanism: decrease adenylate cyclcase via Gi coupled receptors
- Uses of opioids: analgesia. Also used for cough suppression (***dextromethorphan***), and as anti-diarrheal agents (*loperamide, diphenoxylate*).
  - Can combine opioids and analgesics: ***Oxycodone*** can be combined with acetaminophen → percocet
- Side effects: respiratory depression (lose response to hypercapnia, hypoxia), pupillary constriction, nausea and vomiting, smooth muscle constriction, dependence, constipation, urinary retention.
  - ***Meperidine***: opioid agonist that causes less smooth muscle contraction, so could be useful for analgesia in biliary colic (will not increase tone in sphincter of Oddi)
- Dependence involves physical and psychological dimensions. Physical = withdrawal (vomiting, diarrhea, mydriasis, chills); psychological = need for opioid induced euphoria
- Tolerance: tolerance develops to all side effects except pupillary constriction and constipation.
- Opioids can directly induce histamine release without activation of IgE. Anaphylactoid reaction, but not a true allergic reaction.
- Antagonists: ***naloxone, naltrexone***




**Other Cases and Topics:**

**Glaucoma:** engineering problem: decrease aqueous humor by 1. increasing outflow or 2. decreasing production of aqueous humor

1. Increase outflow: basically need cholinergic agonists, which acts as miotic agents and contract ciliary muscle which opens trabecular network and allows outflow. Can use direct agonists or acetylcholinesterase inhibitors.
    - Agonists: ***Pilocarpine***
    - Acetylcholinesterase inhibitors: ***echothiophate***
2. Decrease production
    - Beta blockers (beta 1 selective): ***timolol***. Antagonize beta receptors which stimulate production.
    - Carbonic anhydrase inhibitors (***acetazolamide***) decrease HCO-3 levels which limits Na+/HCO-3 cotransport necessary for aqueous production.

**Gout:** precipitation of uric acid

- ***Colchicine:*** used for acute gout as anti-inflammatory agent by depolymerizing microtubules thus inhibiting leukocyte chemotaxis and organelle degranulation
- ***Allopurinol:*** for chronic gout by inhibiting enzyme xanthine oxidase which limits production of uric acid
- ***Probenecid***: used in chronic gout. Inhibits reabsorption of uric acid from renal tubule. (Probenecid inhibits secretion of penicillin into tubule, so concentrations remain high)

**Drug Allergy:** Both of these cause drug induced lupus
***Hydralazine***:
***Procainamide***:

**Oral Hypoglycemics:** Various mechanisms:

- ***Metformin:*** type of biguanide that decreases serum glucose. Side effect: lactic acidosis
- ***Glyburide, tolbutamide:*** types of sulfonylurea. These agents increase K+ influx into islet cells which stimulates insulin release and hypoglycemia. Older agents like ***glyburide*** have ***disulfiram*** like side effects.
- ***Acarbose,*** *miglitol****:*** Types of alpha-glucosidase inhibitors which prevent breakdown and uptake of glucose from intestines.
- ***Rosiglitazone:*** type of thiazolidinedione activate PPAR signaling pathways that increase peripheral sensitivity to insulin

**Lithium:** used to treat mania and manic depression and SIADH. Mechanism is blocking IP3 pathway. Side effects include diabetes inspidus = polydipsia and polyuria.

**Migraine:**
***Sumatriptan:*** Triptans are serotonin (5HT1 subtype specific) agonists. Effect is likely due to vasoconstriction of specific cerebral vessels.
***Ergotamine:*** stimulate smooth muscle and sympatholytic. May work in same mechanism as triptans.

**Folate:** Major cofactor in one carbon metabolism. Molecular structure is combination of pteroate, ***p-aminobenzoate***, and poly glutamate groups. Involved in synthesis of purines, dTMP, and methionine.

- Antibiotics: humans do not synthesize folates, but microbes do. Two key enzymes are dihydropteroate synthase and dihydrofolate reductase (same enzyme as methotrexate). These two enzymes are inhibited by ***sulfamethoxazole*** and ***trimethoprim*** (combination is called *Bactrim*).

- ***Methotrexate***inhibits DHFR. Inhibiting DHFR traps all folate in oxidized form. To prevent deleterious effects on normal cells, give reduced form of folate called ***Leucovorin*** (=Leucovorin rescue).

**Placental Transfer:** ***Thalidomide*** caused phocomelia.

**Alcohol:** ***Ethanol***

- ***Disulfiram*** is used as a treatment in alcoholics; it inhibits the enzyme aldehyde dehydrogenase so that when ethanol is ingested and converted to acetylaldehyde, the acetylaldehyde builds up and produces a terribly uncomfortable effects (metronidazole has a disulfiram like effect)
- *Ethylene glycol*: toxic chemical found in antifreeze whose toxicity results from its metabolism to oxalic acid, glycolic acid, and glyoxilic acid; antidote is ethanol which competes for degradation by aldehyde dehydrogenase
    - *Fomepizole* (4-methyl pyrazole): alcohol dehydrogenase antagonist used as antidote to ethylene glycol or methanol (or other alcohol/glycol) poisoning.

**Cancer Analgesia:** various pain meds include NSAIDs, tricyclics, opioids