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Sigs:

- | | | | |
|----------------------|-------------------|----------------------|----------------------|
| 1. ss = one half | 4. au = each ear | 8. od = right eye | 12. ung = ointment |
| 2. ac = before meals | 5. as = left ear | 9. ou = each eye | 13. WA = while awake |
| 3. pc = after meals | 6. ad = right ear | 10. s = without | |
| | 7. os = left eye | 11. ID = intradermal | |

Equivalent measurements:

- 1 cup = 8 oz
- 1 pint = 16 oz = 473 mL
- 1 quart = 2 pints = 946 mL
- 1 gallon = 4 quarts = 3785 mL
- 1 oz = 28.4 g
- 1 pound = 454 g
- 1 grain = 65 mg

Percentage preparations:

$$v/v = \frac{\text{ml}}{100 \text{ mL}}$$

$$w/w = \frac{\text{g}}{100 \text{ g}}$$

$$w/v = \frac{\text{g}}{100 \text{ mL}}$$

♦Creams (hydrocort cream)

♦NS , D5W

[2] CALCULATIONS

1. Conversion from aminophylline to theophylline: **aminophylline x 0.8 = theophylline dose [vice versa = x/0.8]**
 - a. A physician writes an order for aminophylline (37.5 mg/hr). There is only theophylline in stock, how many mg of theophylline will the pt receive per hr?

37.5 mg aminophylline x 0.8 = **30 mg theophylline**
2. Ratio strength
 - a. Express 0.04% as a ratio strength → $0.04/100 = 1 \text{ part} / x$ $x=2500 = 1:2500$
 - i. Converting back to % = **1/2500 → 0.0004 → 0.04% OR 1/2500 = x/100**
 - b. What is the percentage strength of imiquimod in the rx?

Imiquimod 5% cream	15 g
Xylocaine	20 g
Hydrophilic ointment	25 g

5% cream = 5g/100g x 15 g = 0.75 g imiquimod

0.75g/60g rx = x g/100 g → $1.25/100 = \mathbf{1.25\%}$
 - c. Lidocaine 4.3% QS 120 mL sterile water. Calc how much lidocaine is needed

$\frac{4.3 \text{ g}}{100 \text{ mL}} = \frac{x \text{ g}}{120 \text{ mL}}$ $x = 5.16 \text{ g}$
3. PPM (Parts per million) , PPB (Parts per billion = 1,000,000,000)
 - a. Express 0.00022% w/v as PPM

$\frac{0.00022 \text{ g}}{100 \text{ mL}} = \frac{x \text{ g}}{1,000,000}$ $x = \mathbf{2.2 \text{ PPM}}$
 - b. Convert 30 PPM to %

$\frac{30}{1,000,000} = \frac{x}{100 \text{ mL}}$ $x = \mathbf{0.003\%}$

4. $BMI = \frac{\text{weight (kg)}}{\text{height (m)}^2}$

$BMI = \frac{wt (lb)}{Ht (in)^2} \times 704.5$

<18.5	Underweight
18.5-24.9	Normal weight
25-29.9	Overweight
>30	Obese

a. A man is 6'7" and weighs 250 lbs, calculate his BMI.

$$79 \text{ inch} \times \frac{2.54 \text{ cm}}{1 \text{ in}} \times \frac{1 \text{ m}}{100 \text{ cm}} = 2.0066 \text{ m}$$

$$BMI = 113.63 \text{ kg} / 2^2 = 113.63 / 4 = 28.4$$

5. IBW (Ideal Body weight) * use when pt is overweight, NOT underweight

$IBW (\text{males}) = 50 \text{ kg} + 2.3 (\text{each inch} > 5 \text{ ft})$

$IBW (\text{females}) = 45.5 \text{ kg} + 2.3 (\text{each inch} > 5 \text{ ft})$

❖ Used for aminoglycoside dosing (AG are charged particles, so are not lipophilic. Stays in the kidneys; we want a high peak so it can get to its site of action and a non-detectable trough (<2 mcg/mL) to protect the kidneys.

6. Cockcroft-Gault

$CrCl = \frac{(140 - \text{age})(\text{weight in kg})}{72 \times SCr} \times 0.85 \text{ if female}$ (for obese pts, adjusted BW may be preferred)

a. Ideal body weight is commonly used for drugs that are hydrophilic (aminoglycosides, theophylline)

b. CrCl <30 = severe renal insuff ; CrCl <15 = ESRD

7. Specific Gravity – ratio of density of substance to density of water

$\text{Specific Gravity} = \frac{\text{weight (g)}}{\text{volume (mL)}}$

• SG water = 1 (1g water = 1 mL water)

• Subst. with SG < 1 are lighter than water & vice versa

a. What is the weight of 750 mL of concentrated acetic acid (SG = 1.2)

$$1.2 = \frac{x \text{ g}}{750 \text{ mL}} \quad x = 900 \text{ g}$$

8. Body Surface Area (units are in m²)

$$BSA (m^2) = \sqrt{\frac{Ht (Cm) \times Wt (kg)}{3600}}$$

9. Flow rates

a. An IV order contains 2 mL of a 1:1000 solution of epinephrine and 250 mL of D5W. At what flow rate in mL/min, should the infusion be administered to provide 0.3 mcg/kg/min of epinephrine to an 80 kg pt?

$1:1000 = 0.001 = 0.1\% \rightarrow 0.1 \text{ g}/100 \text{ mL}$

$$80 \text{ kg} (0.3 \text{ mcg/kg} \cdot \text{min}) (1 \text{ g}/10^6 \text{ mcg}) (100 \text{ mL}/0.1 \text{ g}) (252 \text{ mL sol} / 2 \text{ mL epi}) = 3 \text{ mL/min}$$

10. Strength adjustment (Q1 x C1) = (Q2 x C2)

a. Using 20 g of a 9% Boric acid ointment base, the RPh will manufacture a 5% ointment base, how much diluent is required?

$$(20 \text{ g})(9\%) = (X \text{ g})(5\%) = 36 \text{ g}$$

$$\text{How take } 36\text{g}-20\text{g (already present)} = 16 \text{ g diluent required}$$

b. What is the ratio strength (w/v) of 50 mL containing 1:20 (w/v) ammonia solution diluted to 1,000mL?

$$(50 \text{ mL})(5\%) = (x)(1000 \text{ mL}) \quad x = 0.25\% \quad \text{now to change } 0.25\% \text{ to ratio strength:}$$

$$0.25\% \rightarrow 0.25 / 100 = 1 \text{ part} / X \quad X=400 \rightarrow \text{ratio strength is } 1:400$$

11. Alligation

a. You are asked to prepare 1 gallon of tincture containing 5.5% iodine. The pharmacy has 3% and 8.5% iodine tincture. How many mL of each will be used? 1720 mL of 8.5%, 2065 mL of 3%

12. Half life : $T_{1/2} = 0.693 / k$ (k =elimination rate constant)

- a. A pt with renal failure received 1 g of vancomycin on 3/21 at 1300. The peak was taken 1 hr later and was 26.8 mg/L. On 3/24 at 1400. The concn was taken and was 13.4 mg/L and a 1 g dose was given at the same time. The desired trough is 10-15 mg/L, when should the pt receive the next 1 g dose? Assume the renal clearance stays the same.

$T_{1/2}$ is about 3 days (the time between the 1st and 2nd dose since the 2nd concentration was 1/2 of the first. Now add 13.4 + 26.8 (the concentration you would expect since another dose was given) = 40.2. so after 2 half lives (6 days) the concn should go down to 10.05, within our desired trough.

13. TPN

- a. Normal diet component – TPN component

Protein (fish, meat) → amino acids

Carbs → dextrose

Fat → lipids

Vitamins → MVI

Minerals → electrolytes & trace elements

*Dextrose = carbs in TPN are given as dextrose monohydrate (3.4 kcal/g), glucose has 4 kcal/g

**Lipid emulsions = contain glycerol, so they are not straight 9 kcal/g as if they were pure fat and the calories are calculated per mL of the formulation used.

- b. TPN indications: req. long term (>7 days) suppl. nutrition – there is no justification for TPN <4 days. Pts with severe gut dysfxn (Crohn's disease, UC, bowel obstruction, short bowel syndrome from surgery)

Dextrose*	3.4 kcal/g
Amino acids (protein)	4 kcal/g
Lipids **	9 kcal/g
10% lipid emulsion	1.1 kcal/mL
20% lipid emulsion	2 kcal/mL

- c. Determining Fluid needs : **weight > 20 kg = 1,500 mL + (20mL)(WT in kg-20kg)**

- d. Calculating protein calories :

Ambulatory, non-hosp (non stressed pts) **0.8 – 1 k/kg/day**

Hospitalized or malnourished pts **1.2 – 2 g/kg/day**

- e. Calculating Non-protein Calories – Total Energy Expenditure (TEE) and Basal Energy Expenditure (BEE)

BEE is the amt of energy in the resting state exclusive of eating & activity **BEE = 15-25 kcal/kg**

TEE is the BEE + excess metabolic demands. **TEE = BEE x activity factor x stress factor**

Activity factor is **1.2** if confined to bed, **1.3** if ambulatory

Amino acids (proteins) should not be counted as part of the TEE for pts that are critically ill (TEE calories should be made up of carbs + lipids)

- f. Calculating Amino Acids : AA come in stock preparations of 5%, 8.5%, 10%, 15%.

If the pharmacy stocks Aminosyn 8.5%, how many mL will be needed to provide 108 g of protein?

$$8.5g / 100 \text{ mL} = 108g / x \text{ mL} \quad x = 1271 \text{ mL}$$

- g. Calculating Dextrose : do not exceed 4 mg/kg/min (some use 7 g/kg/day)

A 57 yo male is receiving 1,145 mL of D30W, 850 mL of Aminosyn 8.5% and 350 mL of Intralipid 10%. What % of the non-protein calories are rep. by dextrose? **75%**

- h. Calculating Lipids : 10% lipid emulsion=1.1 kcal/mL 20% lipid emulsion=2 kcal/mL
A pt is receiving 660 mL of 10% Intralipid on Saturdays along with his normal daily TPN. What is the daily amt of calories provided by lipids? **103.7 kcal/d** (divide the weekly dose by 7)
- i. Determining amt of Electrolytes
- Na is the principal EXTRAcellular cation. It comes in many concentrations (0.9%, 0.45%). Sodium Chloride 23.4% is used for TPN preps and contains 4 mEq/mL
 - Sodium can be added to TPNs as Sodium Chloride or Sodium Acetate - use acetate if pt is acidic (Sodium acetate is converted to sodium bicarbonate)
 - K⁺ is the principal INTRAcellular cation. Calcium is req for many fxns including cardiac conduction, muscle contraction, and bone homeostasis. Normal Ca (8.5-10.5). Almost half of Ca is bound to albumin. Low albumin can lead to incorrect calcium concentration. *If albumin is low, calcium will need to be corrected.*
Corrected Ca = (Ca serum) + [(4 - albumin) x 0.8]
 - Phosphate and calcium need to be added carefully to avoid precipitation. Choose calcium gluconate vs calcium chloride bc its less reactive (CaCl has 3x more elemental Ca than Ca gluconate).
Calcium + Phosphate added tog. Should not > 45 mEq/L
- j. Determining the grams of Nitrogen contained in the protein **(1 g Nitrogen per 6.25 g protein)**

14. **Isotonicity** – related to number of particles in solution. We have to find the dissociation factor (i)

- Non-ionic compnds do not dissociate and have a dissociation factor of 1
- Dissociation factor based on number of dissociated ions. NaCl = 2 CaCl₂ = 3

Dissociated ions	dissociation factor, i
2	1.8
3	2.6
4	3.4
5	4.2

- Body fluids are described as having an osmotic pressure equivalent to 0.9% NaCl. Drug have a “NaCl equivalents” or “E values”

$$E = \frac{58.5 (i)}{\text{MW drug} \times 1.8}$$

MW drug x 1.8

Calculate the E value for potassium iodide, which dissociates into 2 particles (MW 166). = 0.35

The E value for ephedrine sulfate is 0.23. how many grams of sodium chloride are needed to make the following rx isotonic? Ephedrine sulfate 0.4 g - sodium chloride qs - Purified water qs 30 mL

- Determine amt of sodium chloride represented from ephedrine sulfate → 0.4×0.23 (E value) = 0.092 g
- Determine how much NaCl is needed to make product isotonic: $0.9 / 100 = x / 30 \text{ ml}$ → 0.27g
- Subtract 1 from 2 : $0.27 - 0.092 = \mathbf{0.178 \text{ g NaCl}}$

You receive an order for 10 mL tobramycin 1% ophthalmic solution. You have tobramycin 40 mg/mL solution.

Tobramycin does not dissociate and has a MW of 468. Find the E for tobramycin and determine the amt of NaCl needed to make the solution isotonic. Pg 49 = **83 mg NaCl**

From my calculation notes:

mEq = valence **mOsmol** = particles (CaCl₂ : valence = 2 mOsmol = 3)

Dextrose MW = 180

180 g = 1 mol

180 mg = 1 mmol

0.180 g = 1 mmol = 1 meq = 1 mOsmol

NaCl : 0.0585g = 1 mmol = 1 mEq = 2 mOsmol

KCl : 0.0745 g = 1 mmol = 1 mEq = 2 mOsmol

15. **Osmolarity** : # particles of solute/L solution -or- mOsmol / L

- a. Ionic solutes (ex: NaCl) dissociates into 2 solutes in solution. Non-ionic solutes (glucose, urea) do not dissociate.
- b. Some cmpnds which it may be useful to know dissociations:
Sodium acetate → 2 particles Calcium chloride (CaCl₂) → 3 particles Sodium Citrate → 4 particles Dextrose → 1
- c. $\text{mOsmol/L} = \frac{\text{Wt of substance (g/L)}}{\text{MW (g)}} \times (\# \text{ of species}) \times 1000$

What is the osmolarity of normal saline (0.9% NaCl) MW = 58.5 g? 308 mOsm/L

my way: (0.9/100ml) (1000ml/L) (1 mol NaCl/58.5g) (1000 mmol/ mol) (2mosmol/1 mmol) = 307.7

How many mOsm of CaCl₂ (MW 147) are represented in 150 mL of a 10% (w/v) calcium chloride solution?

mOsm/L = 15 g/ 147 g x 3 x 1000 = 306 mOsmol

A solution contains 200 mg Ca⁺ ions per liter. How many milliosmoles are rep in the solu (MW = 40)? 5 mOsmol/L

16. **Millimoles**

How many millimoles of calcium chloride (MW 147) are represented in 147 mL of 10% (w/v) calcium chloride solution?

100 mmol

17. **Milliequivalents (MEQ)**

- a. Milliosmoles refers to the number of particles in solution
- b. Millimoles refers to the molecular weight
- c. Milliequivalents represents the amt of mg of a solute equal to 1/1000 of its gram equiv weight, taking into account the valence of ions. $\text{mEq} = (\text{mg} \times \text{valence}) / \text{MW}$

- d. **Valence** = the number of pairs of e⁻ holding the molecule together Cl-Ca-Cl (2) Na-Cl (1)
Calcium chloride (CaCl₂) = 2
Magnesium sulfate (MgSO₄ 2-) = 2
Ferrous sulfate (FeSO₄ 2-) = 2
Potassium chloride (KCl-) = 1
Ammonium chloride (NH₄Cl) = 1 (bond btw ammonia and Cl)
Sodium acetate (NaC₂H₃O₂) = 1 (bond btw acetate and sodium)

A 20 mL vial is labeled potassium chloride (2 mEq/ml), how many grams of potassium chloride are present? MW KCl = 74.5 g

My way: 20 ml x (2 meq/a ml kcl) x (1 mmol/1 meq) x (0.074 g/ 1 mmol) = 2.96 g

18. Temperature conversion: $(F - 32) / 1.8 = C$

19. Absolute neutrophil count – neutrophils make up most of the WBC and rep the primary cells that fight infection

ANC < 2000 = high risk for infection, ANC < 1000 = very high risk for infection

$\text{ANC} = \text{WBC} \times \text{neutrophils (neutrophils = segs + bands)}$

WBC = 4300, 48% segs, 2% bands → 4300 x (0.48 x 0.02) = 2150

20. Calcium carbonate to calcium citrate

Carbonate **40%** elemental calcium. Calcium citrate contains **21%** elemental calcium

21. Acid, Bases, pH, ionization and buffers

if given a $pK_a \rightarrow$ drug is a wk acid if given a $pK_b \rightarrow$ drug is a wk base

anytime you are given a pK_a , it always refers to the acid form losing a proton to give the base form, thus it is a “weak acid”

- An acid is compound that dissociates (releasing protons into solution). Once the proton is released, the compound is now a conjugate base
- A base is a compound that picks up the proton.
- pure water is neutral at $pH = 7$. Blood has a pH of ≈ 7.4 . Stomach acid has a pH of ≈ 2
- pK_a is the pH at which the compound is protonated, & half is not protonated.
- A strong acid = will become 100% dissociated, while weak acids = very limited dissociation
- If the $pH > pK_a$, more of the acid is ionized & more of the conjugate base is un-ionized (cmpnd is dropping off protons – more ionized, so its acting as an acid)
- if $pH < pK_a$, more of the acid is un-ionized, and more of the conj base is ionized.
- An IONIZED drug is soluble but cannot cross lipid membranes. an UN-IONIZED drug is not soluble but can cross the membranes and reach the proper receptor sites. (most drugs are wk acids, they are soluble and pick up a proton to cross the lipid layer)
 $A-H \text{ (Acid)} + H_2O \text{ (base)} \rightleftharpoons H_3O^+ \text{ (conj acid)} + A^- \text{ (conj base)}$

- i. **wk acid : $pH = pK_a + \log (\text{salt/acid})$ wk base : $pH = pK_w - pK_b + \log (\text{base/salt})$**

citric acid and sodium citrate \rightarrow sodium citrate = salt citric acid = acid

(salts end in “- ate”)

ammonia and ammonium chloride \rightarrow ammonia = base ammonium chloride = salt

22. Compounding examples:

a rx reads as follows: prepare 150 g of a 3% coal tar preparation. how much petrolatum will be needed to make the rx?
 $(3g/100g) = (xg/150g) = 4.5 \text{ g}$ 150 g total – 4.5 g (active ingred) = **145.5 g petrolatum**

23. Aliquot

Minimum weighable quantity (MWQ) = Sensitivity req (SR) / 0.05

A rx calls for 15 capsules, each containing 1 mg of doxazosin. a torsion balance has an SR of 6.5 mg. how would you weigh 15 mg of doxazosin with an accuracy of $\pm 5\%$ using lactose as the diluent?

- need 15 mg of doxazosin
- calculate MWQ = 130
- find a number a little greater than 130 that is a factor of 15 $\rightarrow 10 \times = 150 \text{ mg doxazosin}$
- take the aliquot number, $(130) \times (10) = 1300 \text{ total dilution}$.
- to find the amt of lactose, take $1300 - 150 = 1150 \text{ lactose}$; to find how much to make a capsule of doxazosin, take $1300 / 10 = 130 \text{ mg of dilution}$ will contain 15 mg of doxazosin

[3] COMPOUNDING REQUIREMENTS & TERMINOLOGY

1. ISO Class 5 (Class 100), ISO Class 7 (Class 10,000)
2. Clean room garb = low shedding coverall, head cover, face mask and shoe covers
3. 2 types of mortar & pestles:
 - a. Glass → good for liquids & chemicals that are oily or will stain the porcelain (many chemo agents)
 - b. Wedgewood or porcelain (ceramic) → good for reducing particle size of dry powders and crystals
4. Surfaces & spatulas:
 - a. Glassine weighing paper (vs bond paper) → use for ointments, creams & some dry chemicals
 - b. Parchment ointment paper → do not use for creams and other aqueous mixtures bc the paper will absorb water
 - c. Metal spatulas → generally used, except with chemicals that can react (below)
 - d. Plastic spatulas → use for chemicals (metals: K⁺, Iodine) that can react with stainless steel
5. Emulsions: 2 phase system of 2 immiscible liquids (oil in water, water in oil) - *they are immiscible and do not form a suspension*
 - a. Emulsifiers: acacia, agar, pectin, lipophilic esters of sorbitan (arlacel, span) and hydrophilic esters (myrj, tween)
 - b. Hydrophilic-lipophilic balance (HLB) determines how much surfactant will be req to form the mixture
6. Ointments & creams:
 - a. Lotions, creams, ointments are all oil in water preparations
 - b. Oleaginous and hydrocarbon based ointments = do not absorb water, are occlusive, do not wash off = white petrolatum
 - c. Absorption ointment = occlusive, do not wash off, but do absorb water = lanolin, aquaphor, aquabase
 - d. Water-in-oil emulsions = Eucerine, Nivea, rose water ointment
 - e. Oil-in-water emulsions = cetaphil, dermabase, Keri lotion, Lubriderm, hydrophilic ointment
7. Gels – are used as thickeners ; common gels are the alginates (inclu: Na⁺, K⁺, Ca alginate), agar, carrageenan, gelatin
8. Suspensions: solid in a liquid
 - a. Suspending agents: hydrocolloids (acacia, alginic acid, gelatin, xanthan gum) , methylcellulose, carbamers, polyvinyl alcohol, clays (bentonite, veegum)
9. Suppositories : bypass the oral route and avoid 1st pass metabolism
 - a. Common bases: cocoa butter, glycerin, hydrogenated veg oil, & polyethylene glycol
10. Capsules
 - a. Unit doses made in gelatin capsule; capsule sizes (largest to smallest) : 000 – 00 – 0 – 1 – 2 – 3 – 4 – 5

[4] PHARMACOKINETICS & DRUG FORMULATIONS

1. Dissolution: if a drug does not break up (dissolve) in the gut, it cannot be absorbed
 - a. Primary pathway of drug degradation in the gut is hydrolysis
 - b. *Most drugs dissolve in an acidic medium (gut) and are absorbed (mainly) in the SI → bc of the villi that inc SA*
Enteric coated formulations dissolve in the more basic enviro of the SI
2. Absorption: percentage of drug that enters the body
 - a. F = bioavailability (IV form = F = 100%) bisphosphonates have poor oral abs (<10%) therefore IV bisphos req a much lower dose
3. Distribution:
 - a. Lipophilic compounds are uncharged, and can pass easily thru lipid membranes
 - b. Most drugs are weak acids and can pick up a proton to become uncharged
 - c. Polar, charged compounds (aminoglycosides) cannot pass easily thru cell walls (therefore stay in the blood compartment therefore may be nephrotoxic)
 - d. Protein binding: small Δ 's can cause large changes in drug distribution
 - i. Most signif protein involved is albumin (normal 3.5-5)
 - ii. High PB drugs: phenytoin, warfarin → if albumin is low, drug concn will be higher than shown by the serum level (therefore must calc corrected phenytoin level)
4. Long acting formulations
 - a. Slow release drugs are designed to avoid irritation to GI lining. Do not crush or chew drugs with suffix that indicates it is a long acting formulation: XR, ER, LA, SR, CR, CRT, SA, TR, TD, have 24 hr in the name or end in -cont for controlled release (MS Contin, Oxycontin)
 - b. Toprol XL, Sinemet CR – can be cut but not crushed & still work as ER
5. First Order Kinetics **most drugs follow this*
 - a. The amt of drug given is proportional to the inc seen in plasma concn.
 - b. Michaelis-Menten Kinetics (saturable kinetics) : begins as 1st order, but when metabolism becomes saturated, the concn inc rapidly & Δ 's to zero order (once a certain dose is reached and met. enzymes are saturated)
 - i. Ex of MM saturable kinetics: phenytoin, theophylline, voriconazole
 - c. Zero – order: *elimination rate is INDEP. of drug's concn.*

[5] BIOSTATS & PHARMACOECONOMICS

1. Type 1 error (α) : **true null hypothesis, but rejected in error** (it was concluded that there was a difference between the 2 groups, but in reality there was no difference) – a false positive
2. Type 2 error (β) : **false null hypothesis, yet it is accepted in error** (concluded that there was no difference, when in fact there was a difference) – false negative
3. Relative Risk : probability of an event occurring in the exposed group vs. the control group.
 - a. 10K pts, 2 MI in drug gr, 4 MI in placebo gr → RR was reduced by 50%
 - b. RR of 1 = no difference, RR <1 means intervention reduced the risk
 - c. If disease progression occurred in 28% of placebo pts and 16% of metoprolol treated pts. Ratio is $16/28 = 0.57$
→ Subjects treated with metoprolol were 57% as likely as placebo treated pts to have disease progress.

- d. A clinical trial is published about a new drug, Nopainz, for pain reduction. There are 200 patients randomized; 100 patients to Nopainz and 100 patients to placebo. The study found that pain was alleviated in 90 patients taking Nopainz and in 50 patients taking placebo. Calculate the relative risk in this trial? = *0.2 (10 pts that had the pain in the txt group /50 that had pain in the control group)*

4. Relative Risk Reduction : $1 - RR$

- a. Using example above, $RRR = 1 - 0.5 = 0.50 \rightarrow 50\%$ risk reduction in disease progression in pts being treated with drug.

5. Absolute Risk Reduction : difference in outcome rates between the txt and control grp

- a. $4/5000 - 2/5000 = 0.0004 = 0.04\%$

6. NNT : $1 - ARR$

- a. $1/0.04 = 25 \rightarrow$ for every 25 pts treated with the drug, 1 outcome will be prevented.

Types of Data:

1. Discrete data

- a. Nominal data: categories, where the order is arbitrary (marital status, gender, ethnicity)
b. Ordinal data: ranked categories (apgar score, NYHA fxnal class..)

2. Continuous data : can take an infinite number of possible values (height, weight, A1c, BP)

3. Interval data: equal distance between values, but zero is arbitrary (Celsius temp)

4. Ratio data: equal intervals, but with a meaningful zero (height, weight)

Pharmacoecon Methodologies

Methodology	Cost measurement unit	Outcome unit
CEA	Dollars	Natural units (life-years gained, mmHg BP, LDL..)
CMA	Dollars	Assumed to be equiv in comparative groups
CBA	Dollars	Dollars
CUA	Dollars	Quality adjusted life year

1. Cost Effectiveness Analysis (CEA) :

- a. Inputs are usually measured in dollars, outputs are measured in natural units (LDL, length of stay..)
b. Advantage: *outcomes are easier to quantify; clinicians and decision makers are familiar with these types of outcomes.*
c. Disadv: *inability to directly compare diff types of outcomes* (cannot compare the cost effectiveness of implementing a diabetes program vs an asthma program where the outcome units are different)

2. Cost Minimization Analysis (CMA) :

- a. *Used to compare 2 or more interventions w/ equivalency in outcomes and the costs of each intervention are being compared* (ex: 2 ACEi are considered therapeutically equivalent, but the costs may be diff)
b. Disadv: this method is limited in that it can only compare things with the same outcome.

3. Cost Benefit Analysis (CBA) :

- a. *Calculates and compares benefits and costs of an intervention in terms of monetary units* ; identifies the benefits from an intervention and converts them into a dollar amt.

4. Cost Utility Analysis (CUA) :

- a. Specialized form of CEA that includes a *quality of life component.*

[6] PHARMACOGENOMICS

Drugs that require genetic testing

Drug	Used to treat	Testing	Rxn
1. Abacavir (Ziagen)	HIV	Test for HLA-B*5701 If (+), cannot use drug	Hypersensitivity rxn (fever, rash, GI, resp.)
2. Carbamazepine (Tegretol, Tegretol XR)	Seizures, others	Test for HLA-B*1502 if Asian If (+), do not use unless benefits outweigh risks	Dermatologic rxns (TEN, SJS)
3. Trastuzumab (Herceptin)	Breast & gastric cancer	HER2/neu oncogene	HER2/neu oncogene overexpression req. for use

Drugs with known or possible genetic risk factors

Drug	Used to treat	Testing	Rxn
1. Phenytoin (Dilantin)	Seizures	Test for HLA-B*1502 if Asian If (+), do not use unless benefits outweigh risks	Dermatologic rxns (TEN, SJS)
2. Atomoxetine (Strattera)	ADHD	2D6 Poor metabolizer – no recomm, use caution	5 fold higher concn. This can lead to inc adv effects (dec appetite, insomnia, sedation, depression, tremor, pruritus, mydriasis)
3. Codeine	Pain, cough	2D6 extensive met. – use caution b/c EM are common	Over prod of morphine can inc CNS effects, resp depres.
4. Azathioprine, mercaptopurine	Solid organ cancers and leukemia	TPMT (thiopurinomethyltransferase)	Deficiency of TPMT= inc risk of myelosuppression
5. Warfarin (Coumadin, Jantoven)	Clot prevention	VKORC1 → in the VKORC1 SNP, the common G allele is replaced w/ an A allele; w/ the A haplotype, less VKORC1 is produced & req lower dose of warfarin	CYP2C9 met. the S isomer (more potent isomer) → 2C9*2, 2C9*3 are loss of fxn alleles, so are assoc with more bleeding

[7] DRUG ALLERGIES, ADRs, & ADR REPORTING

Drug side effects that are NOT allergies

1. Stomach upset/nausea : many pts get upset stomach from codeine (but not hydrocodone or other drugs in morphine class) or with erythromycin (but not azith or other macrolides)
2. Mild rash : opioids can common cause histamine induced skin rash
3. Photosensitivity : many drugs can cause photosensitivity, this req. limited sun exposure and using sunscreens that block UVA (causes aging, skin cancer) and UVB (causes sunburns).
 - a. Broad spectrum = covers both UVA & UVB
 - b. Some ex: Sulfa abx, tetracyclines, NSAIDs – ibuprofen & naproxen (propionic acid) cause p/s

True Drug Allergies

1. Skin rash or urticaria (hives)
 2. Wheezing or other breathing problems
 3. Swelling – facial / lip
 4. Drop in BP, dizziness
- ◆ If rxn is mild → stop the drug is the only action required
 - ◆ More severe cases → antihistamines are used to counteract the histamine-release, steroids and occasional NSAIDs can also be used to dec swelling
 - Epinephrine may be needed to keep airway open

Drug classes that cause allergic rxns

1. Beta lactam : anyone allergic to one of the PCN should avoid the entire group; cephalosporins are closely related to PCN and have a small risk of having an allergic rxn [on exam, avoid any beta lactam unless there is no alternative]
2. Sulfa allergy: *most commonly reported with sulfamethoxazole (Bactrim, Septra)* & pts should avoid using sulfapyridine, sulfadiazine, sulfisoxazole
 - a. Non-arylamine sulfonamides (thiazides, loops, sulfonyleureas, acetazolamide, zonisamide, celecoxib) usually do not cross react – but on exam, recognize these to have a rxn
 - b. Zonisamide & celecoxib- no case reports, but still contraindicated for the exam with sulfa allergies
3. Opioid allergy: discussed in pain section ; fentanyl, meperidine, methadone – do not cross react with opioid of the morphine type
4. Peanut / Soy allergy : peanuts and soy are in the same family and can have cross-reactivity
 - Drugs to avoid w. peanut allergy:
 - a. Ipratropium/albuterol (Combivent) – new formulation Combivent Respimat does not contain soy or CFCs
 - b. Clevidipine (Cleviprex)
 - c. Propofol (Diprivan)
 - d. Progesterone in Prometrium
5. Egg allergy:
 - a. Seasonal and H1N1 influenza shots or nasal mists
 - b. Clevidipine (Cleviprex)
 - c. Propofol (Diprivan)

[8] MEDICATION ERRORS, PATIENT SAFETY, AND THE JOINT COMMISSION

1. **Root cause analysis (RCA)** *investigates an event that has already occurred (it is retrospective). The info obtained is used to design changes that aim to prevent future errors*
 - a. **Sentinel event** – the unexpected occurrence involving death or serious physical/psychological injury or risk
 - b. RCA is often considered to be a repetitive process, and is freq. viewed as a **continuous quality improvement (CQI) tool**.
2. **Failure Mode and Effects Analysis (FMEA)** : a **proactive** method that is done **prospectively** to identify pathways that can lead to errors and to identify ways to reduce the error risk.
3. Error of Omission vs Errors of Commission
 - a. Error of Omission - leaving something out that is needed for safety, such as missed instructions or failure to provide a dose at the req. time
 - b. Error of Commission - something was done incorrectly, such as prescribing bupropion to someone w/ hx of epilepsy, or giving the wrong dose to a pt.

4. Reporting medication errors: *in a hosp. setting, the hospital's pharmacy & therapeutics (P&T) committee should be informed of medication errors as well as the Medication Safety Committee. The P&T Committee is req. to record errors and responses to the Joint Commission (TJC)*
- **Medication Guides:** present **imp. adverse events** that can occur w. over 300 meds.
 - a. They are **FDA approved patient handouts**
 - b. If a med. Has a MedGuide, it must be dispensed with w/ the orig rx and each refill
 - c. Req. for many indiv agents and some entire classes of meds (anticonvulsants, antidepressants, NSAIDS, ADHD stimulants and atomoxetine)
 - **Consumer Medication Information (CMI) Leaflets**
 - a. CMIs for all meds, are voluntarily provided w. new rx by retail pharmacists
 - b. Explains how the medication works, how to take it, common s/e, potential interactions
 - **Risk evaluation & Mitigation Strategies (REMS) Drugs**
 - a. REMS is an FDA prog. That **req. specified training and various restrictions (pt requirements, user registries)**
 - b. Ex: Clozapine pt registry; APPRISE prog for erythropoietin use in oncology ; iPLEDGE prog for isotretinoin, etc.
 - **Common types of Hosp. (Nosocomial) Acquired infections**
 - a. UTIs from indwelling catheters → **remove the catheter ASAP** – preventing catheter assoc infxn is a new Joint Commission goal in 2012
 - b. Blood stream infxn **from IV lines (central lines have the highest risk) & catheters**
 - c. Surgical site infxn (**see abx ppx section**)
 - d. Decubitis ulcers
 - e. Hepatitis
 - f. **Clostridium difficile, other GI infxn**
 - g. **Pneumonia (mostly due to ventilator use), bronchitis**

Hand Hygiene

1. **Alcohol based hand rubs** (gels, rinse/foam) are **considered more effective in healthcare setting** than plain soap/antimicrobial soap & water
2. **Antimicrobial hand soaps** w/ chlorhexidine (Hibiclens, others) may be preferable to soap & water to reduce infxn.
3. Use **soap & water (not alcohol based rubs)** – **after caring for pt with diarrhea or known C. difficile or spore forming organisms** → alcohol based hand rubs have poor activity against spores.

Laminar flow hoods

1. HEPA filters remove 99.97% of air particles **≥ 0.3 mm**
2. Preparation has to be at least 6 inches back from the front of the hood
3. If hood is turned off, it should be turned on for at least 30 mins prior to use
4. Vertical flow hoods (biological safety cabinets/chemotherapy hoods) blw air from the top down to protect the person preparing the med

[9] FDA DRUG DEVELOPMENT PROCESS

For prescription drugs, drug approval process begins with preclinical (animal) research → Investigational New Drug application (IND) - or abbrev new drug app if requesting a generic → Phase I, II, III, IV

1. **Phase I** : focuses on safety and pharmacology of a compound. Low doses of the drug are given to a small group of healthy volunteers
2. **Phase II** : examines the effectiveness of a compound. Multiple arms are often studied to investigate diff. doses
3. **Phase III** : must obtain FDA approval before enrollment for pivotal trials
4. After phase III, manfu files for new drug app (NDA). The FDA now has 1 yr to review the data. Fast track approval is also avail for agents treating serious medical condits w. no other drug substitute.
5. **Phase IV** = post marketing surveillance ; for Δ's t existing drug, Suppl New Drug App (SNDA) is used

Phase	Purpose	Subjects	Scope & Length
1	Safety profile & dosing range, PK/PD, open label, often 1 center, may not be done in US	Can be healthy volunt. or pts with illness	20-80 subjects 6-12 mths
2	Safety & efficacy (dose response) IIa – proof of concept; pilot study IIb – well controlled target pop.	Used in intended pop.	100-300 pts 1-2 yrs
3	Safety & efficacy at the dose & schedule you are seeking approval IIIb – post NDA, submission trial looking at addt indic	Subjects w/ indications the drug is seeking	Hundreds-thousands 2-3 yrs
4	New indications, QOL, surveillance studies	Subjects with indic the drug is seeking	Hundreds-thousands 1-5 yrs

[10] NATURAL PRODUCTS & VITAMINS

Gamma-tocopherol = Vitamin E

1. Manufacturing of these products may not follow good manufacturing practices (GMP)
2. A dietary suppl. Manfu does not have to prove a product's safety and effectiveness before it is marketed.

- ❖ **Ginkgo biloba** & other agents → **inc bleeding risk w/ no effect on INR**.
 - Bromelains, danshen, dong quai (this may ↑INR), vit E, evening primrose oil, high doses of fish oils, garlic, ginseng, glucosamine, grapefruit, policosanol, willow bark
- ❖ **St. John's wort enzyme induction** → 'broad spectrum inducer' 3A4 >> 2C9 > 1A2
 - Cannot be used w/ : oral contraceptives, transplant drugs, warfarin..
- ❖ **Hepatotoxic** : chaparral, comfrey, kava

Vitamin	Names
A	Retinol
B1	Thiamine
B2	Riboflavin
B3	Niacin
B6	Pyridoxine
B9	Folic acid
B12	Cobalamin
C	Ascorbic Acid

Vit B: T.R.N.P.F.C

Homeopathic products & Medical foods

1. Homeopathic products : *based on "the law of similars" or the concept that "like is cured by like" (belief that giving very small amts of the illness will protect the pt or cure them of the illness)*
 - a. Manuf labels a product homeopathic – they are permitted to make health claims VS.
 - b. Natural products – are not allow by law to claim benefit for particular conditions
2. Medical Foods: *these products can also make health claims since they are not FDA approved drugs*
 - a. Supposed to meet nutritional need for a group that cannot be met with usual foods
 - b. Ex: formulation of folic acid called *Depkin* → being marketed for help in treating depression (states that it contains L-methylfolate, the active form of folate – it is the only folate that can be taken up by the brain where it helps balance chemical messengers that affect mood, 5-HT, DA, NE)

Vitamin Supplementation

1. **Calcium & Vit. D** intake remains insuff for the majority of adults

- a. Critically imp in children (to build bone stores), pregnancy (fetus can deplete the mother's stores), around menopause (when bone loss is rapid)

NIH recommended intake for Calcium				
Age	Male	Female	Preg	Lactating
9-18 yo	1,300 mg	1,300 mg	1,300 mg	1,300 mg
19-50 yo	1,000 mg	1,000 mg	1,000 mg	1,000 mg
50+ yrs	1,200 mg	1,200 mg		

- b. *Vit D. is required for Ca++ absorption ;*
Ca++ absorption is *saturable*, so doses should be divided

Calcium citrate (Citracal)	Calcium carbonate (Oscal, Tums)
1. Better absorption	1. Acid-dependent absorption- (needs acid for abs.)
2. Taken with <u>or</u> w/o meals	2. Take with meals
3. Larger pill	3. 500-600 mg Ca++/tab
4. 315 mg Ca++/tablet	

The solubility of calcium salts is a pH-dependent process; therefore, increased pH due to treatment with PPIs could lead to decreased amounts of calcium salts being absorbed. For example, the most common calcium supplement available, calcium carbonate, is insoluble at high pH levels and therefore absorption is decreased with higher pH levels; however, calcium citrate does not require extra stomach acid for absorption

c. **Vitamin D recom intake** : ≤ 70 yrs = 600 IU QD , 71+ yrs = 800 IU QD

- i. 50,000 unit D2 suppl is used in renal disease or short term in adults with deficiency to replenish stores
- ii. Cholecalcierol (Vit D3) is the preferred source, although D2 is often used and will provide benefit

2. **Folic acid** intake among women of child-bearing age can also be insuff

- a. Any woman planning to conceive (and all of child bearing age) should take **400-800 mcg/day = 0.4-0.8 mg/day** to prevent brain and spinal cord defects – neural tube defects.
- b. Take at least 1 mth before pregnancy & cont for 2-3 mths into pregnancy , then will cont with prenatal vit.
- c. Rx prenatal vit usually contain ~ 1 mg of folic acid

3. **Thiamine (Vit B1)** insuff – results in wernicke's encephalopathy (ataxia, tremor, vision changes)

- a. Common in alcoholism, malabsorption (from Crohn's, obesity surgery, advanced HIV)
- b. As symptoms of wernicke's fade, Korsakoff syndrome tends to develop (permanent neurologic damage)

4. **Vitamin E** : deficiency is rare bc present in many foods; excess intake is assoc with CVD risk

- a. **Do not exceed 150 IU /day**

Vitamin requirements for babies & children

- 1. Vitamin D: **exclusively breastfed infants or babies drinking <1L formula need 400 IU of Vit D/day (can use poly-Vi-sol)**
- 2. Iron Requirement :
 - a. **4-6 mths**: breast-fed babies need 1 mg/kg/day from 4-6 mths old until consuming Fe rich foods
 - b. **Adolescent girls** : at risk of anemia once they begin menstruating

[11] DRUG INTERACTIONS

Big Inducers (PS PORCS)	Big Inhibitors (G ♥PACMAN)
<ol style="list-style-type: none"> 1. <i>Phenytoin</i> 2. <i>Smoking</i> → theophylline, clozaril cocaine will ↑ if stop smoking 3. <i>Phenobarbital</i> 4. <i>Oxcarbazepine</i> 5. <i>Rifampin</i> → & rifabutin, rifapentine 6. <i>Carbamazepine</i> → also an autoinducer 7. <i>St. John's Wort</i> 	<ol style="list-style-type: none"> 1. <i>Grapefruit</i> 2. <i>Protease inhibitors</i> → don't miss ritonavir 3. <i>Azole antifungals</i> → oral & IV agents : fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole 4. <i>Cimetidine</i> → H₂RA that is most difficult due to Dis and androgen blking effects (causes gynecomastia = swollen/painful breast tiss. or impotence) 5. <i>Macrolides</i> → clarithromycin & erythromycin, telithromycin. NOT azith. 6. <i>Amiodarone</i> → & dronedarone 7. <i>Non-DHP CCB</i> → diltiazem & verapamil

❖ P-glycoprotein (PGP) : efflux transporters in the gut and other organs that pump drugs back into the gut (out of bloodstream).

- a. PGP inhibitors will ↑ drug concentration
- b. PGP inhibitors = *cyclosporine*, ketoconazole, itaconazole, lopinavir, ritonavir, indinavir, conivaptan, erythromycin, verapamil, quinidine, St. John's wort
- c. PGP inducers = rifampin, phenytoin
- d. PGP substrates = Dabigatran (Pradaxa), rivaroxaban (Xarelto)

Drugs with significant interactions – watch for these

1. Amiodarone : mod. Inhibitor of 2C9, 2D6, 3A4, PGP
 - a. Will ↑ levels of **warfarin** & **digoxin** (INR/QT prolongation prob.) → Must ↓ 30-50% of dose of these meds if starting amiodarone
 - b. Use lower doses of (SAL) simvastatin, atorvastatin, lovastatin
 - c. Electrolyte abnormalities (esp. **K⁺**, Na, Ca, Mg) should be corrected before starting antiarrhy therapy
 - d. No grapefruit
2. Azole antifungals : all are 3A4 inhibitors
 - a. Itraconazole & ketoconazole have pH dependent absorption ; ↑pH causes ↓absorption . avoid using with antacids, H₂RAs, PPIs (must stop PPI/H₂antag while on these azoles due to large dec in azole concn)
 - b. Voriconazole is notable for Dis; metabolized by several enzymes and can inc dangerously when given with inhibitors and with small dose inc (follows 1st order then Michaelis-Menten kinetics)
 - c. Vori is contraindicated with CYP inducers such as carbamazepine, cisapride, rifampin, st. john's, etc.
3. Colchicine : should not be used w/ PGP or strong 3A4 inhibitors, esp in pts with renal/hepatic impairment
4. Digoxin: mainly renally cleared, so look for reduced renal fxn, K⁺ levels
 - a. Amiodarone will inc digoxin & warfarin levels
 - b. Hypokalemia (<3.5) will ↑ digoxin levels
 - c. ↓ digoxin levels : cholestyramine, colestipol, metoclopramide
5. Grapefruit juice: Avoid grapefruit with:
 - a. simva, atorva, lovastatin
 - b. buspirone, amiodarone, carbamazepine, cyclosporine, tacrolimus, diazepam, triazolam, verapamil, nifedipine, felodipine, nisoldipine, nifedipine, telithromycin, voriconazole.
6. Lamotrigine & Valproate : valproate CYP inhib, will ↑ LTG levels
 - a. increased risk of severe rash (SJS, Toxic epidermal rash) – titrate slowly

7. Lithium : 100% renally cleared (cannot differentiate btw Na or Li, so when Na concn is ↑, Na and Li excretion will ↑.
 - a. ↑ Li levels = ↓ salt intake, NSAIDs, ACEi, ARBs, dehydration
 - b. ↓ Li levels = ↑ salt intake, caffeine, theophylline
 - c. ↑ risk of serotonin syndrome if given with Li = SSRIs, SNRIs, triptans, linezolid, other serotonergic drugs
 - d. ↑ neurotox (ataxia, tremors, nausea) = verapamil, diltiazem, phenytoin, carbamazepine
8. Monoamine oxidase inhibitors : DI can cause serotonin syndrome, hypertensive crisis, & can be fatal
 - a. Rasagiline (Azilect), Selegiline (Deprenyl, Eldepryl, Emsam)
 - b. Monoamines that have reduced metabolism with MAOi: DA, Epi, NE, 5-HT, tyramine
 - c. DO NOT use MAOIs with : ephedrine, and analogs (pseudoephedrine, etc), buspirone, linezolid, Li, meperidine, **SSRIs, SNRIs, TCAs**, tramadol, levodopa, mirtazapine, cyclobenzaprine, wellbutrin, St. John's, etc.
9. NSAIDs:
 - a. All NSAIDs (including COX 2 selective) inc BP (~6mmHg) & have renal toxicity and should be avoided with signif renal disease
 - b. NSAIDs cannot be used with Lithium due to risk of Li toxicity
 - c. All NSAIDs, except ASA have risk of CV toxicity (celecoxib has the highest risk)
10. Oral contraceptives, ring & patch
 - a. **St. John's Wort** (do not use OC's concurrently)
 - b. **ABX** (ampicillin, griseofulvin, sulfonamides, tetracycline rifampin – with rifampin, must use alt. method for 1.5 mths afterward)
 - c. **Anticonvulsants** (barbiturates, carbamazepine, phenytoin, felbamate)
 - d. **Anti-retrovirals** (do not use with these due to inc OC metabolism ∴ dec efficacy: atazanavir, lopinavir, belfinavir, nevirapine, ritonavir)
 - e. **Smoking** (dec efficacy & is dangerous while using OC's)
11. Oxycontin & other oxycodone products : 3A4 inhibitors ↑ opioid level (inc s/e and risk of resp. depression)
 - a. Oxycontin has BBW for use with CYP inhibitors
12. PD5 inhibitors (sildenafil, tadalafil, vardenafil)
 - a. Contraindicated with nitrates due to severe hypotn
 - b. Use with caution w/ alpha blockers (esp. non-selective **doxazosin** (Cardura)) --selective α1A agent, Flomax has less dizziness, orthostatic hypotn but still have same caution use
13. Rifampin : strong inducer of 2C9, 2C19, 3A4
 - a. Will ↓ warfarin & oral contraceptives
14. Statins:
 - a. Simva, Atorva, Lovastatin – 3 statins with most DIs (inc risk of muscle damage w. amiodarone, dronedarone, cyclosporine, protease inh, ketoconazole, grapefruit juice, diltiazem)
 - i. Hold these 3 with Telithromycin therapy due to ↑ muscle damage
 - b. Cannot use CSA with pitavastatin (CSA ↑ pitava and pravastatin levels)
 - c. Protease inhibitors- safest choice is **pravastatin**, or low dose atorvastatin or rosuvastatin (not >10 mg)
 - d. For TG → Gemfibrozil (Lopid) w/ statins have ↑ muscle tox (fenofibrates – Tricor, Trilipex, is a safer combo)
 - e. Niacin w/ statins have ↑ muscle & liver toxicity (Niaspan – long acting niacin, can be used with **lower doses** of simva/lovastatin if needed)
15. Tetracycline & Quinolone abx
 - a. These chelate w/ cations (Al, Mg, Ca, Fe, Zn), didanosine, sucralfate, dairy, and ↓ absorption → must separate by 2 hrs

16. Theophylline: follows 1st order then MM kinetics (like phenytoin and voriconazole)

- Met by 1A2 and 3A4 – be careful with inh/inducers
- ↑ theophylline levels (due to 1A2 inh) : OC, zafirlukast, zileuton, acyclovir, cimetidine, ciprofloxacin, ethinyl estradiol, fluvoxamine, isoniazid
- ↑ theophylline levels (due to 3A4 inh) : amiodarone, azoles, clarithromycin, CSA, erythromycin, diltiazem, verapamil, simva, atorva, lovastatin, etc
- ↑ theophylline levels (other mech) : allopurinol, erythromycin, propranolol, ephedrine, possibly phenyleph, pseudoephedrine
- ↓ theophylline levels: inducers
- Theophylline will ↓ Lithium levels (due to inc renal excretion) & ↓ zafirlukast

17. Warfarin : substrate of 2C9(major), 1A2 & 3A4 (minor) & is a moderate inhibitor of 2C9 (avoid use with tamoxifen)

- *2C9 inducer = rifampin → will dec INR *2C9 inhibitor = amiodarone, bacrim → will inc INR
- NSAIDS (ASA, ibuprofen), Ginkgo biloba, high dose fish oil (>3g/day), garlic, ginseng, grapefruit – inc bleeding risk w/ no effect on INR
- SSRI, SNRI – can inc bleeding risk
- Green teas, Coenzyme Q10 – may dec effectiveness of warfarin

18. Other anticoags:

- Dabigatran (Pradaxa)-no CYP interactions, PGP substrate
- Rivaroxaban (Xarelto) – substrate of 3A4, PGP
- Clopidogrel (Plavix) – prodrug converted by 2C19

Additive Drug Interactions

1. Hyperkalemia risk: K+ is renally cleared

- Additive K+ accumulation : ACEi, ARBs, K-sparing agents - amiloride, triamterene, eplerenone, spironolactone, KCl, oral contraceptives (Yasmin, Natazia, Yaz → have progestin, drospirenone a K+ sparing diuretic)
 - Triamterene is part of a combo Maxide, Diazide (triam/HCTZ)

2. CNS depression

- Additive CNS effects : alcohol, opioids, skeletal muscle relaxants (soma), anticonvulsants, benzos, barbiturates, hypnotics, mirtazapine, trazodone, dronabinol, propranolol, clonidine
 - Mirtazapine (Remeron) – used for sedation & ↑ app / wt gain. Used in 1) Skilled nursing facilities 2) Oncology 3) Skinny & depressed

3. QT Prolongation : reflects vent depolarization & repolarization

Additive QT prolongation:

- Preexisting cardiac cond.
- Class Ia & III antiarrhythmics (amiodarone, dronedarone, sotalol, quinidine)
- Abx: quinolones (cipro, levo, moxifloxacin...), macrolides (azith, eryth, telith, clarithromycin), Azoles
- Antidepressants: tricyclic (amitriptyline, doxepin..), SSRI (citalopram)
- Antipsychotics : ziprasidone (has BBW for QT prolong), haloperidol..
- Many more (pg 149) – QTdrugs.org

Drug	Usual therapeutic range
Carbamazepine	6-12 mcg/mL (or 4-12)
Levothyroxine	FT4 normal range 0.8-1.7 mcg/dL TSH normal range 0.3-3 uIU/mL
Lithium	0.6-1.2 mEq/L (can 1.5 for acute symptoms)
Phenytoin	10-20 mcg/mL
Theophylline	5-15 mcg/mL
Digoxin	0.8-2 ng/mL
Procainamide	4-10 mcg/mL
NAPA	15-25 mcg/mL
Valproic acid	50-100 mcg/mL
Warfarin	INR 2-3; 2.5-3.5 for valves and other indications

[12] RENAL DISEASE & DOSING

1. Proximal Tubule : large amts of water are reabsorbed here, along with Na⁺ and Cl⁻
2. Loop of Henle :
 - a. Descending limb: reabsorbs water, impermeable to Na and Cl⁻
 - b. Ascending limb: reabsorbs Na⁺ and Cl⁻, impermeable to water
 - c. **Loop diuretics inhibit the NaK pump** in the ascending loop ; loops cause **dec reabsorption of Ca⁺⁺, ∴ contributes to the devel. of osteoporosis** w/ long-term use
3. Distal convoluted tubule :
 - a. regulates K, Na, Ca, and pH ; only ~5% of Na⁺ is reabsorbed here
 - b. **Thiazide diuretics inhibit the Na-Cl pump in DCT ; increases Ca⁺⁺ absorption ∴ has protective effect on bone** with long term use
4. Collecting duct :
 - a. Is affected by ADH and aldosterone
 - b. **Aldosterone** also works in the distal tubule; 1° fxn is to inc Na⁺ and water retention and to lower K⁺
 - c. **Spironolactone & eplerenone are aldosterone antagonists ∴ ↑ K⁺**

Impaired renal excretion examples:

1. Gabapentin (Neurontin) – commonly used for diabetic neuropathy, although not indicated for this. It primarily causes CNS s/e (dizziness, somnolence), must renal adjust at CrCl <60 (1/2 the dose) or else pt will experience excessive sedation & dizziness
2. Metoclopramide (Reglan) – a DNU drug in the elderly, is 1° used for nausea & poor GI motility in the elderly. It is a DA blocking agent & is renally cleared. Too high of a dose, the pt can present with Parkinsonism (difficulty w/ mvmt due to DA blockade). Pt can also have inc CNS s/e (confusion, dizziness)

Proteinuria, BP control & the use of ACEi & ARBS

1. *Once proteinuria has been identified, ACEi/ARBs will be used unless C/I.* Control BP at **<130/80** for kidney disease
2. ACEi/ARB help preserve renal fxn and reduce proteinuria & provide CV protection
3. Use of ACEi/ARB **can cause acute decline in GFR during initiation** (most commonly in HF pts or those taking **NSAIDS – which should be avoided in renal disease**) - renal fxn usually returns to normal after several wks

Anemia & Bone metabolism problems in advanced renal disease

1. To compensate for hyperphosphatemia, the parathyroid gland inc release of PTH. 1° hyperphos is treated w/ dietary phosphate restriction, then phos binders & Vit D supplementation
2. 3 types of Phosphate Binders: ***phosphate binders bind to meal-time phosphate in the gut coming from the diet . If a dose is missed during a meal, there is no point in taking a dose or doubling it**
 - a. **Aluminum based** (AlternaGel, Amphojel, etc) – effective but Al is neurotoxic and toxic to bones; can only be used short-term
 - b. **Calcium based** (calcium acetate & carbonate) – *many renal pts are taking Vit D (which ↑ Ca levels) and cannot tolerate addt Ca⁺⁺*
 - c. **Aluminum free calcium binders** - *do not contain Al or Ca ; but are expensive*

DRUG	DOSE	S/E, MONITORING, CONTRAINDICATIONS
Aluminum-based Aluminum hydroxide (AlternaGel, Amphojel, etc.)	15-30 mL TID w. meals	Constipation, poor taste, nausea Inexpensive, no effect on Ca++, used short term only
Calcium based Calcium acetate (PhosLo, Phoslyra, others) Calcium carbonate (Tums)	1,334 mg TID w. meals 500 mg TID, w. meals, chewable or not	❖ <i>Can cause hypercalcemia (prov. more Ca++ if needed)</i> Constipation, nausea low gastric pH can ↓ efficacy Inexpensive, may contribute to hypercalcemia
Aluminum-free, calcium-free Lanthanum carbonate (Fosrenol) Sevelamer carbonate (Renvela) Sevelamer hydrochloride (Renagel)	<i>*best option, but expen.</i> 500 mg TID w. meals, chewable-must chew thoroughly 800-1,600 mg TID w. meals, tablet/powder (mix for suspension) 800-1,600 mg TID w. meals	❖ <i>no effect on Ca++ ; all can cause nausea</i> Expensive, <u>NOT</u> affected by gastric pH Constipation Expensive, affected gastric pH, ↓ LDL & total CH Constipation, risk acidosis Can ↓ fat-soluble vitamins (some may be told to take Vit. at other times) Expensive, affected by gastric pH, ↓ LDL & total CH

PTH: [Net = ↑ Ca ↓ Phosphate]

1. ↑ renal & GI reabs. Of Ca++
2. ↑ Bone resorption (Ca & Phos)
3. ↑ Synthesis of calcitriol (activating renal hydroxylation of 24-OH D3 to 1,25 OH D3)
4. ↑ Phos excretion (to prevent detrimental ↑ in phosphate)

Low serum Ca++ → INC PTH secretion
High serum Ca++ → DEC PTH secretion

Calcitriol: [Net = ↑ Ca ↑ Phosphate] *do not give if phos is already elevated*

1. ↑ GI abs of Ca & Phosphate
2. ↑ renal reabs of Ca & Phosphate
3. ↑ bone resorption

**PTH encourages calcitriol active. But calcitriol instructs parathyroid to cut PTH secretion (Neg feedback) to prevent blood Ca from ↑ing out of control*

INC formation of calcitriol = PTH, ↓ Sphosphate
DEC formation of calcitriol = calcitriol, ↑ Sphosphate

Txt Vitamin D Deficiency

1. Vit D2 = ergocalciferol **Vit D3 = cholecalciferol (active form of Vit D)**
2. **Calcitriol (Rocaltrol)** is a synthetic form of Vit D3 – *often used in pts with advanced renal disease/dialysis*
3. **Vit D suppl. ↑ Ca absorption in gut & ↓ renal excretion ; ↑ Ca resorption from bone (done in conjunction with PTH)**
 - a. Can result in hypercalcemia / hyperphosphatemia

Txt of Hyperkalemia

1. Hyperkalemia is **defined as K⁺ above 5.3 or 5.5 mEq/L**
2. K⁺ is the **most abundant INTRAcellular cation**
3. K⁺ **excretion is increased by aldosterone, diuretics (strongly loops, weakly thiazides)**, high urine flow (osmotic diuresis), and neg. charged ions in distal tubule (bicarbonate)
4. Acute rise in K⁺ is often not caused by excessive K⁺ intake b/c it would be offset by the release of insulin (which causes K⁺ to shift intracellularly). It is more commonly caused by dec. renal excretion due to renal failure
 - a. Diabetic pts are more susceptible to hyperK⁺ due to insulin deficiency, & ACEi/ARB meds
5. **Drugs that can ↑ K⁺ levels:**
 - a. K⁺ sparing diuretics (aldosterone blockers)
 - b. ACEis, ARBs
 - c. NSAIDs
 - d. Oral contraceptives w/ drospirenone (Yaz, etc.)
 - e. Cyclosporine, tacrolimus
 - f. Heparin, pentamidine
 - g. Trimethoprim/sulfamethoxazole
 - h. Digoxin toxicity
 - i. K⁺ suppl (IV fluids, TPN)
6. Pts can be asymptomatic or symptomatic (muscle wkness, bradycardia, fatal arrhythmia)
7. **To ↓ K⁺:**
 - ❖ **ECG** may be needed to check for cardiotox – *if req. admin Ca⁺⁺ to stabilize the cardiac tissue* (Ca⁺⁺ does not lower K⁺, only used to stabilize the heart)
 - a. ↑ K⁺ uptake into cells: **Glucose + Insulin** (glucose is used to stim. Insulin secretion) (insulin drives K⁺ into the cell, but it also drives glucose into the cell, ∴ must give w/ glucose also)
 - b. If metabolic acidosis is present → give sodium bicarb
 - c. To ↓ K⁺, Consider **β agonist (nebulized albuterol)** – monitor tachycar, CP
 - d. ↑ renal excretion w/ :
 - 1) loop diuretic 2) **fluorohydrocortisone** (Florinef) – esp in hypoaldosteronism pts
 - e. **Cation exchange resin sodium polystyrene sulfonate (Kayexelate)** – can dec K⁺ by 2 mEq/L w. 1 enema
 - i. Given **PO or rectally (rectal admin preferred for emergency txt)**
 - ii. If given **PO, do NOT mix with sorbitol** (risk of GI necrosis)
 - iii. **S.E : ↓ appetite, n/v/c (less commonly diarrhea)**

$$\frac{\text{K}^+}{\text{Gut fluid}} \quad \frac{\text{K}^+ + 2)}{\text{SPS K}^+ \quad \text{SPS K}^+} \quad \text{↷}$$

→ 1) goes into stool, so now body will move K⁺ from blood to gut bc of passive diffusion
 - f. Emergency dialysis may be needed

[13] DRUGS USED IN PREGNANCY

A	• Controlled studies in animals & women → no risk in 1 st trimester
B	• Animals studies show no risk in 1 st trimester & NO controlled studies in pregnancy women • <u>OR</u> animal studies shown adverse effect BUT not confirmed in controlled studies in women
C	• No controlled studies in humans + animal studies have shown adverse events • OR studies in humans & animals not avail
D	• Positive evidence of fetal risk , but benefits may outweigh risk of life-threatening/serious disease
X	• Animals & human studies show fetal abnormalities, Use is contraindicated in pregnancy

Common Teratogens *if a case indicates hCG+, the pt is pregnant

- | | | |
|------------------------------|---------------------------|---------------------------------------|
| 1. Alcohol | 6. Isotretinoin | 12. Leflunomide, lenalidomide, |
| 2. ACEi/ ARBs | 7. Lithium, valproic acid | thalidomide (causes missing of |
| 3. Statins | 8. NSAIDS | long bone) |
| 4. Carbamazepine, phenytoin, | 9. Ribavirin | 13. Dutasteride, finasteride |
| phenobarbital | 10. Misoprostol | 14. Warfarin |
| 5. Topiramate | 11. Methotrexate | |

Folic Acid in women of child bearing age

1. **When a young woman enters the pharmacy the pharmacist can ask if she's consuming adequate folic acid (400-800 mcg QD), calcium (1,000 mg QD), and Vit D (600 IU QD)**
2. **It's safe to recom to women planning to conceive (and those in child bearing age) to take folic acid suppl.** At least 1 mth prior to pregnancy – to help prevent neural tube defects (brain and spinal cord defects)
 - a. Folic acid should be cont for first 2-3 mths of pregnancy then prenatal vitamins may be used
 - b. **Rx prenatal vit (PrimaCare ONE, Zenate, etc) usually contain 1mg folic acid = rx dose of folic acid)**

Vaccinations during Pregnancy

1. Influenza vaccine (shot, inactivated) – recom in all stages of preg
2. No live vaccines (MMR, varicella, live influenza nasal, etc.) 1 mth before and during preg
3. Preg women >20 wks gestation should receive Tdap if a booster is needed. If vaccination hx is unclear, a 3 dose series is needed (1 Tdap, 2 Td). If a woman delivers w.o the vaccination, she should still receive it post delivery. – this protects baby and mother from pertussis (whooping cough)

Common OTC treatable Conditions in Pregnancy

- | | |
|---|--|
| <ol style="list-style-type: none"> 1. Nausea/Vomiting <ol style="list-style-type: none"> a. 1st recom eating smaller, more freq meals, avoid spicy/odorous foods, take more frequent naps, and reduce stress b. Pharmacologic: Pyridoxine (Vit B6) – 1st line recom by ACOG ± antihistamine doxylamine (Unisom) c. Natural products: ginger (in tea form/cooked) – do not recom supplements <ol style="list-style-type: none"> i. Dried plums are used by certain ethnic groups | <ol style="list-style-type: none"> 2. GERD/Heartburn/Gas Pains <ol style="list-style-type: none"> a. 1st recom eating smaller, more freq meals, avoid foods that worsen GERD ; if symptoms occur while sleeping, recom elevating the head of the bed and not eating 3 hrs before sleep b. Pharmacologic: Calcium antacids (Tums) are 1st line – good choice b/c Ca++ is often deficient in preg. <ol style="list-style-type: none"> i. Use cation w. excessive antacids w. Al or calcium if renal disease is present (Maalox, Mylanta, etc) |
|---|--|

- c. For **Gas** : **simethicone** is safe (Gas X, Mylicon) – mylicon infant drops are safe for infants
 - i. H2 blockers (Pepcid, Tagamet, Axid, Zantac) are Preg Cat B (PPIs are C's or B's)
- 3. Constipation
 - a. 1st recom inc fluid intake, inc fiber, inc physical activity (walking)
 - b. Pharmacologic: **fiber and psyllium is 1st line (Metamucil)** preg cat B
- 4. Cough/Cold/Allergies
 - a. **1st gen antihistamine doxylamine (Unisom)** is preg Cat B – 1st line recom
 - b. Diphenhydramine is preg Cat B (do not use neither of these during lactation; enters breast milk)
 - c. Decongestants (pseudoephedrine, phenylephrine, oxymetazoline), dextromethorphan & guaifenesin are Preg Cat C, but may be recom by the physician
- 5. Pain
 - a. 1st line = **APAP** – Cat B, this is the analgesic and antipyretic DOC
 - b. Ibuprofen is Cat D, Naproxen is Cat C – do not recom OTC NSAIDS during pregnancy
 - c. Caution for lactation: most opioids are excreted in breast milk; DO NOT use codeine (Tylenol #3, others) since rapid metabolizers of 2D6 will produce excessive amts of morphine which may be fatal to infant.

ABX use in Pregnancy

- 1. **Safe to use:**
 - a. *Penicillins* (amox, ampicillin, both B's)
 - b. *Cephalosporins*
 - c. *Erythromycin & azithromycin* = B's, clarithromycin = C
- 2. **Do not use during pregnancy:**
 - a. *Quinolones* (cartilage damage)
 - b. *Tetracyclines* (teeth discoloration)
- 3. Vaginal fungal infxn → use topical antifungals (creams/suppose) at least 7 days
- 4. UTI
 - a. B lactams that cover the organisms can be used: cephalexin (500mg QID) or ampicillin
 - b. Nitrofurantoin (Nitrobid) 100 mg BID – but not in last several wks of preg
 - c. Fosfomycin (Monurol) 3 gms – 1 packet, mixed w. water x1
- d. Sulfameth-trimeth (Bactrim) – has been commonly used; safety profile is not known & is best avoided if possible – due to concern of overuse interfering with folic acid metabolism.
- 5. Chlamydia → Azith 1g x 1
- 6. Gonorrhea → cephalosporin, or if C/I, Azith 2g x1 (high dose can cause GI cramping)
- 7. Bact. Vaginosis → Clindamycin 300 mg BID or Metronidazole 500 mg BID or 250mg TID
 - a. *Topical vaginal* therapy for vaginosis is *not recom* during preg (high risk of uterine wall rupture)
- 8. Vaginal Trichomoniasis → Metronidazole 2 g x1 . txt may be deferred after 37 wks

Asthma in Pregnancy

1. Inhaled CS (*Budesonide* is the preferred CS) are 1st line controller therapy - budesonide respules are preferred for infants
2. Inhaled albuterol is the recom rescue therapy

Hypothyroidism → must test & treat with levothyroxine (Cat A) - *or else baby will dev. Neurologic brain damage*

Hyperthyroidism *most common in women of child bearing age* → both drugs are preg Cat D, but may still need to be used

1. Propylthiouracil (PTU) – use if trying to conceive or in 1st trimester , then switch to
2. Methimazole
3. Monitor for liver injury (PTU has BBW for liver tox.)

Venous Thromboembolism/Mech Valves

1. Heparin (UFH) or LMWH (*heparin when used long term wastes bones*)
2. No warfarin during preg (Cat. X)
3. The newer anticoagulants are Cat. C – not currently in the recommendations

Smoking – do not use tobacco during preg, it can cause

1. Spontaneous abortions
2. Low birth weight
3. Sudden infant death
4. If woman smokes <5 cigs/day → encourage to quit w/ behavioral support
5. If woman smokes >5 cigs/day → use bupropion (Cat. C)
 - a. All nicotine products are Cat D except for the gum (Cat. C)

[14] DRUG REFERENCES

INN : International Nonproprietary names for Pharmaceutical Substances

NDC : National Drug Code – the universal product identifier for human drugs

Drug References -L.M.F.A.P.D.-

1. Lexi-Comp
2. Micromedex
3. Facts & Comparisons
4. AHFS – Am Hosp. formulary service DI
5. Physician's Desk Reference (PDR)
6. Drug info handbook (Lacy's)

Drug Pricing

1. **The Red Book** – includes Average Wholesale Price (AWP) & suggested retail price
2. If a product is not listed in the Orange book, it does not have an approved appl (NDA/ANDA) ∴ not avail
3. If a product is not listed in the Red book, it may not be marketed at the present time, but may still be an approved drug with the FDA.

Specific Drug References

1. Reporting Adverse Drug Rxns → FDA's MedWatch prog.
 - For Vaccines = FDA's VAERS
2. Reporting Medical errors in Hosp. → P&T Comm, staff meetings, Medication Safety Comm.
3. Reporting Medical errors in any setting:
 - ISMP's Medication Error Rep. Prog (MERP)
 - FDA's MedWatch
 - MedMARx prog
4. IV Stability → Trissel's Stability if Compounded formulations, AHFS Drug info, Micromedex
5. Compounding & Manuf
 - Handbook of Extemporaneous Formulations
 - Inter. Journal of Pharmaceutical Compounding
 - Stab. Of Compounded Formulations
 - US Pharmacopoeia National Formulary
 - Allen's Compounded Formulations
 - Remington: Science & Practice of Pharmacy
6. Pediatric → Harriet Lane Handbook, Pediatric Dosage Handbook, AHFS Drug Info, Micromedex
7. Foreign Drug Identification
 - Martindales
 - European Drug index
 - USP Dict of USAN & Intern. names
 - Drugs Avail Abroad
 - Micromedex
 - Intern. Drug Directory
8. Natural Products → Natural Medicines: Comprehensive database, US pharmacopoeia, PDR for Herbal Meds, Complete German Commission E Monograph
9. Pharmacotherapy Decision making OTC → Handbook of Nonprescription Drugs (OTC)

Bioequivalence

1. **Orange Book** – can look up by active ingred, proprietary name, applicant holder, or applicant number
2. Published by the FDA. Avail at fda.gov/cder/ob
3. Ratings:
 - AA – products in conventional DF not presenting bioequiv problems
 - AB – meets bioequiv req. thru in vivo and/or in vitro testing ; this is the most common – drugs coded AB are therapeutically equiv and can be interchanged (brand to generic)
Ex: Cardizem SR and its generic is AB1 , Dilacor XR is AB2, Cardizem CD is AB3.
Products rated AB1 are bioequiv to each other, AB2 are equiv to each other, etc.
 - AN – solutions & powders for aerosolization
 - AO – injectable oil solutions
 - AP – injectable aqueous solu
 - AT – Topical product

10. Pharmacotherapy Decision making OTC & Rx

- Pharmacotherapy: A Pathophysiologic Approach (DiPiro)
- Applied Therapeutics: The clinical use of drugs (Koda-Kimble)
- Pharmacist's Letter
- Sanford Guide (For ID)
- Harrison's Principles of Internal Medicine
- Drugs of Choice from the Medical Letter
- Washington Manual of Medical Therapeutics
- The Merck Manual

11. Pharmacology/Pharmaceutics

- Goodman & Gilman
- Merck Index
- Remington: Science & Practice of Pharmacy
- Handbook of Pharmaceutical Excipients

12. Psychology →DSM-IV

13. Pregnancy & Lactation

- Brigg's Drugs in Preg & Lactation
- Micromedex
- Breastfeeding: A guide for the Medical Profession
- ACCP's Safety of Drugs in Preg & Lactation

14. Tablet-Capsule ID

- Facts & Comparisons
- USP Drug info
- Physician's Desk Reference (PDR)
- Ident-A-Drug
- Micromedex
- Mosby's

Key Guidelines:

1. Cholesterol →ATP3
2. HTN → JNC7, AHA
3. Diabetes → ADA, AACE
4. Antithrombotic therapy → CHEST

[15] DISPOSAL OF PRESCRIPTION DRUGS

1. The federal rx drug disposal guidelines recommend : mixing unwanted drugs (inclu . controlled subst) with unpalatable substances and placing them in a non-descriptive container & placing them in the trash – unless it states that the drug can be flushed down the toilet/sink
2. *Instruct pts to* : Do not flush rx drugs down the toilet/drain unless label instructs to do so
 - a. For drugs not labeled to be flushed, take advantage of community drug take-back programs or other programs such as house-hold hazardous waste collection events.
3. Pharmacy involvement in taking back unwanted drugs (this is ongoing, and not ‘take back days’ as described above:
 - a. In CA and many other states, pharmacies and other designated sites, have the ability to help pts dispose of unwanted rx drugs & OTC (but NOT controls – these must be returned to law enforcement)
 - b. Pharmacies can 1) use prepaid envelopes to return drugs to waste disposal facilities 2) establish a collection bin for ongoing collection at pharmacies
 - c. Drugs should NOT be received by staff upon collection, **Drugs collected should be separated from their containers by the pts**
 - d. Locking the “take back” container : should be 2 separated locks – 1 with pahramcy and other with licensed integrated waste hauler that picks up the “hazardous household waste”
 - e. Some pharmacies do not participate in the Take Back programs, but offer “TakeAway” mailers – only for Rx drugs & OTC, not controls.
4. In absence of Take Back programs or access to mailers → follow local guidelines for Home Hazardous Waste Collection
 - a. Keep med in original container, **scratch out pts name info**
 - b. **Place some water into the container** + add something nontoxic and unpalatable (kitty litter, charcoal, Comet, spices)
 - c. Seal with tape (if blister packs of meds, then **wrap in multiple layers with duct tape**)
 - d. Place in **packaging that does not show what’s inside** and place in trash.
5. **List of controlled substances that in order to prevent danger to ppl and pets, the FDA feels that they can be flushed down the toilet/sink** : Fentanyl, morphine, methylphenidate, meperidine, diazepam, hydromorphone, methadone, oxymorphone, oxycodone/APAP/ASA, sodium oxybate

Syringe Disposal

1. Drop box or Supervised collection sites : doctor’s offices, hosp, pharmacies, health depts, fire stations – check avail in area
2. Mail back programs
3. Syringe exchange programs (SEP) – exchange used needles for new needles . nasen.org
4. At home needle destruction devices – they sever, burn, or melt the needle. Plastic syringe can then be placed in trash if needle has been removed
5. Use needle-syringe safety tips: throw away entire needle/syringe assembly into the sharps container, **do not recap the needle, never compress/press down the contents of the container**

[16] INFECTIOUS DISEASE

Aminoglycosides (AMGs) – want a high peak

1. Interferes with bact. Protein synthesis by binding to 30S & 50S ribosomal subunits & interfering with the bact. cell membrane
2. Exhibits **concentration dependent kill** & **have post abx effect (PAE)** – continued suppression of bact growth when abx levels are below the MIC of the organism

Gentamicin Peak 5-10 Trough <2 Tobramycin Peak 5-10 Trough <2 Amikacin Peak 20-30 Trough <5	<ol style="list-style-type: none"> 1. Mainly active against Gram – (eg. <i>pseudomonas</i>) 2. Used for synergy in treating Gram + cocci (eg Staphylococcus/Enterococcus endocarditis) 3. Tobramycin comes in an inhaled form. (TOBI) used for CF 4. Amikacin – has broadest activity 5. Dose on IBW – use AdjBW if TBW>30% of IBW (morbidly obese) 	<ol style="list-style-type: none"> 1. BBW: neurotoxicity (vertigo, ataxia) & nephrotoxicity 2. S/E : Nephrotoxicity & ototoxicity - use with caution in elderly, impaired renal fxn, other nephrotox drugs (ampho B, NSAIDS, Vanc, dyes, cyclosporine, etc) 3. Monitoring: renal fxn, hearing tests, peak and trough if using traditional dosing, random level w/ extended interval dosing 4. Preg Cat D 5. May ↑ levels of neuromuscular blocking agents
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3. Dosing of AMGs

Traditional dosing	Gent/Tobra: 1-2 mg/kg/dose	CrCl >60	CrCl 40-60	CrCl 20-40	CrCl<20
	Amikacin: 5-7.5 mg/kg/dose	Q8H	Q12H	Q24H	LD, Monitor levels
	Take trough right before next dose, take peak 30 min after end of infusion <i>Δ dosing interval, not dose**</i>				
Extended Interval dosing	Gent/Tobra: 4-7 mg/kg	Draw random level 6-16 hrs post dose, determine freq			
	Amikacin: 15-20 mg/kg	based on Hartford nomogram			
	Extended dosing is less nephrotoxic, and more cost effective				

Penicillins (PCNs) **for exam, if pt has PCN allergy, do not use cephalo. due to cross reactivity even though it is small**

1. B lactams that **inhibit bact. Cell wall synthesis**
2. Exhibits time dependent kill

Amoxicillin (Amoxil, Moxatag) + clavulanate (Augmentin)	<ol style="list-style-type: none"> 1. Mainly active against Gram + cocci (staph, strep) Some Gram - bacilli No atypical 2. Amoxicillin – DOC in acute otitis media, H. pylori regimen, pregnancy, ppx for endocarditis (before dental proced.) 3. Agents combined w/ β lactamase inh. have broader spectrum of activity & popular in hosp for many infxn 4. Reduce dose in renal impairment <u>except</u> with: -N.O.D.C- nafcillin, oxacillin, dicloxacillin, cloxacillin 5. Can be used for empiric coverage when combined w/ β lactamase inh (sulbactam, clavulanate) 	<ul style="list-style-type: none"> • S/E: allergic rxn, rash, pruritus, GI upset, diarrhea, agranulocytosis, ↑ LFTs • Monitoring: renal fxn, anaphylaxis w. 1st dose Preg Cat B Test interactions: false + urinary glucose test and galactomamman test for aspergillosis • Augmentin oral susp: must be refrigerated • Amoxil oral susp: may be refrig to improve taste, but is table at RT for 14 days • Moxatag : take 1 hr after meal • Pen VK: take on empty stomach • Pen VK Susp: should be refrig after reconstitution • D/I: Uricosuric agents (probenecid, allopurinol) can ↑ levels of PCN by affecting renal excretion May ↓ effectiveness of some oral contracep
Ampicillin (Principen) Ampicillin + sulbactam (Unasyn)		
Penicillin (Pen VK)		
Piperacillin + tazobactam (Zosyn)		
Ticarcillin + clavulanic acid (Timentin)		

Cephalosporins

1. B lactams that **inhibit bact. Cell wall synthesis**
2. Exhibits **time dependent kill**

1st generation	Better G+ than G- activity	<ul style="list-style-type: none"> • S/E: allergic rxns (anaphylaxis), rash, GI upset, diarrhea, seizures w/ accum, colitis, ↑ LFTS • Monitoring: renal fxn, signs of anaphylaxis w/ 1st dose • Cross sensitivity (<10%) w. PCN allergy – do not use in pts with PCN allergy • Preg Cat B • <i>Reduce dose in renal impairment</i> <u>Except</u> cefoperazone, ceftriaxone • Cephalosporins w/ N-methylthiotetrazole (NMTT or 1-MTT) side chain → can lead to hypoprothrombinemia (bleeding, ↑INR) & a disulfiram like rxn with alcohol ingestion → cefamandole, cefmetazole, cefoperazone, cefotetan • Drug interactions: same as PCN • <i>ceftriaxone – only ceph that can be given once a day (in normal renal fxn pts)</i>
Cefazolin (Ancef, Kefzol)	250-2,000 mg Q8 (IV) <i>DOC when cutting thru skin (G+ on skin)</i>	
Cephalexin (Keflex)	250-500 mg Q6 (PO)	
2nd generation	Better G- than 1 st , similar G+ to 1 st	
Cefprozil (Cefzil)	250-500 mg Q12-24 (PO)	
Cefuroxime (Ceftin, Zinacef)	250-1,500 mg Q8 (PO/IV)	
3rd generation	Better G- than 2 nd gen less staph (G+), but better strep than 2 nd gen	
Cefdinir (Omnicef)	300 mg Q12 or 600 mg Q24 (PO)	
Cefixime (Suprax)	400 mg divided Q12-24 (PO)	
Cefpodoxime (Vantin)	200-400 Q12 (PO)	
Ceftazidime (Fortaz, Tazicef)	1-2g Q8-12 (IV) <i>Covers pseudomonas</i>	
Ceftriaxone (Rocephin)	1-2 g Q12-24 (IV/IM) <i>one time drug -commonly</i>	
4th generation	Best G- , G+ similar to 1 st gen	
Cefepime (Maxipime)	1-2 g Q8-12 (IV) <i>pseudomonas</i>	
5th generation	Best G+ , Covers <u>MRSA</u> , some G- similar to ceftriaxone	
Ceftaroline fosamil (Teflaro)	600 mg Q12 (IV)	

Carbapenems

1. B lactams that **inhibit bact. Cell wall synthesis**
2. Exhibits **time dependent kill**

Imipenem/Cilastatin (Primaxin)	250-1,000 mg Q6 (IV) <i>Cilastatin → combined w. imipenem to prevent degradation by renal dihydropeptidase -highest risk of seizures in this list</i>	<ul style="list-style-type: none"> • Active against most G+, G- and anaerobic pathogens No atypical coverage • S/E: diarrhea, rash, seizures with higher doses & pts w/ impaired renal fxn (esp imipenem) • Monitoring: renal fxn, anaphyx w. 1st dose • Preg B (except imipenem, C) • Do not use with PCN allergy (50% cross reactivity) • Drug interactions: Uricosuric agents (probenecid, allopurinol) can ↑ levels of PCN by affecting renal excretion • Carbapenems can ↓ concn of valproic acid (leading to loss of seizure control) • Avoid imipenem w/ ganciclovir → due to inc seizure risk
Meropenem (Merrem)	500-2,000 mg Q8 (IV/IM)	
Ertapenem (Invanz)	1 g QD (IV/IM) <i>Not active against pseudomonas or Acinetobacter</i>	
Doripenem (Doribax)	500 mg Q8 (IV) <i>All cover pseudomonas except ertapenem</i>	

Fluoroquinolones

1. Inhibits bact DNA topoisomerase IV and DNA gyrase (topo II) → this prevents supercoiling of DNA
2. Concentration dependent killing
3. Drug interactions
 - a. Cations that can chelate & inhibit FQ absorption → Antacids, didanosine, sucralfate, bile acid resins, Mg, Al, Ca, Fe, Zn, MVI → separate FQ by 2 hrs BEFORE and 4-6 hrs AFTER (proquin XR is 4 hrs before or 2 hrs after)
 - b. Can ↑ warfarin, sulfonyleureas, & QT prolongation drugs (moxi prolongs QTc the most)
 - c. ↑ FQ levels: NSAIDS, probenecid

Ciprofloxacin (Cipro, XR, Proquin XR, Ciloxan oph, Cetraxal, Ciprodex Otic) <i>-potent 1A2 inh, wk 3A4</i>	Ciprofloxacin dosing: <i>cipro/levo is 2nd line for UTI – Bactrim is 1st</i> 250-750 mg PO or 200-400 mg IV CrCL > 50 : Q8-12 CrCl 30-50 : Q12 CrCl < 30 : Q18-24	<ul style="list-style-type: none"> • Extensive G+, G- • Avg to excellent atypical coverage (levo, moxi, gemifloxacin – excellent) • BBW: Tendon inflamm &/or rupture (↑ risk w. concurrent steroids, txp pts, pts >60 yo) • S/E: photosensitivity, hypo (mostly) and hyperglycemia, arthropathy in children, crystalluria, potential for seizures, QT prolongation • Preg Cat C • <i>Cipro oral susp</i> – should not be given via NG tube/feeding tubes- separate by 1hb, 2ha • <i>Proquin XR</i> – should be given with biggest meal • CAN be used for PCN allergic pts
Levofloxacin (Levaquin, Iquix & Quixin oph)	Levofloxacin dosing: CrCL > 50 : 500 mg QD CrCl 20-49 : 500 mg, then 250mg QD CrCl < 20 : 500 mg then 250mg Q48 Moxifloxacin: 400 mg Q24 (IV/PO) Dose adjust in renal impair. <u>except</u> for moxi	
Moxifloxacin (Avelox, Vigamox oph)		
Ofloxacin (Floxin)		
Norfloxacin (Noroxin)		
Gatifloxacin (Zymar oph)		
Gemifloxacin (Factive)		

Macrolides

1. Binds to the 50S ribosomal unit → inhibiting RNA dependent protein syn.
2. Erythromycin & clarithromycin are major 3A4 inhibitors, azith is minor 3A4 inhibitor
 - a. Do not use eryth and clarith w/ agents that prolong QT interval

Azithromycin (Zithromax, Z-pak, Zmax, Azasite oph)	<div> <div> <div>□□</div> <div>□□□□</div> </div> 250 mg x2 Day 1 250mg x1 days 2,3,4,5 -or- 500mg QD x 3 days -or- Gonorrhea 2g x1 <i>Do not refrig azithromycin oral susp (Zmax)</i> better G- compared to erythromycin </div>	<ul style="list-style-type: none"> • Active against G+, some G-, good atypical • S/E: Gi upset (diar, abd pain/cramping esp with erythro) liver dysfxn, QT prolongation • Preg Cat B / C (C=clarithromycin)
Clarithromycin (Biaxin, Biaxin XL)	250-500 mg BID or 1g QD <i>Take Biaxin XL w/ food. Do not refrig Biaxin oral susp</i>	<ul style="list-style-type: none"> • CAN be used in PCN allergic pts • Azith – use w. caution in CrCL <10
Erythromycin (E.E.S., Ery-tab)	EES 400 mg QID Erythromycin base/stearate: 250-500 mg PO QID <i>Must refrig erythromycin ethylsuccinate (EES) oral granule susp</i> <i>Erythromycin powder susp – stable at RT x 14 d</i>	<ul style="list-style-type: none"> • ER susp (Zmax) is not bioequiv w. Zithromax • Er susp (Zmax) must be consumed within 12 hrs after reconstitution on empty stomach • <i>Azasite oph</i> – viscous solution, store at RT (cold makes it more viscous)

Tetracyclines

1. Binds to 30S ribosome → inh bact protein synthesis
2. Tetracycline abs ↓ by: antacids containing (Mg, Al, Ca), divalent cations (Fe, sucalfate, bile acid resins, bismuth subsalicylate) → take 1-2 hrs before or 4 hrs after
3. May ↑ INR with warfarin
4. Can ↓ effectiveness of oral contracep.
5. Many anticonvulsants ↓ tetracycline levels. Avoid use with retinoic acid (pseudotumor cerebri)

Doxycycline (Vibramycin, Vibra-tab, Oracea, Doryx, etc)	100 mg Q12 Take Oracea on an empty stomach (1 b/ 2a meal) Take other forms w. food to ↓ GI irritation	<ul style="list-style-type: none"> • Active against: Atypicals, spirochetes, rickettsial diseases, anthrax, syphilis, acne (<i>doxy/mino</i>) • S/E: GI upset, photosensitivity, tooth discoloration (up to age 14), colitis, exfoliative dermatitis, rash • Contraindications: Children <8 yo, pregnancy (Cat D - <i>retards bone growth</i> and skeletal dev) • Take w/ 8 oz water to minimize GI upset. Remain upright for 30 mins • Do not adjust dose of doxycycline in renal impairment
Minocycline (Minocin, Dynacin, Solodyn)	50-100mg Q12-24	
Tetracycline (Sumycin)	250-500 mg Q6	

Sulfonamides

1. Sulfamethoxazole – interferes w/ bact. Folic acid synthesis via inhibition of dihydrofolic acid formation from PABA
2. Trimethoprim – inhibits dihydrofolic acid reduction to tetrahydrofolate → resulting in inhibition of enzymes of folic acid pathway
3. **Use with caution w/ warfarin** (sulfonamides are moderate 2C8/9 inhibitors). Sulfonamide levels may be ↓ in 2C8/9 inducers
4. May ↑ levels of sulfonylureas, phenytoin, dofetilide, azathioprine, MTX
5. Therapeutic effects may be diminished by leucovorin/levoleucovorin

Sulfamethoxazole-trimethoprim (Bactrim, Septra, others) SS = 400 mg SMZ/80 mg TMP DS = 800 mg SMZ/160 mg TMP <i>Always a 5:1 ratio</i>	Adult UTI: 1 DS tab BID x 3 days Adult bronchitis: 1 DS tab x 14 days PCP ppx : 1 DS or SS tab QD Children UTI/AOM: 40 mg/kg SMZ + 8 mg/kg TMP divided BID x 10 days <i>Based on trimethoprim cmpnt</i>	<ul style="list-style-type: none"> • Activity against G+ , some G – • No atypical or anaerobes • S/E: GI upset (n/v/d), skin rxns (mild -rash, urticarial, severe-SJS, TENS), crystalluria (take w/ 8 oz water) , photosensitivity • Contraind: Sulfa allergy, Pregnancy (at term), anemia due to folate deficiency, marked renal/hepatic disease • Preg C/D (at term) • Bactrim IV: store at RT, short stability (~6hrs), dilute w/ D5W. Protect from light • Bactrim susp : store at RT, protect from light
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Other Agents (only listed are the drugs bolded in book)

[Gram + Agents]

1. Vancomycin (Vancocin) – time dependent kill

- PO is used to treat *C. difficile* (not IV) 125-500 mg QID for severe *C. difficile*/recurrent infxns
- DOC MRSA infections: 15 mg/kg Q8-12 IV
- Infuse IV at concn < 5mg/mL
- S/E: nephrotox, ototoxicity, RMS (maculopapular rash from too rapid of an infusion), hypoten, flushing
 - Infuse slowly @ 30 min / 500 mg of drug
- Monitor: Renal fxn and trough
 - Trough: 15-20 mcg/mL → pneumonia, endocarditis, osteomyelitis, meningitis, bacteremia
 - Trough: 10-15 mcg/mL → other infxn
 - Consider alternative agent if MIC of org ≥ 2 mcg/mL
- ↑ toxicity with other nephron & ototox. Drugs (AMGs, amphotericin)

2. Linezolid (Zyvox)

- 400-600 mg Q12 PO/IV
- Treats G+, MRSA, VRE faecium & faecalis
- S/E: Myelosuppression (duration related, >14 d), Headache, diarrhea, ↑ pancreatic enzymes
- Weak MAO inhibitor- avoid tyramine containing foods (wine, fermented food), serotonergic (TCAs, SSRI, MAOI) & adrenergic drugs (hypertensive crisis – caffeine, tryptophan, phenylalanine)
- do not dose adj in renal impairment

[Broad Spectrum agents]

6. Telithromycin (Ketek)

- Activity against G+, G-, some anaerobes & atypicals
- BBW : do not use in myasthenia gravis , causes resp failure
- can cause QT prolongation, acute hep. failure
- Contraindications: allergy to macrolides
- Monitoring: visual acuity
- Potent 3A4 inh (↑ levels of azoles, CCB, digoxin, SAL, CSA, warfarin)

3. Quinupristin & dalfopristin (Synercid)

- Treats MRSA, VRE faecium (not faecalis)
- S/E: hyperbilirubinemia, phlebitis, inflammation, edema & pain at infusion site, arthralgias, myalgias
- Do not dose adj in renal impairment
- Give w/ D5W only in ≥ 250 mL

4. Daptomycin (Cubicin)

- Treats MRSA, VRE faecium & faecalis
- Monitoring: CPK levels Qweek
 - Additive risk of rhabdo when used with statins
- DO NOT use to treat pneumonias – it is inactivated by surfactant
- Compatible w. NS (not D5W)

5. Aztreonam (Azactam IV, Cayston – inhaled for CF)

- Covers pseudomonas & many other G- → alt G- coverage when aminoglycosides can't be used
- S/E: rash/diarrhea/n/v
- Used in PCN allergic pts (not cross reactivity)

7. Tigecycline (Tygacil) – deriv of minocycline

- Activity against G+ including MRSA, VRE f,f, G-, anaerobes, atypicals
- No activity against pseudomona, proteus, providencia
- S/E: not to be used in children ≤ 8 , Preg Cat D
 - FDA alert: risk of death when used to treat serious infxn (VAP)
- May ↑ INR if on warfarin (non- CYP inter.)
- No dosage adj needed for renal impairment

[Other agents]

8. Clindamycin (Cleocin)
 - a. 150-450mg PO 3-4x/day , 600-900 mg IV Q8
 - b. G+(not enterococcus) & anaerobes
 - c. BBW: can cause severe fatal **colitis** (*C.diff stool smells horrible, bad cramping, febrile, weak*)
 - d. S/E: n/v/d/r, abx assoc diarrhea including pseudomembranous colitis
 - e. Do not dose adj in renal impairment
9. Metronidazole (Flagyl, Metrogel topical)
 - a. 250-500 mg Q6-8 (IV/PO) ; Use 500 mg TID x 10-14d for **C. diff** (mild-mod infxn)
 - b. Activity against anaerobes & protozoal infxn
 - c. DOC for bact vaginosis, trichomoniasis, giardiasis, amoebiasis, pseudomembranous colitis (C.diff)
 - d. S/E: metallic taste, furry tongue, darkened urine, disulfiram like rxn w. alcohol (no ethanol for 24-48 hrs post last dose), periph neuropathy
 - e. IR can be taken w/o regard to food; take ER on empty stomach
 - f. Preg Cat B (C in 1st trimester)
 - g. No dose adj needed for renal impairment, adj when CrCL <10
10. Rifaximin (Xifaxan) – deriv of rifampin
 - a. DOC for **traveler's diarrhea** caused by non-invasive **E.coli**
 - b. Also used to treat hepatic encephalopathy
11. Fosfomycin (Monurol) - 3 g in 3-4 oz water x 1
 - a. Single dose to treat uncomplicated UTI due to E.coli and E.faecalis
12. Nitrofurantoin (Macrochantin, MacroBID)
 - a. **Macrochantin : 50-100 mg PO QID** **MicroBID : 100 mg PO BID**
 - b. Used for UTI due to E.coli, S. aureus, Enterococcus, Klebsiella & Enterobacter
 - c. C/I : renal impairment (CrCl <60), pregnancy at term
 - d. Can cause pulm toxicity long term
 - e. Preg Cat B (D at term)
 - f. Take w/ food to enhance absorption

Organism classification:

1. Gram + mainly are the following: Staphylococcus, Streptococcus, Enterococcus, Clostridium, Listeria
2. Gram – mainly are: Neisseria, Acinetobacter, Moraxella, Enterobacter, Escherichia coli, Haemophilus influenza, Helicobacter pylori, Klebsiella pneumoniae, Legionella pneumophila, proteus mirabilis, pseudomonas aeruginosa, salmonella
 - ❖ Gram(+) organisms →stain purple/bluish
 - Gram (-) organisms →stain pink/reddish
3. Atypicals : Chlamydia, Mycoplasma
4. Spirochetes : Borrelia, Leptospira

Perioperative ABX PPX

1. Txt usually begins **within 1 hr** before incision & continues for **no more than 24 hrs** after surgery (48 hrs for post cardiac surgery)
2. In general, 1st or 2nd gen cep are DOC → **cefazolin**, **cefuroxime** -or- vancomycin
3. In PCN allergic pts → **vancomycin** (given within 2 hrs before incision) -or- clindamycin
4. Surgeries that involve the **bowel** or put pt at risk for **anaerobic** infxn → **cefotetan** -or- cefoxitan, amp/sulbacta, ertapenem

SKIN AND SOFT TISSUE INFXN (SSTIS)

❖ Empiric therapy for purulent cellulitis

Outpatient – duration of therapy = 5-10 d

Primary txt for cutaneous abscess is I & D

[If non purulent, use β lactam (e.g. cephalexin)]

1. Clindamycin 300-450 mg TID
2. TMP-SMX 1-2 DS BID
3. Doxycycline 100mg BID
4. Minocycline 200 mg x1, then 100 mg BID
5. Linezolid 600 mg BID

❖ Empiric therapy for complicated SSTIs (pending cx)

Inpatient SSTI- duration of therapy 7-14 days

1. Vancomycin IV
2. Linezolid 600 mg IV/PO BID
3. Daptomycin 4 mg/kg/dose QD
4. Televancin 10 mg/kg/dose QD
5. Clindamycin 600 mg IV/PO TID

UTI

- ♦ s/s of lower UTI (cystitis) = dysuria, urgency, burning, nocturia, suprapubic heaviness, hematuria (fever uncommon)
- ♦ s/s of upper UTI (pyelo) = flank pain, abd pain, fever, n/v, malaise, costovertebral angle pain

❖ Acute uncomplicated cystitis in females

- a) Pathogens: E.coli, S. saprophyticus, Enterococcus
- b) DOC: **SMX/TMP DS BID x 3 days** (if <20% local e.coli resistance and no allergy to sulfa)
If not, then use:
 1. Cipro 250 mg BID x 3d (cipro dose is not high bc it concn in urine)
 2. Cipro ER 500 mg QD x 3d
 3. levofloxacin 250 mg QD x 3d
 4. nitrofurantoin 100 mg BID x 5 days
 5. fosfomycin x 1 (3 g in 4 oz water)
 - ♦ **treat Preg women x 7 days** (avoid quinones and TCNs. SMX/TMP can cause hyperbili and kernicterus in 3rd trimester (Cat D, otherwise C))
- c) may add phenazopyridine 200 mg TID x 2 days to relieve symptoms
- d) PPX: ≥ 3 epi/yr \rightarrow SMP/TMP SS QD, macrodantin 50 mg QD, or SMP/TMP DS QD post coitus
- e) Do not recom moxifloxacin – does not reach high levels in urine -or- gemifloxacin (poor activity)

❖ Acute uncomplicated pyelonephritis – need urinalysis, urine and blood cx

- a) Pathogens: E.coli, Enterococci, P. mirabilis, K. pneumoniae, P. aeruginosa
- b) Moderately ill: Outpatient txt (PO)
 1. **Cipro** 500 mg BID
 2. Cipro ER 1000 mg QD
 3. Levofloxacin 750 mg QD
 4. Ofloxacin 400 mg BID
 5. FQ resistance \rightarrow amox/clav, cefdinir, cefaclor, cefpodoxime
- c) Severe – hospitalized (IV)
 1. FQ
 2. AMP + Gent
 3. Pip/tazo
 4. Ceftriaxone x 10-14 days

❖ Complicated UTI – may be due to obstruction, catheterization - need urinalysis, urine and blood cx

- a) Pathogens: E.coli, Klebsiella, Enterobacter, Serratia, Pseudomonas, Enterococcus, Staph
- b) Treat for 7 days if prompt symptom relief, 10-14 if delayed
 1. AMP + Gent
 2. Pip/tazo
 3. Ticar/clav
 4. Ceftriaxone/Cefotaxime +/- FQ
 5. If ESBL producers are present \rightarrow Dori, imi, or meropenem x 2 wks

Phenazopyridine (Azo, Uristat, Puridium) – an azo dye and urinary analgesic

- ♦ Dose = 200 mg TID (Rx), 100 mg TID (OTC)
- ♦ **Take w/ food to minimize stomach upset**
- ♦ **Do not use for > 2 days** bc it may mask worsening sympt
- ♦ **May cause red/orange coloring of urine** & other bodily fluids (contacts and clothes can be stained)
- ♦ CrCl <50 : avoid use

TRAVELER'S DIARRHEA

1. **Prevention is not routinely recom**
Pts may choose to ppx with bismuth subsalicylate (BSS, Pepto-Bismol) – see Diarrhea section
2. Txt: **abx + loperamide** (Imodium – it freezes the gut)
 - a. Do not use loperamide if pt has fever/blood in the stool – 4 mg x1, then 2 mg after each loose stool (Max 16 mg/d)
 - b. Abx = cipro, TMP/SMX, Ofloxacin, Levofloxacin, Metronidazole, Azith 1 g (DOC for preg & children)
3. Etiologies: E.coli, shigella, salmonella, campylobacter
 - a. If diarrhea persists for >7 days, consider parasites as a cause (Giardia, cryptosporidium)

BRONCHITIS (PG 203)

most always self limiting & 50% of cases are viral → **if viral, abx not indicated**, recom antitussive + inhaled bronchodilators (dextromethorphan, codeine or ibuprofen)

COMMUNITY ACQUIRE PNEUMONIA (CAP)

❖ Outpatient txt:

1. **Macrolide** (azith, clarith, erythromycin)
 2. **Doxycycline**
If >65, comorbidities (HF, DM, cancer, organ dysfxn, use of abx in 3 mths)
1. Resp FQ (moxi, gemi, levofloxacin)
 2. Beta lactam (amox, amox/clav, cefpodoxime, cefuroxime) + macrolide (azith, clarith, erythromycin)

❖ Inpatient (non-ICU)

1. Resp FQ (gemi, moxi, levofloxacin)
2. Beta lactam (amox, amox/clav, cefpodoxime, cefuroxime) + macrolide (azith, clarith, erythromycin)

❖ Inpatient (ICU)

1. Beta lactam (ceftriaxone, cefotaxime, amp/sulbactam) + azith or FQ (levo/moxifloxacin)
2. If CAMRSA is a consideration, add vancomycin or linezolid

CLOSTIDIUM DIFFICILE ASSOC DIARRHEA

1. **Mild-Moderate infxn**: Metronidazole 500 mg TID x 10-14 days (do not use after treating a 2nd episode due to neurotox)
2. **Severe infxn**: Vanc 125 mg QID x 10-14 d
3. **Severe, complicated infxn**: Vanc 500 mg QID ± Metronidazole 500 mg TID
 - a. Consider fidaxomicin instead of vanc for pts at high risk or recurrence (Chemotherapy or IS pts) – *equally efficacious as vanc w/ less recurrence*
4. For 3rd recurrence, use vanc taper therapy
5. Avoid antimotility agents due to risk of toxic megacolon
6. Wash hands w/ soap and water. Alcohol sanitizers do not kill C. diff spores

HOSP. ACQUIRE PNEUMONIA (HAP)

1. Primary regimens:

- a. Pip/tazo 4.5 g Q6
- b. Ceftriaxone 1-2g QD
- c. Amp/sulbactam 3 g Q6
- d. Ertapenem 1 g QD
- e. If suspect Legionella or bioterrorism, add/replace w/ Resp FQ (Levo or Moxifloxacin)

2. If suspect pseudomonas aeruginosa, start 2 anti-pseudomonal drugs

- a. Anti-pseudomonal Beta lactam + Anti-pseudomonal FQ (cipro/levofloxacin)
- b. Aminoglycoside (e.g. tobramycin)

Some Pseudomonas B lactams:

1. Carbapenems, except ertapenem
2. Cephalosporin – cefepime/ceftazidime
3. FQ – ciprofloxacin, levofloxacin
4. AMG – amikacin, tobramycin, gentamicin

SEXUALLY TRANSMITTED DISEASES (only listed underlined items). All sexual partners must also be treated concurrently to prevent reinfection

1. **Syphilis :**

- a. Early (1°, 2°, latent <1 yr duration) – DOC Penicillin G benzathine (Bicillin LA) 2.4 MU IM x1
- b. Late (>1 yr, CV, gummas, late-latent, unknown duration) – DOC Penicillin G benzathine 2.4 MU IM weekly x3

2. **Gonorrhea**

- a. Ceftriaxone 250 IM x1, Cefixime 400 mg PO x1, -or- Cefpodoxime 400 mg PO x1
- b. Should also treat pts for chlamydia infxn if not ruled out→
(azithromycin 2 g PO x1 for both gonorrhea and chlamydia - but poorly tolerated GI s/e)

3. **Chlamydia**

- a. DOC azithromycin 1g PO x1

4. **Bacterial vaginosis**

- a. DOC Metronidazole (500 BID x 7d), clindamycin 2% cream (5g intravag QHS x 7 d), Metronidazole 0.75% gel (5 g intravag x 5 d)
- b. Altern: Tinidazole 2g PO QD x 2 or 2 g PO QD x 5d

HERPES SIMPLEX VIRUS

1. Acyclovir (Zovirax) is usually the cheapest regimen. Valacyclovir (Valtrex) is the prodrug of acyclovir and results in higher concn.
2. Famciclovir (Famvir) is a prodrug of penciclovir. Strains resistant to acyclovir are generally also to famciclovir
- dose adjust these agents in renal impairment.
3. Primary txt (initial episode)
 - a. **Acyclovir (Zovirax)** 400 mg TID x 7-10 days
 - b. **Valacyclovir (Valtrex)** 1g BID x 7-10 days
4. Recurrent episodes
 - a. Acyclovir (Zovirax) 800 mg TID x 2d or BID x 5days
 - b. Valacyclovir (Valtrex) 500 mg BID x 3 d or 1 g QD x 5 days
5. Chronic suppression
 - a. Acyclovir 400 mg **BID** or valacyclovir 500-1000 mg **QD**
6. S/E : acyclovir (**Ha**, n/v/d) valacyclovir (**Ha**, GI upset, ↑ LFTs, neutropenia) [both = thrombotic thrombocytopenic purpura and hemolytic uremic syndrome (TTP/HUS, renal failure – rare)]

TUBERCULOSIS

1. Transmitted by aerosolized droplets (sneezing, coughing, talking) & is *highly contagious*
2. **DX by:** tuberculin skin test (TST, PPD), look for induration within 48-72 hrs. Can also do sputum smear, culture, PCP for AFB
3. **Latent TB:** INH 300 mg QD x 9 mths (or 15 mg/kg 2x/wk) -or- Rifampin 600 mg QD x 4 mths
4. **Active TB:** **RIPE**, rifampin + isoniazid + pyrazinamide + ethambutol
 - a. Pts with active TB should be isolated, single negative pressure rooms! Essential.
5. **Recom to add pyridoxine (Vit B6)** 25-50 mg QD to INH regimen to ↓ risk of neuropathy
6. **Use directly observed therapy (DOT) regimen if possible.** DOT regimens are dosed 2-3 x/wk instead of daily
All top 4 drugs are hepatotoxic – except ethambutol (visual problems)
7. **Classic presentation:** productive cough w/ blood, fatigue, night sweats, poor appetite.

Lupus-like syndrome (s/s:
butterfly rash, achy joints,
fatigue)

1. Methyldopa
2. Hydralazine
3. INH

Rifampin (Rifadin)	Take 1 hr before or 2 hr after meal on an empty stomach Potent inducer of 1A2, 2C9, 2C19, 3A4	S/E: flu like syndrome, rash, pruritus, hepatotox, ↑ uric acid , orange-red discoloration of body secretions (contacts lens)
Isoniazid (INH)	Take 1 hr before or 2 hr after meal on an empty stomach Major 3A4 & 2C19, mod 2D6 inhibitor	BBW: severe hepatitis may occur S/E: ↑ LFTs , hepatitis, periph neuropathy , lupus-like syndrome ↑ intake of folic acid, niacin, Mg . Take with Vit B6
Pyrazinamide	Can ↑ rifampin , ↓ CSA . Can cause fatal hepatotox w/ rifampin	S/E: hepatotox , nausea , hyperuricemia Contraindications: Acute gout
Ethambutol (Myambutol)	Take w/o regards to meals	S/E: optic neuritis , ↓ visual acuity Monitoring: vision tests

ACUTE OTITIS MEDIA (AOM)

- Signs of infxn: rapid onset, middle ear effusion, fever, tugging/rubbing ears, crying
- Many infxns are viral (abx will not work)
- Observation (48-72 hrs) w/o abx is an option (depending on age/severity)
 - Children <6 mths → give abx – even w/ uncertain diagnosis
 - Children 6 mths-2 yrs → give abx if severe illness, otherwise observe
 - Children ≥2 yrs → abx if severe illness, otherwise observe
- Treat pain w/: APAP or ibuprofen. >5 yo can use topical benzocaine (Auralgan, Americaine Otic)
- 1° txt - HD Amoxicillin – HD will cover most S. pneumoniae and is safe & cheap
- More severe cases/amox does not work – amox/clav (Augmentin) , or can use cefindir, cefpodoxime, cefprozil, cefuroxime
- Pts w/ anaphylaxis w/ PCN – azithromycin, clarithromycin, erythromycin-sulfisoxazole, TPM/SMX, clindamycin
- <2 yo or severe disease = 10 days
≥2 w/ mild-mod disease = 5-7 days
- Vaccines:
 - Prevnar 13** (pneumococcal conjugate vaccine – 13 serotypes) – *given to children 2-23 mths*
4 doses of PCV13 IM at 2,4,5,12-15 mths.
 - Pneumovax** (the adult polyvalent vaccine-23 serotypes) – *not a conj vaccine so babies don't/can't recog it*
Recom for children >2 yo who are at risk for pneumococcal disease (sickle cell hemo., HIV, other Immunocom, chronic med condit) & those >65 yo

Amoxicillin (Amoxil)	90 mg/kg/day in 2 div doses
Amox/Clav (Augmentin) <i>14:1 ratio</i>	90 mg/kg/day amox cmpnt, 6.4 mg/kg/day clav in 2 divided doses Augmentin ES 600 is a powder. Each 5 ml = 600 amox, 42.9 clav
Azithromycin (Zithromax)	10 mg/kg/day on D1, 5 mg/kg/day on D2-5
Ceftriaxone (Rocephin)	50 mg/kg IM/IV x 3 days (amx 1g/day) - for those who cannot tolerate PO meds (vomiting)

INFECTIVE ENDOCARDITIS

1. TXT :
 - a. MSSA – Nafcillin or oxacillin 2 g IV Q4 x 6 wks +/- Gentamicin 1 mg/kg x 3-5 days (PCN allergy/MRSA → Vanc ± Gent)
 - b. Gentamicin is used for synergy
 - c. Other orgs – Pen G + Gent, or Ampicillin, Vanc if resistant to Pen G, Linezolid if resistant to prev abx (see pg 215)
2. PPX: needed for cardiac conditions before dental procedure (native valve, CHD, prev IE, heart txp)
 - a. Give single dose 30-60 mins before procedure
 - b. Amoxicillin 2 g ; PCN allergy → Clindamycin 600 mg or Azith or Clarithromycin 500 mg

MENINGITIS

1. Classic s/s : Fever, Nuchal rigidity, Altered mental status
 - a. In children, may also see bulging fontanelles
2. Lumbar puncture is mandatory for all suspected bact. Meng
3. Most likely orgs: S. pneumonia, N. meningitidis, H. influenza, L. monocytogenes
4. Abx dosages must be maximized to optimize penetration into CNS
 - a. Cefotaxime, ceftriaxone, meropenem (all 2 g) + Dexamethasone + Vancomycin
 - b. For severe PCN allergy – Chloramphenicol + Vancomycin +/- SMX/TMP

RICKETTSIAL DISEASES

1. Carried by many ticks, fleas, lice
2. Rocky mnt spotted fever, lyme disease, typhus, ehrlichiosis, tularemia
3. Txt: Doxycycline 100 mg PO BID (txt days differ for each disease, usually 7-14 days)
4. for tularemia – DOC is gentamicin or tobramycin 5 mg/kg/day DIV Q8

Systemic Fungal Infections

- ♦ Some fungal orgs: Aspergillus spp, Blastomycosis spp, Candida spp, Cryptococcosis spp, Coccidioidomycosis spp, Histoplasmosis spp, etc
- ♦ Candida infxn are generally treated with fluconazole. (C. krusei is resistant, C. glabrata needs higher doses)

Amphotericin B

Amphotericin B desoxycholate (conventional) - (Amphocin)	HypoK+, hypoMg++, nephrotoxicity
Lipid formulations <ul style="list-style-type: none">• Amphotericin B Lipid complex (Abelcet)• Liposomal ampho B (AmBisome)• Ampho B cholesteryl sulfate complex (Amphotec)	<ul style="list-style-type: none">• Ampho B desoxy – most nephrotoxic• amBisome – can cause back/chest pain w/ 1st dose• infusion related rxns = amphotec > Ampho B desoxy > Abelcet > AmBisome• <u>Premedicate for infusion related rxns (fever, chills, hypotns, nausea) :</u> Give 30 – 60 mins prior to infusion:<ul style="list-style-type: none">○ APAP / NSAID○ Diphenhydramine 25 mg IV +/- hydrocortisone○ Meperidine IV <i>for reducing the duration of rigors</i>○ Saline boluses <i>to reduce the nephrotoxicity</i>

Azoles – ↓ergosterol synthesis & inhibit cell membrane formation

- ❖ All Azoles are 3A4 inhibitors
- ❖ Itraconazole & Ketoconazole – have pH dependent abs (↑ pH ↓ absorption) avoid using w/ antacids, H2RA, PPIs
- ❖ Voriconazole – DOC for Aspergillus infxn & visual changes ; concn can inc dangerously due to 1st order followed by MM
Concurrent use or vori w/ 3A4 subs is contraindic: cisapride, carbamazepine, barbs, ergot derivs, rifampin, St. John's wort, ritonavir.

<p>Itraconazole (Sporanox) – <i>do not use in HF (BBW)</i></p> <p>Fluconazole (Diflucan) 100-400 mg QD PO/IV 1:1</p> <p>Ketoconazole (Nizoral, Kuric, Xolegel)</p>	<p>S/E : n/v/d/abd pain, ↑ LFTs</p> <p>Itraconazole : oral capsules & oral solution are NOT interchangeable (diff BA)</p> <ul style="list-style-type: none"> ❖ Capsule – take w. food (low BA) & req. gastric acidity for absorption ❖ Solution – take on empty stomach (high BA) <p>Ketoconazole shampoo - ↑ hair & altered hair texture</p>
<p>Voriconazole (VFEND) ☀</p> <p>♦ More active against Aspergillus, C. glabrata, C. krusei, Fusarium vs. itraconazole/fluconazole</p>	<p>❖ Take 1 hr before or 1 hr after meals (empty stomach)</p> <p>S/E: visual changes, photosensitivity; Correct Ca, Mg, K prior to initiating therapy</p> <p>C/I: 3A4 substrates</p> <p>Monitoring: LFTs, electrolytes, visual fxn (Caution while driving at night, avoid direct sunlight) – <i>PDEi is another drug where we counsel on not driving at night</i></p>
<p>Posaconazole (Noxafil) 🌐</p>	<p>Must be taken with full meal</p> <p>S/E: ↑LFTs</p>

Echinocandins – inhibit synthesis of β(1,3)-D-glucan, an essential cmpnt of the fungal cell wall

<p>Caspofungin (Cancidas)</p>	<p>S/E: ↑ LFTs (caution use w/ CSA & in hepatic impairment), hypokalemia, ↓ h/h</p>
<p>Micafungin (Mycamine) Candidemia : 100 mg IV QD Esophageal candidiasis : 150 mg IV QD over 60 mins</p>	<p>S/E : ↑ LFTs, bone marrow suppression, hypokalemia</p> <p>can cause histamine-mediated symp(rash, pruritis, facial swelling, flushing, and hypotension) To decrease the potential→ infuse over 1 hour.</p>
<p>Anidulafungin (Eraxis) Candidemia : 200 mg IV D1, then 100 mg IV Esophageal candidiasis : 100 mg D1, then 50 mg QD</p>	<p>S/E : ↑ LFTs, hypokalemia</p> <p>❖ All 3 agents are given QD and do not req dose adj in renal impairment. Little DI</p>





TXT GL FOR VARIOUS FUNGAL INFXN

- Aspergillus spp – invasive pulmonary disease
 - Voriconazole** 6 mg/kg IV Q12 on day 1, then 4 mg/kg BID
- Candida albicans – blood stream infxn
 - Fluconazole, caspofungin, micafungin **x 2 weeks after last positive blood cx**
- Oral candidiasis – thrush
 - Non-aids : clotrimazole troches, nystatin susp, fluconazole
 - Aids pts: fluconazole, itra, posaconazole, echinocandins or amph B **x 7-14 days**
- Esophageal candidiasis
 - Azoles, echinocandins, amphotericin B **x 14-21 days**

VAGINAL CANDIDA INFXNS

1. **Candida albicans**
2. **Predisposing factors:** broad spec abx, oral contraceptives (high estrogen), poorly controlled db, pregnancy, chronic steroid use, HIV
 - a. **See if pt has DM or HIV**, an infxn could mean the disease is uncontrolled
3. **s/s: intense pruritus, thick, curd-like vaginal discharge**
4. **Do not recom self-txt until after a 1st infxn has been dx by PCP**
5. **TXT:**
 - a. **topical azole – typically used and do not cause systemic s/e.** they are all equally effective & have >80% cure rate (except nystatin which is less effective)
(butoconazole, clotrimazole, miconazole, nystatin tablets, terconazole, fluconazole (Diflucan) 150 mg x1
Fluconazole is OTC in Canada, but not in US
 - b. **only topical azole therapies, applied for 7 days are recom in preg women.**
 - c. **Severe infxn / pregnancy : 7 day regimen**
 - d. **Recurrent infxn (>4 ep/yr) : 7-14 day regimen**
6. **Counseling: creams and supp are oil based ∴ can weaken latex condoms ; if you get your menstrual cycle during txt, cont. txt.**

Counseling Points

1. **Acyclovir (Zovirax) – Antiviral**
 - a. **Cream: s.e include dry/cracked lips, burning, stinging, or flaky skin may occur.**
2. **Amoxicillin products** 
 - a. **Take w/ meal or snack**
 - b. **All beta lactams can cause a rash. If rash looks severe, pt should be seen right away**
 - c. **Suspension should be refrig (esp. augmentin)**
3. **Azithromycin (Zithromax)**
 - a. **Tablets and IR oral susp +/- Food**
 - b. **ER susp – take on empty stomach (1hb, 2ha)**
4. **Clarithromycin (Biaxin)**
 - a. **Common s/e: d/n/abd pain, abnormal metallic taste**
 - b. **Tablet & oral susp +/- Food . Can be taken with milk**
 - c. **Biaxin XL**  **– take with food**
 - d. **Liquid susp – not refrig.**
5. **Clindamycin (Cleocin)** 
 - a. **Common s/e: diarrhea (>10%), abd pain, nausea, abn taste**
 1. **can cause serious intestinal cont (C.difficile assoc diarrhea / pseudomembranous colitis) – will have watery stool several times/day, possible cramping, bloody stool. Do not self treat w/ antidiarrheal med**
 - b. **+/- Food 3-4x/day**
 - c. **take w/ full glass of water**
 - d. **liquid susp is not refrig**
6. **Ciprofloxacin (Cipro)** 
 - a. **Common s/e: n/d, rash, dizziness. Rarely seizures can occur**
 - b. **Photosensitivity – can burn more easily, use sunscreen & protective clothing**
 - c. **Can cause tendon rupture/swelling of tendon (tendinitis) - if notice pain/inflam of tendons on back of ankle (Achilles), shoulder, hand— stop med and contact dr.**
 - d. **Not 1st choice for those <18 yo due to joint problems**
 - e. **Do not use with tizanidine (Zanaflex)**

7. Levofloxacin (Levaquin) ☀️ 🚫

- a. Same as cipro. Levo is QD (cipro is QD or BID)
- b. Tablets +/- Food . Suspension 1hb, 2ha
 - 1. Take 2 hrs before or 4-6hrs after antacid, vitamins, Mg, Ca, Fe, Zn, dairy, bismuth subsalicylate, sucralfate (Carafate), didanosine (Videx)
- c. Maintain adequate hydration to prevent crystalluria
- d. May ↑ INR if using warfarin. May ↓ blood sugar if using blood sugar lowering meds
- e. Need to lower dose in kidney disease

8. Doxycycline (Doryx) ☀️ 🚫

- a. Common s/e: stomach upset, mild diarrhea, n/v, headache
 - 1. Tell Dr. if any of these unlikely but serious s.e occur: stomach pain, yellowing go eyes/skin, vision Δs, mental/mood changes
- b. Photosensitivity - can burn more easily, use sunscreen & protective clothing
- c. Drink plenty of fluids while using this med
- d. Take 2 hrs before or 4-6hrs after antacid, vitamins, Mg, Ca, Fe, Zn, dairy, bismuth subsalicylate, sucralfate (Carafate), didanosine (Videx)

9. Erythromycin (EES)

- a. Typical dosing is 400 mg Q6
- b. Common s/e: n/d, abd pain, cramping
- c. Chew tablet thoroughly before swallowing. Take +/- Food
 - 1. To reduce s/e, take w. food/milk (b/c nausea commonly occurs)
- d. Liquid susp combo w. sulfisoxazole (Pediazole) is refrig.

10. Fluconazole (Diflucan), Ketoconazole (Nizoral), Itraconazole (Sporanox)

- a. Common S/E: headache, n, abd pain
- b. Fluconazole – commonly given as 150 mg x1 for vaginal fungal infxn
- c. Contact dr right away if see: brown/dark colored urine, pale stool, fatigue, skin/whites of eyes are yellow – liver damage
- d. Kidney disease – lower dose
- e. Ketoconazole, itraconazole → do not use w. antacids (2 hr separation), & stop use of PPIs & H2RAs while on these meds.

11. Metronidazole (Flagyl) 🚫

- a. Generally taken 250-500 mg TID-QID
- b. Common s/e: nausea (12%), headache, loss of appetite
- c. Do not use w.o alcohol products for at least 1-2 days afterwards
- d. Take w/ food or milk to help prevent stomach upset

12. Oseltamivir (Tamiflu) – antiviral

- a. Txt should begin within 2 days of onset of influenza symptoms
- b. (Adult) TXT = 75 mg BID x 5 days PPX=75 mg QD x 10 days
- c. (1-12 yo) TXT= 30-75 mg BID, based on weight x 5 days PPX = 30-75 mg QD x 10 days
- d. Common s/e: n/v. May cause a severe rash
 - 1. Children & adolescents may be at an ↑ risk of self-injury & confusion.
- e. Let Dr. know if pt has received a nasal influenza vaccine in last 2 wks (drug may inhibit replication of live virus)

13. Nitrofurantoin (Macrochantin, Macrobid) ☹️

- Take with food.
- Do not use magnesium trisilicate containing antacids (these antacids can bind to nitro & prev. full abs)
- s/e: nausea, headache. If they worsen, contact dr.
- may cause urine to turn dark yellow/brown (usually harmless and is temporary)
 - dark brown urine can also be a sign of rare s/e (liver probs or anemia). Seek medical atten if notice dark urine along with: persistent n/v, stomach problems, yellow skin/eyes, fatigue, tachycardia
- may rarely cause serious lung problems. Seek medical atten if see persistent cough, CP, SOB, trouble breathing, joint/muscle pain
- may cause C.diff. this can occur during txt or even weeks-mths after txt stopped. Tell Dr. if you develop persistent diarrhea, abd/stomach pain, blood/mucus in stool

14. SMX-TMP (Bactrim, Septra) ☀️ 🚫

- Take with full glass of water to prevent crystalluria
- Susp. does not need to be refig. Keep at RT. Shake prior to use.
- Photosensitivity

Do NOT refig

- Azithromycin oral susp (Zmax)
- Clarithromycin oral susp (Biaxin oral susp)
- Clindamycin
- Voriconazole
- cefdinir (Omnicef)

May refig

- Amoxil oral susp
- Augmentin *

Refrigerate

- Erythromycin ethylsuccinate oral granule susp (EES)
- Erythromycin susp w/ sulfisoxazole (Pediazole)
- Augmentin oral susp
- Pen VK Susp (after reconstitution)
- Valacyclovir susp (Valtrex)
- Cephalexin susp (Keflex)
- Cefpodoxime (Vantin)

Take with meals:

- Ciprofloxacin (Proquin XR) – take with biggest meal
- Nitrofurantoin
- Amoxicillin products

15. Terbinafine (Lamisil)

- Used to treat certain types of fungal infxn (fingernail or toenail). May take several mths after you finish txt to see full benefit. It takes time for new nails to grow and replace infected one
- s/e: diarrhea, stomach upset, temp change of taste
- Rarely causes liver damage. Look for s/s of liver damage (loss of appetite, stomach cramps, dark urine, yellow eyes/skin, pale stool)

16. Valacyclovir (Valtrex) – for herpes simplex

- +/- Food
- common s/e: headache, n/v, stomach pain, dizziness
- store caplets at RT, suspension in refig

17. Voriconazole (VFEND) ☀️

- common s/e: rash, eyesight changes, n/v/d, headache, chills, fever
 - avoid nighttime driving, can cause vision probs (blurry vision)
 - notify if s/s liver damage
- photosensitivity
- tablets have lactose (milk sugar)*, liquid contains sucrose (table sugar) – caution in pts that cannot digest dairy, lactose, table sugar
- take med 1 hr before / 1 hr after meals
- do not use if pregnant / breast feeding

Stable at RT

- Erythromycin powder susp (x 14 days)
- Amoxil oral susp
- Bactrim susp
- Linezolid susp
- SMX-TMP susp.

Take on empty stomach:

- Pen VK
- Er susp (Zmax)
- Amoxicillin (Moxatag) take 1 hr after meal
- Doxycycline (Oracea)

[17] IMMUNIZATIONS

1. Active & Passive immunity
 - a. Active immunity : (usually permanent) produced by the person's own immune system. 2 ways to acquire = 1) survive an infxn 2) vaccinations
 - b. Passive immunity : (dec w/ time) protection by products produced by an animal/human & is transferred. Ex: mother to baby; blood products (immune globulin & plasma)
2. Live attenuated & Inactivated vaccines
 - a. Live attenuated (weakened) – retain ability to replicate & produce immunity but usually do not cause illness
 - b. Inactivated – either whole viruses/bacteria or fragments. Antibody titers against inactivated antigens diminish with time, ∴ some inactivated vaccines req. boosters/supplemental doses.
3. Timing and spacing of vaccines:
 - a. **The necessary interval between an antibody containing blood product & MMR / varicella containing vaccine (except zoster vacc) is always 3-11 mths**
 - b. Consult "Pink Book" to determine specific recom interval for diff vaccs
 - c. **According to the ACIP, there are no contraindications to simultaneous admin of any of the vaccs currently avail in the US.**
 - d. If live parenteral vaccines (MMR, MMRV, varicella, zoster, yellow fever) & live intranasal/intradermal influenza vaccines (LAIV) are NOT admin at the same time → they should be separated by at least 4 wks
4. **Increasing the interval btw doses of a multidose vaccine → does NOT diminish the effectiveness .**
But Decreasing the interval btw doses may interfere w. antibody response and protection (following high risk exposure, shorter may be used)
5. **PPD test & live vaccines : should be administered on the same day**, but if not → wait 4 weeks before giving TB test in order to avoid getting a false negative TB test (this will delay TB txt and risky for the pt)
6. Vaccine side effects:
 - a. **Local** – most common, least severe (*pain, swelling & redness at site of injection*)
 - b. **Systemic** – *fever, malaise, myalgias, headache, loss of appetite* ; usually mild and occur 7-21 days after vaccine is given
 - c. **Allergic** – *anaphylactic rxn*, most severe, but rare (1/500,000) ; mediated by IgE & occur within mins-hrs of receiving vaccine. (*urticaria – hives, swelling of mouth and throat, diff breathing, wheezing, abd cramping, hypotns, shock*)
 - d. Report adverse event to **VAERS**
 - e. Protocol for anaphylaxis
 - i. Epinephrine 1:1000 dilution IM (0.01 mg/kg max 0.5 mg/dose)
 - ii. Admin diphenhydramine PO or IV
 - iii. Keep pt in supine (flat on back) . But if pt is having problems breathing, then elevate head; if BP is low, elevate legs
 - iv. Can repeat dose of Epi 2x if symptoms still present & no help has arrived.
7. **2 conditions are temporary contraindications to vaccination w/ live vaccines : 1) pregnancy 2) immunosuppression**
8. 2 conditions are temporary precautions to vaccination : 1) mod-severe acute illness 2) recent receipt of an antibody containing blood product (MMR & varicella containing vaccines- except zoster)
9. Live vacc should not be admin to severely IS pts. Certain drugs may cause IS =
 - a. cancer txt (alkylating agents/antimetabolites/radiation therapy) → wait at least 3 mths
 - b. Large doses of corticosteroids
≥20 mg /day or prednisone or ≥2 mg/kg/day for ≥14 days [intraarticular inj, MDI, topical, short course for <14 days does not count]
10. **Pregnancy vaccinations**
 - a. Do not give the live influenza vaccine (FluMist) 1 mth before or during pregnancy
 - b. >20 wk gestation should receive Tdap if need a booster. If hx is unknown, give 3 dose series (1 Tdap, 2 Td)
 - c. Defer HPV vaccine during pregnancy

Storage:

1. Store vaccines on shelves away from the wall.
Do not store on doors of freezer/refrig (temp is not stable)
2. Check temp 2x/day. Keep temp logs for 3 yrs

Administration:

1. All vaccines can be given at same time. If a vaccine is missed, any 2 live vaccines not given at the same time must be given at least 4 wks apart
2. IM inj – in deltoid muscle w/ **1"** syringe ; 90°
3. SC inj – in fatty tissue above triceps with **5/8"**, 23-25 gauge syringe ; 45°
 - ❖ SC vacc given in community: Varicella, Zoster, pneumococcal polysaccharide vacc (PPSV23, Pneumovax – SC or IM)

1. **Egg allergy** –
do not use Influenza & Yellow Fever vacc
2. **Gelatin or Neomycin allergy** –
do not use varicella vaccines Zostavax & Varivax
3. **Streptomycin, polymyxin B, neomycin allergies** –
do not use inactiv. Polio vaccine (IPV)

IM	SC
1. Tetanus, Diphtheria (Td), or pertussis (Tdap)	1. MMR
2. Hep , Hep B	2. Varicella
3. Human papillomavirus (HPV)	3. Meningococcal polysacc (MPSV4)
4. Trivalent inactiv influenza (TIV)	4. Zoster (shingles)
5. Quadrivalent meningococcal conjugate (MCV4)	5. <i>Polio (IPV) – IM or IV</i>
6. <i>Polio (IPV) – IM or IV</i>	6. <i>Pneumococcal polysacc vacc (PPSV) – IM or IV</i>
7. <i>Pneumococcal polysacc vacc (PPSV) – IM or IV</i>	

INFLUENZA (THE FLU)

1. Nasal mist (FluMist) – only healthy (no chronic disease), non pregnant females & males age 2-49.
2. Uncomplicated influenza illness is characterized by abrupt onset of: fever, cough, sore throat, headache, non-productive cough, rhinitis. These typically last for 3-7 days.
3. Neuraminidase inhibitors – inhibits neuraminidase enzyme that affects the release of viral particles
 - ❖ **Oseltamivir (Tamiflu)** : *start within 48 hrs of symptoms*
 1. Txt : **75 mg BID x 5 days** Ppx: **75 mg QD x 10 days**
 2. S/E: **aches, pains, rhinorrhea, dyspepsia, URI.** (rare = sudden confusion, delirium, hallucinations, self injury – often in children)
 - ❖ **Zanamivir (Relenza)**
 1. S/E: same confusion side effects.
Bronchospasm risk: do not use if asthma/COPD/any breathing probs
4. Other antivirals : 100 mg BID
 - ❖ Rimantidine (Flumadine) for influenza A
 - ❖ Amantadine (Symmetrel) for influenza A – but has higher adverse effects (↑ insomnia, dizziness)

[18] HUMAN IMMUNODEFICIENCY VIRUS (HIV)

1. RNA retrovirus that attacks the immune system (mainly CD4+ T cells , causing loss of cell-mediated immunity)]
2. HIV can be spread thru blood, semen, vag fluid, pre-ejaculate, breast milk & amniotic fluid
3. **Initiate ART** :
 - a. Hx of AIDS defining illness or CD4 ct <350 cells/mm³
 - b. Pregnant women
 - c. HIV assoc nephropathy
 - d. Co-infected with Hep B virus, when HBV txt is indicated
4. **Recommend ART** in:
 - a. CD4 ct between 350-500
5. **Consider ART** (optional):
 - a. CD4 ct >500, who do not meet any of the above criteria

Antiretroviral Regimens Recom for txt-Naïve pts

1. NNRTI + 2 NRTIs
 2. PI (boosted w/ Ritonavir) + 2 NRTIs
 3. INSTI + 2 NRTIs
-
1. NNRTI + 2 NRTI: **[TEE]**
Efavirenz/tenofovir/emtricitabine (Atripla)
 2. PI w/ booster + 2 NRTI : **[TEA-R, TED-R]**
Atazanavir + ritonavir + tenofovir/emtricitabine
Darunavir + ritonavir + tenofovir/emtricitabine
 3. INSTI + 2 NRTIs **[TER]**
Raltegravir + tenofovir/emtricitabine
 4. Pregnant women
Lopinavir + ritonavir + zidovudine/lamivudine
-Use BID dosing not QD dosing of lopinavir + ritonavir in preg women

-only listed are things underlined in book-

Nucleoside/tide Reverse Transcriptase Inhibitors (NRTIs)


- ❖ MOA: binding to catalytic site of **reverse transcriptase**, interfering with RNA dependent DNA polymerase.
- ❖ BBW: **lactic acidosis** & severe hepatomegaly with stenosis, sometimes fatal **esp w/ stavudine, didanosine & zidovudine**
- ❖ *Do not undergo hepatic metabolism* (fewer DI than others)
- ❖ Ribavirin may ↓ levels of all NRTI

<ul style="list-style-type: none"> • Abacavir (Ziagen) 300mg BID or 600 mg QD • Abacavir + lamivudine (Epzicom) 1 tab QD • Abacavir + lamivudine + zidovudine (Trizivir) 1 tab BID 	BBW: <ul style="list-style-type: none"> • serious hypersensitivity rxn. • Must screen for HLA-B*5701 allele before starting therapy- if positive, ↑ risk for hypersensitivity rxn, do not use – record as abacavir allergy in pt record
<ul style="list-style-type: none"> • Didanosine (Videx, Videx EC) 	<ul style="list-style-type: none"> • Videx EC – take on empty stomach (1hb, 2ha meal). Store in tightly closed bottle at RT • BBW: Pancreatitis (sometimes fatal) , dose related • S/E : peripheral neuropathy (20%), n/v , ↑ LFT/steatosis • Contraind: concurrent use w/ allopurinol or ribavirin (levels of didanosine will ↑)

<ul style="list-style-type: none"> • Emtricitabine (Emtriva) • Emtricitabine + tenofovir (Truvada)- 1 tab QD • Emtricitabine + tenofovir + efavirenz (Atripla) – 1 tab QD <p><i>Recom for initial ART</i></p>	<ul style="list-style-type: none"> • Take Atripla on empty stomach, QHS • BBW: May exacerbate Hep B once drug is discontinued for HBV resistance may develop • S/E : Hyperpigmentation (usually of palms +/- soles, can also include lip, tongue, arms, nails) • Avoid use with lamivudine
<ul style="list-style-type: none"> • Lamivudine (Epivir) • Lamivudine + zidovudine (Combivir) • Lamivudine + abacavir (Epzicom) • Lamivudine + abacavir + zidovudine (Trizivir) – 1 tab BID 	<ul style="list-style-type: none"> • BBW : Do not use Epivir-HBV for txt of HIV ; May exacerbate Hep B once drug is discon or BV resistance may dev • Avoid use with emtricitabine
<ul style="list-style-type: none"> • Stavudine (Zerit) 	<ul style="list-style-type: none"> • BBW: Pancreatitis (sometimes fatal) seen in combo w. didanosine • Contraind: do not combine with zidovudine (antagonistic – dec efficacy of both drugs)
<ul style="list-style-type: none"> • Zidovudine (Retrovir) • Zidovudine + lamivudine (Combivir) • Zidovudine + lamivudine + abacavir (Trizivir) 	<ul style="list-style-type: none"> • Contraind: do not combine with stavudine (antagonistic- dec efficacy of both drugs)
<ul style="list-style-type: none"> • Tenofovir (Viread) • Tenofovir +emtricitabine (Truvada) • Tenofovir + emtricitabine + efavirenz (Atripla) 	<ul style="list-style-type: none"> • BBW: May exacerbate Hep B once drug is discontinued for HBV resistance may develop • S/E: Fanconi syndrome, renal insuff, osteomalacia & ↓ bone density




Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- ❖ Binds to **reverse transcriptase** & blocking RNA dependent DNA dependent DNA polymerase activity
- ❖ All NNRTI & PIs are met. in liver. All are 3A4 substrates
 - inducers 3A4 (nevirapine, etravirine, efavirenz)
 - inhibitors 2C9, 2C19, 3A4 (delavirdine, efavirenz, etravirine)
 - both inducer & inhibitors (efavirenz, etravirine)

<ul style="list-style-type: none"> • Delavirdine (Rescriptor) 	
<ul style="list-style-type: none"> • Efavirenz (Sustiva) • Efavirenz + emtricitabine + tenofovir (Atripla) <p><i>Recom. For initial ART</i></p>	<ul style="list-style-type: none"> • S/E: CNS (impaired concentration, drowsiness, vivid dreams), & psychiatric symptoms (depression, mania, suicide) – take on empty stomach to red. • Preg Cat D – not to be used in preg women
<ul style="list-style-type: none"> • Etravirine (Intelence) 	
<ul style="list-style-type: none"> • Nevirapine (Viramune, Viramune XR) 	<ul style="list-style-type: none"> • Need a 14 day lead-in period • BBW: Severe hepatotox rxns may occur (liver failure, death) Severe life threatening skin rxns (SJS,TENS)
<ul style="list-style-type: none"> • Rilpivirine (Edurant)  • Rilpivirine + emtricitabine + tenofovir (Complera) 	<ul style="list-style-type: none"> • Take w/ meal • Keep in orig container away from light • Contraind: with strong 3A4 inducers (carbamazepine, oxcarba, phenobarb, phenytoin, rifampin, rifabutin, St John's)

Protease Inhibitors (PIs)

- ❖ Inhibits the HIV-1 protease (causing enzyme incapable of cleaving the Gag-Pol polyprotein → production of immature non-infectious virions)
- ❖ **Class S/E :**
 1. Hyperglycemia
 2. Lipodystrophy (loss of subcutaneous fat in face, buttocks, arms and legs)
 3. Lipohypertrophy; fat accum in various areas of the body (buffalo hump, ↑ abd obesity, ↑ breast in f/m)
 4. Dyslipidemia; ritonavir boosted PIs may ↑TG ↑LDL ↑HDL ↑amylase
 5. Hepatitis & hepatic decompensation (highest with tipranavir) ↑ LFTs, ↑ bilirubin
 6. Immune reconstitution syndrome
 7. Bleeding in pts with hemophilia
 8. Hypersens rxns (rare)
- ❖ All NNRTI & PIs are met. in liver. All are 3A4 substrates
 - Most PIs are strong 3A4 inhibitors (ritonavir is a potent inhibitor, use at low doses to inc the level of other PIs)
 - Tipranavir is a strong 3A4 inducer (it is always boosted with ritonavir)
- ❖ PIs can ↑ or ↓ INR for pts on warfarin
- ❖ When combining with statins- avoid pravastatin, lovastatin, simvastatin – inc statin level = inc risk of rhabdo

Atazanavir (Reyataz)  <ul style="list-style-type: none"> • Take with food (better abs) • <i>Recom. For initial ART</i> 	S/E: <ul style="list-style-type: none"> • May prolong PR interval, ↑CPK, indirect hyperbilirubinemia (can result in uncomplicated jaundice) • Rash including SJS, TENs • Can cause nephrolithiasis/urolithiasis (stone, crystal formation) –may reduce risk if drink ≥48 oz (1.5L) water QD Monitoring: <ul style="list-style-type: none"> • PPIs are not recom in non-boosted atazanavir – txt naïve pts can take dose 12 hrs after PPI; simultaneously or at least 10 hrs after H2 blocker. • Max 80 mg famotidine/day, 20 mg omeprazole/day
Darunavir (Prezista)  Take with food <ul style="list-style-type: none"> • <i>Recom. For initial ART</i> 	<ul style="list-style-type: none"> • Use caution in pts w/ sulfa allergy. Rash (SJS, TENs) has been reported • Must be given w. ritonavir
Fosamprenavir (Lexiva)	
Indinavir (Crixivan)	S/E: <ul style="list-style-type: none"> • ↑SCr, dysuria: Hydronephrosis or renal atrophy • Can cause nephrolithiasis/urolithiasis (stone, crystal formation) –may reduce risk if drink ≥48 oz (1.5L) water QD • Must dispense in orig container w/ desiccant to protect from moisture
Nelfinavir (Viracept)	
Ritonavir (Norvir)  Take with food <ul style="list-style-type: none"> • <i>Recom for initial ART</i> 	<ul style="list-style-type: none"> • BBW: may interact w/ many meds • S/E: May prolong PR interval, ↑CPK, ↑ uric acid. (s/e are less signif when lower dose ritonavir is used as a boosting agent for other PIs) • Store capsule @ RT or fridge (if at RT, must use in 30 days) • Store liquid @ RT (do not refrigerate)
Lopinavir + ritonavir (Kaletra)	
Saquinavir (Invirase)	<ul style="list-style-type: none"> • Trazodone is contraind with saquinavir/ritonavir
Tipranavir (Aptivus)	<ul style="list-style-type: none"> • Rare reports of fatal & nonfatal intracranial hemorrhage

Fusion inhibitors (cell entry inhibitors)

- ❖ Blocks attachment of HIV1 virus with CD4 cells by blocking conformational change in gp41 (req. for membrane fusion & entry into CD4 cell)

Enfuvirtide (Fuzeon)	S/E: local site rxns in almost 100% of pts (pain, erythema, induration, nodules & cysts, pruritus)
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CCR5 Antagonist

- ❖ Binds to CCR5 co-receptor on CD4 cell & prevents conformational change for HIV cell entry
- ❖ Maraviroc – PGP, 3A4 substrate. St Johns wort is not recom w/ this drug

Maraviroc (Selzentry)	BBW : hepatotox S/E: rash (SJS) Before starting, pts must undergo a screening test (Trophile) to det tropism of their HIV since this agent will not work for pts with CXCR4 tropic disease or dual/mixed tropic disease
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Integrase Inhibitors

- ❖ Blocks integrase enzyme (needed for viral DNA to enter host)
- ❖ A UGT1A1 substrate (Rifampin is a strong UGT1A1 inducer – will ↓ raltegravir)
- ❖ PPIs can ↑ levels of raltegravir

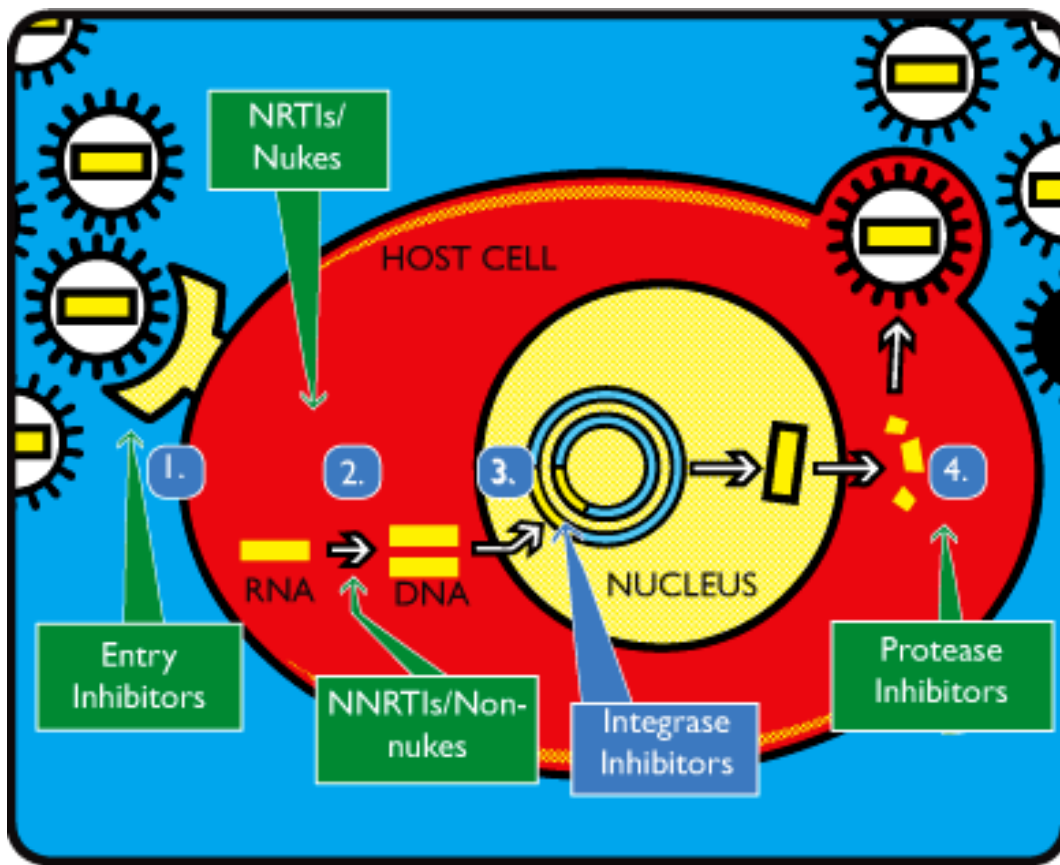
Raltegravir (Isentress)	Recom for initial ART – one of the 1° txt options
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RECOM FOR POST EXPOSURE PPX FOLLOWING OCCUPATIONAL PERCUTANEOUS INJURIES

1. Less severe (solid needle/superficial injury)
 - 2 drug (well controlled HIV)
 - 3 drug (poorly controlled HIV)
 - 2 drug (unknown status)
2. More severe (large hollow needle, deep puncture, visible blood on device)
 - 3 drug (well/poorly controlled HIV)
 - 2 drug (unknown status)
3. 2 drug regimen: [ZLET]
zidovudine + lamivudine, emtricitabine + tenofovir,
or ZE, LT **x 4 weeks**
4. 3 drug regimen : add lopinavir/ritonavir

PPX FOR OPPORTUNISTIC INFXNS

1. Pneumocystis Carinii (PCP) → **TMP/SMX 1 DS QD or 1 SS QD**
 - a. CD4 <200
 - b. Oropharyngeal candidiasis
2. Toxoplasma gondii → **TMP/SMX 1 DS QD**
 - a. Toxoplasma IgG + with CD4 <100
3. Mycobacterium avium complex (MAC) → **Azith 1,200 mg QWeek -or- Clarithromycin 500 mg BID**
 - a. CD4 <50 (after ruling out active infxn)
4. Mycobacterium tuberculosis → **Isoniazid 300 mg QD – or- 900 mg twice weekly + pyridoxine 50 mg QD x 9 mths**
 - a. Tuberculin skin test ≥5 mm
 - b. Prior positive TST w.o adequate txt
 - c. Contact with person with active TB



1. **Entry inhibitors** help stop the virus entering your immune system cell
2. **NRTIs** or 'Nukes' and **NNRTIs** or 'Non-nukes' help stop the virus's genetic material changing to a form similar to your immune system cell's genetic material
3. **Integrase inhibitors** help stop the virus's genetic material entering the nucleus of your immune system cell, where it would normally multiply
4. **Protease inhibitors** help stop new viral genetic material being assembled into new HIV viruses.

[19] HEPATITIS & LIVER DISEASE

1. Symptoms of liver disease

- Nausea/vomiting/diarrhea
- Loss of appetite
- Malaise
- Abd pain in UR quadrant
- Yellowed skin & yellowed whites of eyes
- Darkened urine
- Lightened color stool (white/clay colored) – caused by inc bilirubin in the blood

2. Indicators of liver disease

- ↑ AST/ALT
- ↑ Alkaline phosphatase
- ↑ total bilirubin
- ↓ albumin (protein prod. by liver)

3. Natural product – Milk thistle

- Most studies show benefit (but many were not rigorous enough), it may help protect liver cells (antioxidant, anti-inflamm)
- Does not seem to be harmful & is well tolerated (possible mild diarrhea)

Drugs that can cause Liver Damage

- | | | | |
|---|----------------------------|---|--|
| 1. APAP (acute, high dose) | 14. Ethambutol | 30. Nefazodone (son of trazodone) | 44. Tacrine (ACHEi before Aricept) |
| 2. Acarbose | 15. Felbamate | 31. Niacins | 45. Tamoxifen |
| 3. Adriamycin | 16. Febuxostat | 32. Nitrofurantoin | 46. Terbinafine (Lamisil) – used for onychomycosis |
| 4. Amiodarone | 17. Fenofibrate | 33. NSAIDs : many | |
| 5. Atomoxetine – BBW | 18. Flutamide | 34. Pentamidine | 47. Tizanidine |
| 6. Azathioprine | 19. Gemfibrozil | 35. Phenobarbital | 48. Tolcapone |
| 7. Azoles | 20. Gold | 36. Phenytoin | 49. Valproic acid – BBW |
| 8. Bosentan | 21. Griseofulvin | 37. Pioglitazone, rosiglitazone | 50. Thionamides (PTU, Methimazole) PTU has BBW |
| 9. TNF blockers, other biologics (etanercept, humira) | 22. HIV drugs | 38. Pyrazinamide | 51. Zileuton |
| 10. Bicalutamide | 23. Hydralazine | 39. Quinidine | 52. Zafirlukast |
| 11. Carbamazepine | 24. Imatinib & other “ibs” | 40. Ribavirin | 53. Nat. prod (comfrey, kava) |
| 12. Dronedarone (Maltac) | 25. Interferons | 41. Rifampin | |
| 13. Erythromycin | 26. Isoniazid | 42. Statins | |
| | 27. Methotrexate | 43. Anabolic steroids, testosterone, estrogen | |
| | 28. Methyldopa | | |
| | 29. Mitomycin | | |

VIRAL HEPATITIS

- Viruses that damage the liver : Hepatitis A-E, herpes, CMV, Epstein-Barr, adenoviruses

- Hepatitis A** → usually an acute, self-limiting illness, does not lead to chronic infection

- Transmission thru fecal-oral route
- Hep A vaccine = Havrix, Vaxta , given to children

- Hepatitis B** → acute illness & leads to chronic infxn (cirrhosis, liver cancer, liver failure, death)

- Transmission – contact with infectious blood, semen or other bodily fluids
- Hep B vaccine = Engerix B, Recombivax H, Twinrix

- Hepatitis C** → acute disease, but more commonly silent until chronic disease emerges

- Transmission is same as B
- No vaccine

5. Txt: for Hep B & C = **interferons** (naturally produced cytokines that stimulate an immune response & can prevent replication of virus)
 - a. Non-pegylated forms & pegylated forms (Pegasys or PEG-intron)
 - b. Pegylated forms have polyethylene glycol added to interferon (\uparrow drugs T $\frac{1}{2}$) dose freq from 3/wk to 1/wk
 - c. Hep C & RSV \rightarrow combo interferon + Ribavirin (Rebetol, Copegus)
 - d. Hep B \rightarrow several NRTIs can be used

Interferons (see above)

<p><u>HBV, HCV, many cancers:</u> Interferon-α-2b (Intron A) Pegylated interferon-α-2a (Pegasys)</p> <p><u>HCV:</u> Pegylated interferon-α-2b (PegIntron) Interferon Alfacon-1 (Infergen)</p> <p><u>Combo product:</u> Interferon-α-2b & ribavirin (Rebetron)</p> <p>Other interferons are used for multiple sclerosis – s/e are the same & all require Med Guides:</p> <p>Interferon-β-1b (Betaseron) Interferon-β-1a liquid form (Rebif) Interferon-β-1a lyophilized (Avonex)</p> <p><i>Med Guides</i> must be dispensed with each new rx & refill</p>	<p><u>HCV dosing example:</u> Intron A 3 million units SC 3x/week</p> <p><u>Pegylated formulations are Q week + Ribavirin (Rebetol, Copegus)</u></p> <p><u>Counseling:</u></p> <ol style="list-style-type: none"> 1. Keep prefilled syringes in fridge (never frozen) 2. Inject into abdomen, top of thigh, outer surface of upper arm (rotate sites) 3. Do not inject into vein, if blood is in syringe, do not inject 4. Pinch fold of skin & Inject at 45-90° angle 5. Pt will experience flu like symptoms- can pretreat. 	<p>BBW: May cause/aggravate autoimmune disorders, psychiatric symptoms (depression/suicidal thoughts), ischemic disease and/or infection</p> <p>S/E: <i>many</i></p> <ul style="list-style-type: none"> • Flu like symptoms 1-2 hrs after admin (fever, chills, malaise, tachycardia, myalgia) <ul style="list-style-type: none"> ◦ can pretreat w. APAP, antihistamine) • bone marrow suppression (neutropenia, thrombocytopenia) • CNS (fever, HA, chills, fatigue) • Pulmonary (dyspnea, pulm infiltrates) • Endocrine/metabolic (hypo/hyperthyr, pancreatitis, hyperTG) • Muscle/joint pain • CV (CP, arrhythmias, hypotension) • Eye (Dec vision) • GI (dry mouth, cough, anorexia) • Dermatologic (alopecia, skin lesions, rash) <p>Monitoring: high \uparrow in liver enzymes Withhold txt if ANC <500 -or- platelets <25,000</p>
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Ribavirin (Rebetol, Ribasphere, RibaPak, Copegus, Virazole)

- ❖ An antiviral that inhibits replication of RNA & DNA viruses
 - ❖ Indicated for Hep C virus in combo w/ interferon alfa 2 α /2 β (monotherapy not effective for HCV)
1. *Med Guides* must be dispensed w/ each new rx and refill
 2. **Not recom for pts CrCl <50**
 3. **BBW :** **Signif teratogenic effects** (Preg Cat X) - can stay in blood for as long as 6 mths. 2 reliable forms of contraception must be used during and **6 mths follow up**
 4. **S/E :** **Hemolytic anemia – primary toxicity**
 5. **DI :** Do not use with didanosine (NRTI) – fatal hepatic failure; ribavirin may \uparrow levels of NRTI

Protease Inhibitors for Hep C Only

1. Direct acting antiviral agents used in combo with peginterferon α & ribavirin in adult pts
2. **Contraindici: pregnancy (neg preg test before use & monthly is req)**
 - a. 3A4 substrates. Strong 3A4, PGP inhibitors. Do not use with major 3A4 inh/inducers
3. **Never reduce dose or interrupt therapy (txt failure)**
4. **Never use as monotherapy- must use with peginterferon & ribavirin**
 1. Boceprevir (Victrelis) – S/E: fatigue, anemia (req ESA use), neutropenia, taste distortion (dysgeusia)
 2. Telaprevir (Incivek) – S/E: serious skin rash, fatigue, itching, taste distortion, anemia

NRTI for Hep B (HBV) Only

Entire Class: \downarrow in CrCl <50

- **BBW : Lactic acidosis & severe hepatomegaly w/ stenosis**
 - **Exacerbations of Hep B may occur upon discontinuation**
 - Ribavirin may \uparrow all NRTIs
- ❖ Lamivudine (EpiVir HBV): *do not use EpiVir HBV for txt of HIV*
- Can cause pancreatitis
 - Do not use with emtricitabine; SMX/TMP may \uparrow lamivudine
 - EpiVir HBV tabs and solu are not interchangeable with EpiVir tabs and solu
- ❖ Adefovir (Hepsera) : *BBW – caution in pts with renal impairment or those at risk for renal tox (can cause nephrotox)*
- ❖ Tenofovir (Viread) : *S/E – fanconi syndrome, renal insuff, osteomalacia, \downarrow bone density*
- ❖ Entecavir (Baraclude) : *take on empty stomach (food \downarrow AUC by 20%, 2hb/2ha)*
- ❖ Telbivudine (Tyzeka) : *S/E – myopathy myalgia ; caution with meds that are renally cleared*

[20] DIABETES

- ❖ Type 1 DB: due to lack of insulin
 - Autoimmune disease in which a pts antibody destroys the pancreatic β cells that produce insulin
 - Usually in younger, thinner pts
- ❖ Type 2 DB: combination of insulin resistance & dec insulin production
 - Primary cause is lifestyle.
- ❖ **Drug induced hyperglycemia:** corticosteroids & protease inhibitors are the most likely culprits. Niacin, thiazides, atypical antipsychotics (esp Olanzapine), diazoxide (Proglycem), pentamidine (Nebupent for PCP ppx), beta agonists, phenytoin, CSA, tacrolimus
- ❖ Category for risk of diabetes (Pre-Diabetes)
 - Fasting plasma glucose 100-125
 - 75 g oral glucose tolerance test btw 140-199
 - HbA1c 5.7-6.4%

Signs and Symptoms of Hypoglycemia

1. Shaky/gittery
2. Sweaty / fast heart beat
3. Blurred vision
4. Headache
5. Irritable
6. Hunger
7. Confusion/drowsiness
8. weakness

BB can cover up/mask the symp of shakiness & anxiety (but not sweating/hunger) this is most notable with non-selective BB (carbetolol, carvedilol, propranolol). Selective agents are more commonly used.

- ❖ Diagnosing Diabetes
 - s/s diabetes (polyuria, polydipsia, unexpected wt loss) + random plasma glucose ≥ 200
 - FPG ≥ 126 mg/dL
 - HbA1c $\geq 6.5\%$
- ❖ Long term complications:
 - Microvascular complications
 - Retinopathy
 - Nephropathy (can lead to renal dysfxn and ESRD)
 - Peripheral neuropathy (loss of sensation in periph nerves & puts pt at risk for foot ulcers)
 - Autonomic neuropathy (erectile dysfxn, gastroparesis)
 - Macrovascular complications
 - Coronary artery disease (MI, HF, HTN)
 - Cerebrovascular disease (stroke, TIA)
 - Peripheral artery disease

Treatment of Hypoglycemia (retest after 15 mins)

1. Glucose tablets (follow instructions on the back- 3-4 tablets and follow again in 15 mins)
2. 3-5 hard candies (Something with sugar in it)
3. Glucose gel (used by EMS workers)
4. Regular soda – not diet soda
5. Orange juice 4oz.
6. Whole Milk-do not take skim/fat free milk they have more water
7. 1-2 teaspoons of sugar/honey/peanut butter
8. **Glucagon SC,IM,IV – only used if pt is unconscious**

DM TXT Goals

- ADA A1c = **< 7 %**
- AACE A1c = **< 6.5 %**
- eAG (estim avg gluc) <154
- preprandial BG = **70-130**
- postprandial BG (1-2h after meal) = **<180**
- LDL <100 in pts w/o overt CVD
- LDL <70 in pts with overt CVD
- BP < **130/80**
- Urine test for albumin - Annually
- Feet examined QD. Annually by podiatrist
- Eye exam – Annually
- Consider ASA (76-162mg) for primary prevention in those with \uparrow CV risk (10 yr risk >10%) = men > 50 yo, women >60 yo, with at least 1 addt risk factor (FH of CVD, HTN, smoking, dyslipidemia, albuminuria)

Biguanide

<ul style="list-style-type: none"> • Metformin (Glucophage, Glucophage XR, Fortamet, Glumetza) IR : 500, 850, 1000 mg ER : 500, 750, 1000 mg • Riomet liquid (500 mg/5mL) • Met + glipizide (Metaglip) • Met + glyburide (Glucovance) • Met + pioglitazone (Actoplus Met) • Met + rosiglitazone (Avandamet) • Met + sitagliptan (Janumet) • Met + saxagliptan (Kombiglyze XR) • Met + repaglinide (PrandiMet) 	<p>Start IR 500 mg QD – BID or 850 mg QD</p> <p>Start ER 500-1000 mg with dinner</p> <p>Titrate to 2g QD</p> <p>↓ A1C 1-2%</p> <p>ER formulations may appear in stool (Glumetza – may see shell, Fortamet – may see lumpy tablet)</p>	<p>S/E: diarrhea/loose stools (20% of pts, but it goes away), abd discomfort</p> <ul style="list-style-type: none"> • Weight Neutral, NO hypoglycemia <p>Renal Contraindication: Males SCr ≥ 1.5 Females SCr ≥ 1.4 or CrCl <60</p> <p>BBW: lactic acidosis (rare but fatal) -contrast dye inc risk, hold x 48 hrs and recheck renal fxn prior to starting Met.</p> <p>Caution: in heart failure. Pt may experience hypoperfusion</p> <p>Can ↓ folate & B12 abs – can lead to neuroathic damage (consider suppl.)</p>
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1. ↓ *hepatic glucose output*, ↓ intestinal absorption of glucose & ↑ insulin sensitivity
2. Counseling:
 - a. Some pts dev. Rare condit called lactic acidosis. Symptoms of lactic acidosis: wkness, inc sleepiness, slow HR, cold feeling, muscle pain, SOB, stomach pain, light headed
 - b. If need Xray or CT scan using a dye – may need to temp. stop metformin
 - c. Take metformin IR BID with morning and evening meal (diarrhea & abd discomfort may be less with meals), take ER with evening meal

Sulfonylureas

<ul style="list-style-type: none"> • Chlorpropamide (Diabinese) • Tolbutamide (Orinase) 	<p>↓ A1C 1-2%</p> <p>Older agents, not commonly used</p>	<p>S/E: Hypoglycemia, wt gain, ↓ efficacy after long term use</p> <p>Renal:</p> <ul style="list-style-type: none"> • ADA recom. Not to use chlorpropamide & glyburide in renal dysfxn. • Glyburide has an active metabolite that is renally cleared & may accumulate . It is not recom in CrCl <50
<ul style="list-style-type: none"> • Glipizide (Glucotrol, Glucotrol XL) • Glipizide + Metformin (Metaglip) 	<p>IR 2.5-10 mg BID</p> <p>XL 2.5-10 mg QD (max 20 mg QD)</p>	
<ul style="list-style-type: none"> • Glimepiride (Amaryl) • Glimepiride + pioglitazone (Duetact) • Glimepiride + rosiglitazone (Avandaryl) 	<p>2-4 mg, max 8 mg QD</p>	
<ul style="list-style-type: none"> • Glyburide (Diabeta, Micronase) • Micronized glyburide (Glynase Pres Tab) • Glyburide + Metformin (Glucovance) 	<p>1.25-5 mg QD</p> <p>Glynase Pres Tab : 1.5-12 mg QD</p>	

1. Stimulating insulin secretion from pancreatic beta cells.
Do not use with meglitinides due to similar MOA
2. DI: primarily with insulin, since both can cause hypoglycemia (s/s hypoglycemia)
 - a. Other drugs that can cause hypoglycemia: alcohol, azoles (fluconazole, voriconazole), penicillamine, pentamidine, quinine, quinolones, pramlintide, SMX-TMP
3. If QD dosing – take dose before breakfast. If BID – take before breakfast & dinner

Meglitinides

<ul style="list-style-type: none"> • Repaglinide (Prandin) • Pegaglinide + Metformin (PrandiMet) 	Take 15-30 mins before meals	↓ A1C 0.5-1.5%
<ul style="list-style-type: none"> • Nateglinide (Starlix) 	15-30 mins before meals	S/E: hypoglycemia , weight neutral (adv. over sulfonylureas)

1. Stim. Insulin secretion from pancreatic cells. Do not use with sulfonylureas
2. DI: primarily insulin since but can cause hypoglycemia (counsel on s/s)
 - a. Gemfibrozil ↑ Prandin concn (may cause hypoglyc) → recom fenofibrate instead.

Thiazolidinediones (TZDs) - Improves insulin sensitivity in the muscle cells

<ul style="list-style-type: none"> • Pioglitazone (Actos) • Pio + Metformin (Actoplus Met, Actoplus Met XR) • Pio + glimepiride (Duetact) 	15-45 mg QD +/- food	BBW: may exacerbate HF <ul style="list-style-type: none"> • Rosiglitazone can ↑ MI risk S/E: peripheral edema, wt gain, fracture risk, Pioglitazone ↑ risk of bladder cancer
<ul style="list-style-type: none"> • Rosiglitazone (Avandia) • Rosi + Met (Avandamet) • Rosi + glimepiride (Avandaryl) 	2-8 mg QD . Restricted use (2011) due to CVD risk. Pts must be enrolled in avandia-rosiglitazone medicines access prog (REMS)	Hepatic: d/c when ALT >3x normal CV risk: can cause fluid retention, edema. Contraindicated in NYHA 3 or 4. Do not use pioglit in pts with bladder cancer

1. May take several weeks to lower blood sugar
2. Contact Dr. if have s/s liver dysfxn or ↑ water retention

Alpha Glucosidase Inhibitors

Acarbose (Precose)	↓ A1C 0.5 – 0.8 % Both start at 25 mg with first bite of each meal.	S/E: GI (flatulence, diarrhea, abd pain)
Miglitol (Glyset)	Take with full glass of water (needs to be in stomach) – do not use if skipping a meal	Good chol : ↑ HDL ↓ TG ↓ TC, weight neutral Contraindications: IBS, colonic ulcerations, intest obstruction. Do not use with any signif GI disease

1. inhibits enzymes in intestine and pancreas to delay absorption of glucose. Also inhibits metabolism of sucrose to glucose & fructose.
2. These agents do NOT cause hypoglycemia, but if low BG occurs, **pt cannot treat it with sucrose (in fruit juice) or table sugar/candy. Must purchase glucose tablets or gel to have on hand**

DPP4 Inhibitors

<ul style="list-style-type: none"> • Sitagliptin (Januvia) • Sita + metformin (Janumet) • Sita + simvastatin (Juvissync) 	100 mg QD 25 mg if CrCl <30	↓ A1C 0.5 – 0.8 % Take QD in morning +/- food
<ul style="list-style-type: none"> • Saxagliptin (Onglyza) • Saxa + metformin (Kombiglyze XR) – with evening meal 	5 mg QD 2.5 mg if CrCl <50 or with strong 3A4 inhib	S/E: rarely acute pancreatitis
<ul style="list-style-type: none"> • Linagliptin (Tradjenta) 	5 mg QD * no renal dosage adj	See Dr. right away if see s/s pancreatitis (severe stomach pain, +/- vomiting, pain can radiate from abdomen to back)

1. **Prevents the enzyme DPP4** from breaking down incretin hormones, glucagon like peptide 1 (GLP1), and GIP – these hormones ↑ β cell insulin release and ↓ α cell glucagon release – they are incretin enhancers

Glucagon Like Peptide 1 (GLP1) Agonists

Exenatide (Byetta)	Should be given within 60 mins (usually 30) before morning & evening meal <i>-never inject after meal (hypoglyc)</i> Abdomen is preferred site, can use thigh or upper arm	↓ A1C 0.5-1% S/E: nausea (primary) Pancreatitis – most commonly occurs in pts with risk factors (hx of pancreatitis, gallstones, alcoholism, high TG). <i>This is in the req MedGuide</i> Renal: avoid in severe impair (CrCl <30)
Liraglutide (Victoza)	Given +/- food	BBW: contraindi in pts with FH of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome S/E: more wt loss and less hypoglyc than exenatide

1. Analogs of **glucagon like peptide (GLP-1)** which ↑ insulin secretion, ↓ glucagon secretion, slows gastric emptying, improves satiety, and may dec weight

Pramlintide (Symlin)

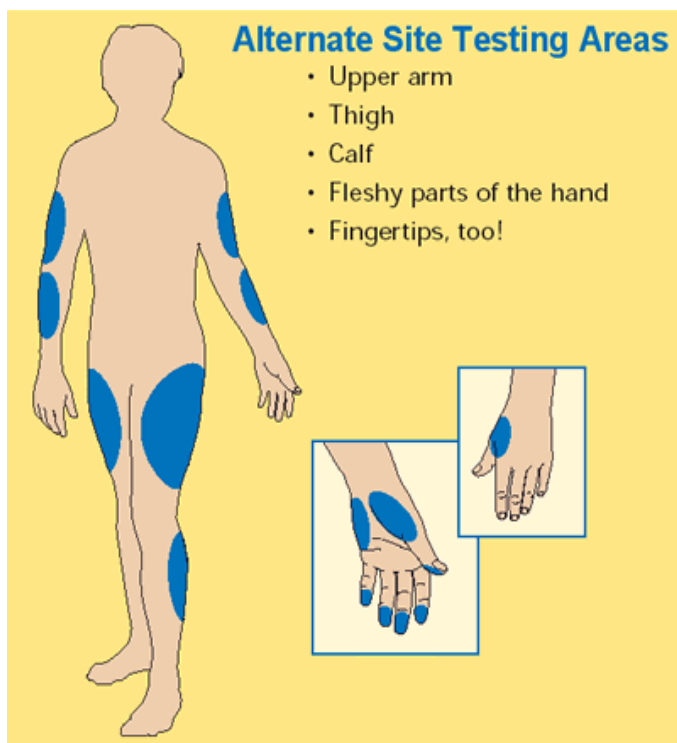
1. Synthetic **analog of amylin** (prod by pancreatic beta cells that slows gastric emptying, prevents inc in serum glucagon after meals)
2. Admin SC in abdomen or **thigh prior to each meal**. – *do not use if skipping meal*
3. **BBW:** co-admin with insulin may induce severe hypoglycemia (must reduce insulin by 50%)
4. **S/E:** **hypoglycemia, nausea, anorexia, wt loss**

Bile Acid Resins- Colesevelam (WelChol)

1. Resins work by binding bile, blocking reabs. Bile is produced from cholesterol and chol levels ↓. The mech in which colesevelam improves glycemia control is unknown
2. Contraindic: bowel obstruction, TG >500, hx of TG induced pancreatitis
3. Take Welchol 4 hrs before: phenytoin, levothyroxine, glyburide, CSA, oral contraceptors (E+P), 4-6 hrs before niaspan

Bromocriptine (Cycloset)

1. Is indicated as an adjunct to diet and exercise to improve glycemia control. It's a DA agonist & works in the CNS to dec. insulin resistance.
2. **Take with food**
3. Extensively met. by 3A4. Do not use with ergot meds (may inc ergot s/e or reduce effectiveness for migraines)



Insulin Therapy

Insulin Adverse Effects: <ol style="list-style-type: none"> 1. Hypoglycemia 2. Weight gain 		Storage Requirements <ol style="list-style-type: none"> 1. DO NOT FREEZE 2. Opened insulin--Refrigerate or Room temp for 28 -30 days 3. Unopened in fridge-- based on expiration date (Unopened should be kept in the fridge**) 4. Can draw up insulin in a syringe and it's good for up to 4 hrs (common for pts on the go) <p>Inject in a 90° or 45° (slight) angle Abdomen is the preferred injection site , do not inject within 1 inch of navel</p>	
Drug-Interactions <ol style="list-style-type: none"> 1. No significant interactions reported 			
Brand (Generic)	Dose	Properties	Precautions
Basal Insulins →targets FASTING SUGARS			
Intermediate Acting Humulin N , Novolin N (NPH)	15 mins before meals BID (it's not uncommon for Type II's to begin with once daily dosing to get started)	Onset: 1-2 hours Peak: 4-8 hours Duration: 24hours Appearance: Cloudy	DO NOT use in renal impairment → switch to glargine/detemir
Long Acting Levemir (Detemir)	Once Daily or BID (has dose dependent kinetics) <ol style="list-style-type: none"> 1. Can be used in pts with renal impairment 	Onset: 4 hours Peak: No peak Duration: 12-24 hours Appearance: Clear	
Long Acting Lantus (Glargine)	Once Daily <ol style="list-style-type: none"> 1. Preferred for pts with renal impairment 2. Dosages 90 units or above, must be split to BID (so 45 BID) 	Onset: 1 hour Peak: No peak Duration: 24 hours Appearance: Clear	<ol style="list-style-type: none"> 1. CANNOT be mixed in the same syringe with other insulins
Bolus Insulins →targets POST-PRANDIAL SUGARS			
Rapid Acting Novolog (Aspart) Humalog (Lispro) Apidra (Glulisine)	<ol style="list-style-type: none"> 1. Right before a meal (5-15 mins before a meal) –tell pts to draw up the syringe, but do not inject the bolus until you take the first bite 2. Has Meal time flexibility- Pts don't have to worry about timing b/c they can just inject right when they eat, don't have to plan. 	Onset: 5-15 min Peak: ~60 min Duration: 4-6 hours Appearance: Clear	
Regular/Short Acting Humulin R (Regular) Novolin R (Regular)	<ol style="list-style-type: none"> 1. 30 mins before breakfast & dinner 	Onset: 30-60 min Peak: 2-4 hours Duration: 6-8 hours Appearance: Clear	<ol style="list-style-type: none"> 2. Renally eliminated so may want to avoid in pts with renal impairment

Pre-Mixed*				
	Onset	Peak	Duration	
Humulin 70/30 <i>NPH/Regular</i>	30 min.	2-4 hours	14-24 hours	<ul style="list-style-type: none"> Generally dosed BID (b/c of NPH; more freq dosing may lead to insulin stacking) <ul style="list-style-type: none"> 2/3 dose QAM, 1/3 dose QPM
Humulin 50/50 <i>NPH/Regular</i>	30 min.	2-5 hours	18-24 hours	
Novolin 70/30 <i>NPH/Regular</i>	30 min.	2-12 hours	Up to 24 hours	<ul style="list-style-type: none"> Generally dosed BID (b/c of NPH; more freq dosing may lead to insulin stacking) 2/3 dose QAM, 1/3 dose QPM Cloudy In use storage time: 42 d
Novolog Mix 70/30 <i>Aspart protamine/Aspart</i>	10-20 min.	1-4 hours	Up to 24 hours	<ul style="list-style-type: none"> Can be given TID Immed. or within 10-15 mins before meals White and cloudy; roll to mix In use storage time: Flexpen (14d) Vial (28d)
Humalog mix 75/25 <i>Lispro protamine/Lispro</i>	15 min.	30 min.-2½ hours	16-20 hours	<ul style="list-style-type: none"> Can be given TID 10-15 mins before or immed. after meals
*Premixed insulins are a combination of specific proportions of intermediate-acting and short-acting insulin in one bottle or insulin pen (the numbers following the brand name indicate the percentage of each type of insulin).				

GESTATIONAL DIABETES

- In pregnancy, goal Pre-prandial < 95 , A1C < 6%
- Standard of care = Nutritional therapy
 - Txt: When meds are needed, ADA recom insulin – it is the only FDA approved med for txt of GDM
 - Long acting insulins (glargine – Lantus, detemir –Levemir) are Cat C and NOT recom.
 - Metformin & glyburide are sometimes use but not 1st line

DIABETIC KETOACIDOSIS (DKA)

- Can occur when there is not enough insulin – so body breaks down fats to make energy
 - This causes the concn of ketones to inc in the blood
- DKA may be the initial presentation in Type I DM -or- bc a person stopped taking insulin therapy
 - Acute illnesses may also precipitate DKA (infxn, pancreatitis, MI, stroke)
- DKA symptoms:**
 - Hyperglycemia, polyuria, polydipsia, polyphagia, blurred vision, metabolic acidosis (fruity breath), dehydration
- Lab abnormalities:**
 - Glucose >300
 - Ketones present in urine & blood
 - pH < 7.2 Bicarb <15
 - WBC 15-40
- Txt DKA:**
 - IV fluids + insulin
 - K should be expected to drop as insulin is administered (bc it causes K to shift intracellularly)

[21] THYROID DISORDERS

- ◆ The thyroid gland is the only organ that contains cells that can absorb iodine
- ◆ Thyroxine (T4) & Triiodothyronine (T3) are produced by the thyroid gland. Iodine and tyrosine are used to form T3 & T4
- ◆ TSH → stimulates secretion of T4 → which then is converted to T3
 - T3 is 3-4x more potent than T4 but has a much shorter T $\frac{1}{2}$
- ◆ High T4 will inhibit the secretion of TSH via neg feedback
- ◆ Its imp to measure the free T4 (FT4) bc T3 & T4 are transported in the blood and bound by proteins
- ◆ In hypothyroidism – low T4, high TSH hyperthyroidism – high T4, low TSH

HYPOTHYROIDISM

1. **Dx:** ↓ FT4 (normal 0.8-1.7 mgg/dL),
↑ TSH (normal 0.3-2 mIU/mL)
 2. **Symptoms** : fatigue, weight gain, cold intolerance, dry skin, fatigue, heavier than normal menstrual periods, memory and mental impairment, goiter (possible), myalgias, HLD, depression, constipation, bradycardia
 3. **Causes of hypothy:** Hashimoto's disease (most common cause), Drugs (lithium, interferon, amiodarone), external irradiation, iodine deficiency
 4. **Complications** : CV disease, goiter, depression, infertility, myxedema (intense cold intol, drowsiness, unconsciousness)
 5. **Pregnancy:** Levothyroxine is a Preg Cat A. Deficient women may have children at risk of impairment in intellectual fxn & motor skills. Preg women will req 30-50% inc in levothyroxine dose
- ❖ **T4 = Levothyroxine (Synthroid, Levothroid, Levoxyl, Unithroid, Tirosint, Levo-T)**
 - ❖ T3 & T4 = Thyroid USP (Armour Thyroid)
 - ❖ T3 = Liothyronine (Cytomel, Triostat) – shorter T $\frac{1}{2}$ leading to fluctuations in T3
 - ❖ T3 & T4 in 1:4 ratio = Liotrix (Thyrolar)
- **S/E:** if a pt is euthyroid, then no s/e should exist. If dose is too high, pt will experience hyperthy symptoms (inc HR, palpitations, sweating, wt loss, arrhythmias, irritability)
 - **Contraind** : acute MI, thyrotoxicosis
 - **Monitoring:** TSH and clinical symptoms Q 6-8 wks
 1. Highly protein bound
 2. IV: PO ratio = 1:2
 3. Thyroid USP – natural porcine-derived thyroid that contains both T3 and T4; less predictable potency and stability. Not preferred, but some feel better using it
 - **Drug Interactions**
 1. ↓ thyroid hormone absorption = Cholestyramine, Ca, Mg, Al, Fe, sucralfate, sodium polystyrene (SPSP, Kayexalate), orlistat (Xenical, Alli), chromium → separate doses by 2 h before, 4 h after
 2. ↓ thyroid hormone levels = estrogen, hepatic inducers
 3. ↓ effect of levothyroxine by dec conversion of T4 to T3 = BB, amiodarone, steroids, PTU
 4. Thyroid hormone can : ↑ anticoag, ↓ digoxin, theophylline, antidiabetic drugs
 - **Counseling:**
 1. Diff brands of levothyroxine may not work the same.
 2. This med is safe while preg & while breast feeding (it does pass into breast milk but is not harmful)
 3. **Take on empty stomach with full glass of water 30 mins before bfast**

HYPERTHYROIDISM (THYROTOXICOSIS)

1. **↑ FT4, ↓ TSH**
2. **Symptoms:** heat intolerance, inc sweating, weight loss, agitation, nervousness, irritability, palpitations, tachycardia, fatigue, freq bowel mvmts, insomnia, light/absent menstrual periods, goiter (possible), tremors, exophthalmos
3. Causes: **Grave's disease** (most common – an autoimmune disorder that stimulate the thyroid to produce too much T4), drugs (**iodide, amiodarone, interferons**)
4. Txt: destroying the gland via radioactive iodine (RAI-131), surgery, medications
 - a. **RAI-131 is the txt of choice in Grave's disease**
 - b. BB can be used for symptom control
 - c. PTU, Methimazole can be used as a temp measure until surgery is complete

Thionamides – inhibit synthesis of thyroid hormones by **blocking oxidation of iodine** in thyroid gland.

PTU – also **inhibits peripheral conv. of T4 to T3**

- ❖ Propylthiouracil (PTU)
- ❖ Methimazole (Tapazole)
 - **BBW:** PTU can cause liver damage & acute liver failure
 - **S/E:** **GI upset**, rash, fever, **hepatitis**, **agranulocytosis** (rare)
 - **Preg Cat D** – PTU for women trying to conceive or in 1st trimester, then **Δ** to Methimazole for 2nd and 3rd trimester
 - **PTU is preferred in thyroid storm**

Iodides – **inhibit secretion of TH**; T4 and T3 levels are reduced for several weeks, but effect will not be maintained

- ❖ Potassium Iodide and Iodine solution (Lugol's solution)
- ❖ Saturated solution of potassium iodide (SSKI)
 - Do not use in breast feeding, Cat D
 - S/E: rash, metallic taste, GI

THYROID STORM

1. A rare but serious condit that happens in people with hyperthyroidism esp during stressful events (infxn, MI, DB, childbirth) or due to lack of txt
2. Ppl with hyperthyroidism should try to live stress free lives
3. Signs/symptoms: fever (>103 F), tachycardia (>140 bpm), tachypnea, profuse sweating, agitation, psychosis, coma
4. Txt:
 - a. PTU (take 30 mins before iodine to block synthesis of TH)
 - b. **+** SSKI or Lugol's solution
 - c. **+** propranolol
 - d. **+** dexamethasone

[22] OSTEOPOROSIS & HORMONE THERAPY

1. DX : **osteoporosis** = T score < - 2.5 **Osteopenia** = -1 → -2.5
2. T score = comparing the women's bone mineral density (BMD) to the *avg peak BMD of a normal, young adult of the same gender*
3. Osteoblasts are cells involved in bone formation, osteoclasts break down bone
4. A bone scan – is performed by a dual energy x-ray absorptiometry (**DEXA, DXA**) from hips, lumber vertebrae.
 - a. Ultrasound devices are not optimal, they provide bone density in 1 location (eg. heel)
5. **Calcium supplementation**
 - a. All rx medicines for low bone density req. concurrent Ca++ and Vit D supplementation. Vit D is req for Ca++ Absorption
 - b. Ca absorption is saturable, doses should be divided

NIH recommended intake for Calcium				
Age	Male	Female	Preg	Lactating
9-18 yo	1,300 mg	1,300 mg	1,300 mg	1,300 mg
19-50 yo	1,000 mg	1,000 mg	1,000 mg	1,000 mg
50+ yrs	1,200 mg	1,200 mg		

Calcium citrate (Citracal)	Calcium carbonate (Oscal, Tums)
1. Better absorption	1. Acid-dependent absorption
2. Taken with <u>or</u> w/o meals (may be preferable w. little to no acid)	2. Take with meals
3. Larger pill	3. 500-600 mg Ca++/tab
4. 315 mg Ca++/tablet	

Risk factors for low bone density:

1. Advanced age
2. Low bone mineral density
3. Prev fx as an adult
4. > 2 alcoholic drinks/day
5. Oral or IM glucocorticoid use (prednisone >7.5 mg x more than 3 mths)
6. Low body wt (<127 lbs, BMI <21)
7. smoking

Drugs that lower bone density:

1. Long term steroid use
2. Anticonvulsants (carbamazepine, fosphenytoin, phenobarb, phenytoin, primidone)
3. Warfarin & heparin
4. Excess thyroid hormone
5. Loop diuretics
6. Aromatase inhib (breast CA)
7. Androgen blockers (prostate CA)
8. PPI chronically (↓ Ca abso due to ↓ gastric pH)

The solubility of calcium salts is a pH-dependent process; therefore, increased pH due to treatment with PPIs could lead to decreased amounts of calcium salts being absorbed. For example, the most common calcium supplement available, calcium carbonate, is insoluble at high pH levels and therefore absorption is decreased with higher pH levels; however, calcium citrate does not require extra stomach acid for absorption

- c. **Vit D. suppl** – recom for people up to **70 = 600 IU QD** , **≥71 = 800 IU QD**
 - i. Cholecalciferol (D3) is preferred

6. **Treatment:**

- a. Osteoporosis: medications, weight resistant exercise (walking) , adequate Ca and Vit D
- b. Osteopenia : exercise, Ca and Vit D , sometimes meds if pt has high fracture risk
- c. **1st line = Bisphosphonates** (inc bone density more than estrogen / raloxifene)
- d. **Teriparatide injection (Forteo)** used in pts with: osteoporosis who are at **high risk** of fractures, hx of fx, or are on long term steroids
- e. Denosumab (Prolia)- new agent, difficult to admin (must be given in Dr. office), also reserved for high risk pts
- f. **Estrogen** is no longer 1st line due to health risks. If used for menopausal symptoms, estrogen ↑ bone density
 - i. **Raloxifene** is most commonly used in women w. fear of breast cancer

Bisphosphonates – inhibits osteoclast activity

green = counseling points

Alendronate (Fosamax)	(-penia) 5 mg QD ppx (-porosis) 10 mg QD txt (penia) 35 mg Week ppx (porosis) 70 mg Qweek txt	S/E: GI upset, joint pain, back pain, dyspepsia, n/v, heartburn, esophagitis (may ↑ esophageal cancer risk) <ul style="list-style-type: none"> Possible risk of jaw decay/necrosis Risk atypical femur fx with long term use >5 yrs (consider stopping after 5 yr) Contraindications: <ul style="list-style-type: none"> Inability to stand/sit upright x 30 mins (60 mins with Boniva) Hypocalcemia Severe renal impairment Missed dose: QD sched – skip until next dose QWeek – take next morning Qmonth – take as soon as remember, unless its < 1 week til next dose
Risedronate (Actonel) Actonel + Calcium : 35 mg Qweek + Ca carb 500 mg x 6 days <i>Atelvia</i> is a long acting risedronate-taken after breakfast. Do not use H2RA/PPI. Take Ca, Mg, Fe, MVI later in the day	5 mg QD 35 mg Week or 75 mg on 2 consecutive days / month 150 mg Qmonth	
Ibandronate (Boniva)	150 mg Qmonth 2.5 mg QD 3 mg IV Q 3 months	

Injectable Bisphosphate

Zoledronic Acid (Reclast) <i>Do not use with Zometa (same drug – used for hypercalcemia of malignancy)</i>	5 mg infusion Q year	S/E : No GI probs, TPS (transient post dose syndrome – flu like 2-3 days after injection (achiness, runny nose, HA) . taking NSAID before and after can help)
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Selective Estrogen Receptor Modulator (SERM) : ↓ bone resorption

Raloxifene (Evista) <i>Used often in women at risk / fear of breast CA</i>	Favorable lipid effect	S/E: hot flashes, n/v, edema, flushing, HTN, mood changes Contraind: pregnancy, hepatic dysfxn, prev TE (↑ risk of thromboembolic events) – d/c at least 3 days before to and during immobilization
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Calcitonin Nasal Spray & Injection – inhibits osteoclastic bone resorption

Calcitonin (Miacalcin, Fortical) <i>Keep unopened bottle in fridge</i>	Inhale 1 spray (200 IU) QD alternate nostril daily	S/E: rhinitis, dizziness, flu like symptoms
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Teriparatide injection - ↑ new bone formation & ↓ osteoclast activity

Teriparatide (Forteo) For pts who are at very high risk for fx, have already had a fx, cannot take other meds	SC inj QD (max 2 yrs) – keep pen in fridge. (inject in thigh/abdomen) Bone pain from this drug could be bone cancer – contact dr if experiencing	S/E: dizziness, ↑ HR (esp with 1 st few doses), injection site pain Caution/CI : bone metastases (inc risk of osteosarcoma)
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Monoclonal Antibody Injectable – binds to RANKL and prev interaction btw RANKL and RANK (prev. osteoclast formation, leads to dec bone resorption and inc bone mass)

Denosumab (Prolia, Xgeva) High risk only	SC ing Q 6 mths (in Dr. office)	S/E: anemia, risk jaw necrosis
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HORMONE THERAPY (HT) - ESTROGEN

1. Menopause- many women experience vasomotor symptoms as their ovaries produce less estrogen.
 - a. ↓ estrogen causes ↑ LH (which causes hot flashes and night sweats).
 - b. Due to decline in estrogen in the vaginal mucosa, vag dryness, burning and painful intercourse may be present
2. Most effective txt for VM symptoms = estrogen (causes ↓ LH and more stable temp control)
3. Estrogen ↑ bone density, but not strong enough to be used for txt
4. Natural products for VM symptoms = black cohosh, red clover, soy, evening primrose.
5. Women with a uterus – do not use estrogen alone (↑ risk for endometrial cancer). Must be combined with progestin.
 - a. Progestin can cause mood disturbances in women, so some choose to use estrogen alone
6. Estrogen inc the risk of endometrial cancer, invasive breast cancer, MI , stroke, PE, DVT, dementia (women >65 yo)
 - a. In 2010, there were new concerns of inc lung cancer risk in women using estrogen + progestin
7. **Formulation considerations:**
 - a. Topical (patch, gel, emulsion) – bypass 1st pass metabolism and lower doses can be used
 - i. Cause less nausea and may expose pt to lower systemic estrogen
 - ii. Can cause nausea, dizziness, bloating, wt changes, changes in sexual interest
 - b. Vaginal products (rings, creams) – bypass the liver (so do not affect cholesterol levels – typically estrogen ↑HDL, TG)
 - i. most useful for pts with vaginal symptoms (dryness, painful intercourse)
 - ii. Do not expose women to systemic estrogen

Estrogen Contraindications

1. Undiagnosed abnormal genital bleeding
2. Active/past breast cancer
3. Estrogen dependent cancer
4. Active/past DVT, PE
5. Active/recent stroke, MI
6. Liver dysfunction
7. Pregnancy

8. **Common HRT products** : *only listed bolded ones*
 - Vivelle, Vivelle Dot (estradiol transdermal system, twice weekly patch)
 - i. Apply patch to lower abdomen, below waistline. DO NOT apply to breasts.
 - Provera (medroxyprogesterone)
 - Premarin (conjugated estrogen tablet)
 - Premarin vaginal cream (conjugated estrogens cream)
 - Prempro (conjugated estrogens/medroxyprogesterone acetate tablet – P component changes (phasic) → medroxyprog taken on days 15-28 only
 - Prempro (conjugated estrogens/medroxyprogesterone acetate tablet (P component stable)
 - Climara , Alora (estradiol patch)
 - Femring (estradiol acetate vaginal ring)
9. **Estrogen Counseling:**
 - a. This product does not contain a progestin, which should be dispensed for women with a uterus. Estrogens ↑ chances of getting cancer of the uterus
 - b. Report any unusual vaginal bleeding (bleeding after menopause may be a warning sign of uterine cancer)
 - c. Estrogens +/- progestin may ↑ your risk of MI / stroke
 - d. It is used primarily for menopausal symptoms – should be continued indefinitely
 - e. Estrogen can help keep bones healthy

TESTOSTERONE THERAPY

- If testosterone replacement is due to a medical procedure, that is considered acceptable therapy.
 - An accepted use is in men with low prostate cancer risk with low testosterone level and related condition such as low muscle mass
- More older males are req. testosterone for purported health claims ([↑ muscle mass](#) and bone density, improved [sexual interest](#), sharpened memory & concen, inc energy
- Use is controversial – the 1° risk is [↑ prostate cancer](#) risk. It can also [↑ cholesterol levels](#) and cause [liver damage](#)
- [Men at high risk of prostate cancer should not use these products.](#) BPH symptoms would be expected to worsen. (if giving a 5α reductase inhibitor for BPH to block conversion of testosterone to its active form, it would not make much sense to give testosterone directly

Testosterone products – C III

Testim gel 1%	Before using pump, must prime by pushing down 3x	S/E: inc Cr, inc appetite , sensitive nipples, inc risk of hepatotoxicity
AndroGel 1%, 1.62% Meter dose pump or foil packets		
Androderm patch <i>Take off before MRI</i>	Apply to back, abdomen, thighs or upper arms Apply each evening between 8pm-12am	BBW: worsening s/s of BPH Secondary exposure to women and children can occur and cause virilization (<i>can cause birth defects in unborn babies. Enlarged genitals, aggressive behavior, excessive hair growth irreg menstrual periods, etc</i>) Contraindications: breast & prostate cancer. Never apply to breast/genitals
Striant buccal tabs	Apply to gum region BID	
Testosterone topical solution (Axiron) – applied to underarms Fortesta (gel) – applied to thighs	<i>Axiron gel – apply deodorant first</i>	

[23] CONTRACEPTION

1. Menstrual Cycle/Phases
 - a. Normal menstrual cycle ranges from 23-35 days (avg 28 days). Menstruation starts on day 1
 - b. Ovulation: mid cycle LH surge causes release of the oocyte (egg) from the ovary → fallopian tube. If the oocyte is not fertilized, it is washed out thru menstruation.
 - i. Ovulation kits test for LH and if (+) it is present.
 - c. Pregnancy : highest chance for pregnancy is between days 8-16 of the cycle. Preg test kits are (+) if hCG (human chorionic gonadotropin) is in the urine
2. Hormonal contraceptives
 - a. **POPs (progestin only pills)** – mostly recom for lactating (breastfeeding) women bc estrogen ↓ milk production
 - b. **COCs (estrogen & progestin combo)** – inhibits production of FSH and LH, this prevents ovulation.
 - i. COCs are used for various indications : dysmenorrhea, PMS, perimenopausal symptoms, anemia due to blood loss, acne.
 - c. Estrogen Adverse effects : nausea, breast tenderness/fullness, bloating, wt gain, elevated BP.
 - i. May req higher estrogen dose if mid cycle (day 14-21) breakthrough bleeding occurs
 - d. Progestin Adverse effects : breast tenderness, headache, fatigue, Δs in mood.
 - i. Higher dose may be req if late cycle (day 21) breakthrough bleeding

Teratogenic drugs that should be discontinued, if possible

1. Alcohol
2. ACEi/ARB
3. Carbamazepine
4. Isotretinoin
5. Lithium
6. Phenytoin
7. Phenobarbital
8. Topiramate
9. Valproic acid
10. Ribavirin
11. Misoprostol
12. Methotrexate
13. Leflunomide
14. Statins
15. Dutasteride
16. Finasteride
17. Warfarin
18. Lenalidomide, thalidomide

Drugs that ↓ efficacy of oral contraceptives

1. **ABX** (ampicillin, griseofulvin, sulfonamides, tetracycline, rifampin, rifapentine) – use backup
 - a. With rifampin, use other form of BC since induction will last long. If switching back, a backup method needs to be used for 1 ½ mths after rifampin is stopped
2. **Anticonvulsants** (barbiturates, carbamazepine, oxcarbamazepine, phenytoin, topiramate, felbamate)
3. **St Johns wort** – do not use OCs concurrently- strong inducer
4. **Antiretrovirals** that inc OC metabolism (atazanavir, lopinavir, nelfinavir, nevirapine, ritonavir)
5. **Bosentan** (Tracleer) used for PAH
6. Do not **smoking**, may ↓ efficacy

Monophasic COC – all active pills contain same level of hormones <ul style="list-style-type: none"> • Apri – desogestrel & ethinyl estradiol • Kariva – desogestrel & ethinyl estradiol • Yasmin 28, Ocella - ethinyl estradiol 	Low estrogen COC (20 mcg estrogen vs 35 mcg) used to ↓ withdrawal symptoms (emotional/physical) and bleeding <ul style="list-style-type: none"> • Aviane, Kariva - ethinyl estradiol & desogestrel • LoSeasonique - ethinyl estradiol & levonorgestrel
Multiphasic COC – dose of hormone changes over course of 21 days <ul style="list-style-type: none"> • Tri-Sprintec , TriNessa, Ortho Tri Cyclen, Ortho Novum 777- ethinyl estradiol & norgestrel 	Extended cycle COCs <ul style="list-style-type: none"> • Seasonale - ethinyl estradiol & levonorgestrel – 3 mths • Seasonique - ethinyl estradiol & levonorgestrel – 3 mths, shorter placebo period (and for PMDD) • Beyaz - ethinyl estradiol & drospirenone & folic acid • Lybrel - ethinyl estradiol & levonorgestrel – 12 mths
POP <ul style="list-style-type: none"> • Camila, Errin, Heather, Jolivette, Micronor, Nora-BE (some names include 'nor') – norgestrel 35 mcg 	

Formulation considerations:

- Breastfeeding → POP
- Clotting disorder / estrogen contraindication → POP
- Migraine with aura → POP
- Estrogenic s/e → use low estrogen formulation
- Spotting / breakthrough bleeding → if mid cycle (day 14-21) inc estrogen, if late cycle (day 21) inc progestin
- Avoiding monthly cycle → seasonale, seasonique, Lybrel
- Fluid retention/bloating → Yasmin/Yaz or Natazia , progestin compnt helps reduce water retention (mild diuretic, retains K⁺ and is CI in renal/liver failure)
- Premenstrual dysphoric disorder → Yaz or sertraline or fluoxetine (Sarafem)
- Acne → most formulations, those approved are Ortho Tri-Cyclen, Estrostep, Yaz

COUNSELING * *FDA req that the Patient Package Insert (PPI) be dispensed with oral contraceptives – they are in the product packaging.*

POP

1. All pills are active; must take exactly around the same time QD. If 3 hrs have passed, back up is needed for 48 hrs.

COCs

1. Start date:
 - a. Sunday : following onset of menses (will menstruate during the week)
 - b. 1st day of menses : if started within 5 days of menses, no backup is needed.
2. Missed 1+ pills in wk 1 → take as soon as you remember & cont same pack. Use backup for 7 days.
3. Missed 1-2 pills in wk 2 or wk 3 → take pill as soon as you remember & cont same pack. When you get to placebo pills, skip them and go straight to new pack
4. Missed 3+ pills in wk 2 or wk 3 → take pill as soon as you remember, cont the same pack. When you get to placebo pills, skip them and go straight to new pack. Use back up for 7 days.

Seasonale & Seasonique – 3 mths

1. They both have 91 pill regimen (84 active). Take pills same time QD
2. Difference is placebo week. Seasonale has 7 days placebo. Seasonique has 7 days of low dose estrogen – to dec bleeding
3. Both must be started on Sunday after period starts – even if still bleeding. If period began on Sunday, start that day
4. Use back up for 7 days

Lybrel – continuous pill w/ no monthly cycle

1. 28 day packs w/ no placebo week. Take same time QD. Must be started within 24 hrs of period
2. Hard to tell if a woman is pregnant
3. Higher discount with this than other COC due to spotting

For extended cycle formulations – missed pills → if >21 days of consecutive use, then 7 days can be missed. If >7 days, follow missed instructions for week 1

Yaz, Yasmin, Natazia

1. Popular COCs since they dec bloating, PMS symptoms, wt gain – due to progestin drospirenone (K⁺ sparing diuretic)
2. Avoid use if kidney, liver, adrenal gland disease. (Check K⁺ level on case)
3. This type of progestin can put pt at slightly higher risk of clotting. Avoid in women with clotting risk

Ortho Evra COC Patch

1. Place on skin of buttocks, stomach, upper arm, upper torso Q week x 21 out of 28 days (3 wks on, 1 wk off)
 - a. Do not apply to breast
2. If patch comes loose >24 hrs or if > 7 days have passed during 4th week, use back up for 1 week while new patch is in place.
3. Same s/e as the pill, except patch has higher systemic estrogen exposure (60% more) – higher clotting risk.
4. Less effective in women >198 lbs. do not use if smoker and >35 yo

NuvaRing

1. Inserted into vagina Q month (in place for 3 weeks, taken out for 1 week)
2. Insert ring day 1-5 of menses, exact position of ring in vagina does not matter
3. If ring is out >3 hrs during week 1, reinsert & use backup for 1 week.
 - a. If < 3 hrs during week 2-3, reinsert
 - b. If > 3 hrs week 2-3, rinse and reinsert and use backup for 7 days

EMERGENCY CONTRACEPTIVE (EC) – restart contraception the following day after last EC dose

1. The morning after pill is a form of contraception that prevents pregnancy up to 120 hrs (5 day) after sexual intercourse.
2. Higher than normal reg daily oral contraceptives can be used, but are not preferred. (5 tabs of Aviane or Alesse x 2, taken 12 hrs apart)
3. Plan B One Step – One 1.5 mg tab levonorgestrol ; Next Choice – two 0.75 mg tabs (separate by 12 hrs)
 - a. This reduces risk of preg by 89% when started within 72 hrs. (these are indicated for up to 3 days)
 - b. If pt vomits within 2 hrs of taking the pill, they should repeat the dose. Recom an OTC antiemetic if nauseated.
 - c. OTC if > 17 yo, Rx if <17 yo. It is legal to sell to men >17 yo as well . FDA approved it under the CARE program
 - d. s/e: nausea
4. Ulipristal (Ella) - Rx
 - a. Chemical cousin of misoprostol, but does not cause uterine contraction. It is used at a lower dose to delay or inhibit ovulation
 - b. Indicated for up to 5 days.
 - c. s/e: headache, nausea, abd pain

[24] PAIN

1. Pts taking opioids chronically (incl the dual mech drugs- tramadol & tapentol) will develop physiological adaptation & suffer from withdrawal symptoms (anxiety, tachycard, shakiness, SOB) if dose is missed
2. Addiction – is diff from physiological adaptation, it involves a strong desire/compulsion to take the drug & difficulties in controlling drug seeking behavior
3. Pseudo-addiction – when the pt is anxious for the drug and may use the med. up too quickly due to poor pain mngment
4. Pain severity:
 - a. mild pain – can be self treated and usually responds to APAP or NSAIDs
 - b. moderate pain – treated with combo agents (hydrocodone/APAP)
 - c. severe pain – treated with opioids

APAP

<ul style="list-style-type: none"> • Acetaminophen (APAP, Tylenol) • APAP + hydrocodone (Vicodin, Norco, Lortab) • APAP + oxycodone (Percocet, Endocet) • APAP + codeine (Tylenol #2, 3, 4) • APAP + tramadol (Ultracet) • APAP + diphenhydramine (Tylenol PM) • IV APAP (Ofirmev) is used inpt to enable lower opioid doses 	<p>325 mg (max 6), 500 mg (max 5), 650 mg ER (max 6)</p> <p><u>Children dosing:</u> 10-15 mg/kg Q4-6 (max 5 doses)</p> <p>Antidote for OD: N-acetylcysteine (NAC) – restores intracellular glutathione. Should be admin immediately. Smells like rotten eggs & causes nausea.</p>	<p>S/E: Rare (can rarely cause renal damage but safer than other agents in renal disease – but too much will cause kidney damage)</p> <p>Liver : overdose can cause liver damage. Heavy drinkers should not exceed 3g/day</p> <p><i>DOC for pain in pregnancy, warfarin</i></p>
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ASPIRIN/NSAIDS

1. COX 1 & 2 are enzymes responsible for catalyzing PGs and thromboxane from arachidonic acid.
 - a. PG inhibition : ↓ inflammation, pain impulse , prev. formation of thromboxane A2 (↓ platelet aggregation)
 - b. COX 1 inhibition - ↑ bleeding risk vs COX 2
 - c. COX 1 – plt formation, GI protection
 - d. COX 2 – pain and inflammation, fever
2. **ASA binds irreversibly to COX 1 and COX 2.**
3. **NSAIDS bind reversibly to COX 1 and COX 2**
4. **NSAID BBW :** ↑ CV risk (MI, stroke, thrombotic events) , ↑ GI adverse events (bleeding, ulceration, perforation of stomach/intestine), contraindicated for peri-op pain for CABG surgery
5. **NSAID s/e:** **upset stomach** (take with food), ↑ chance of MI/stroke, ↑ **ulcer & bleeding in stomach** (should not be used with steroids and anticoagulants), ↑ **BP**, ↑ edema, photosensitivity
6. ↑ MTX, Lithium levels

<p>Aspirin</p> <ul style="list-style-type: none"> • Bayer • Bayer “Advanced” dissolves slightly faster • Ascriptin • Bufferin (↓ stomach upset), Ecotrin • Excedrine (ASA/APAP/caffeine) <p>EC (enteric coated) & buffered products ↓ nausea</p>	<p>ALL NSAIDS - risk factors for GI bleeding:</p> <ul style="list-style-type: none"> • Elderly • Prev bleed • Chronic/HD dose • Hypoxic gut – check for dark, tarry stool, stomach upset, wkness, coffee ground emesis (more serious, fast GI bleed) <p>Highest GI risk: Ketorolac , piroxicam Lowest GI risk: celecoxib Ibuprofen (relatively low risk, less risk than naproxen)</p>	<p>S/E: dyspepsia (more with ASA but also with others), take NSAIDs with food to ↓ nausea ↑ BP, GI irritation/bleed, renal, CNS effects (fatigue, confusion, dizziness)</p> <p>ASA (salicylate) OD can be seen as tinnitus</p> <p>Contraindic: Preg C/D (avoid esp in 3rd trimester) Avoid ASA (not other NSAIDS) in children (<16 yo) with any viral infxn due to risk</p>
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ASA - primarily used for cardioprotection	Can use PPI to protect from chronic NSAID use (but consider dec bone density and inc infxn risk with PPI use)	of Reye's syndrome (s/s: sleepiness, nausea, lethargy, confusion)
Ibuprofen (Motrin, Advil)	OTC : 200-400 mg Q6-8 Rx : 600-800 mg TID	
Naproxen Na Treximet (sumatriptin /naproxen) Vimovo (naproxen /esomeprazole) – PPI to protect the gut	ALL BID OTC: Naproxen Na (Aleve) 220 mg BID Rx: Naprosyn, Anaprox	Higher GI & cardiac risk (but some prefer it bc its BID dosing) Naproxen: DO NOT use doses >440 mg/day in pts with CVD risk
Diclofenac (Cataflam, Voltaren XR) Voltaren gel Arthrotec (diclofenac + 50-200 mcg misoprostol) Flector patch (topical)	50-75 mg BID Misoprostol is used to replace the gut protective PG to reduce GI damage	Arthrotec – Preg Cat X (due to misoprostol) – diarrhea and cramping
Indomethacin (Indocin IR, CR)	Approved for gout	High risk GI tox & CNS s/e (avoid in psych condit)
Piroxicam (Feldene)	Used if failed other NSAIDS. May need PPI to protect gut	High risk GI tox & severe skin rxns (SJS/TEN)
Ketorolac (Toradol)	Always start IV or IM and cont with oral if needed 5 days total max treatment	Severe adverse effects (GI bleed/perforation, post op bleeding, acute renal, liver failure)

COX 2 Selective – lower risk for Gi complications (but still present), ↑ risk MI/stroke (avoid with CVD risk, do not use higher doses in these pts), same risk for renal complications

- ❖ **Celecoxib (Celebrex)** → OA (200 mg BID), RA (100-200 mg BID) – contraindi with sulfa allergy. Preg Cat C (<30 wks), Preg Cat D (>30 wks)

- ❖ **Meloxicam (Mobic)** – some Cox 2 selectivity, but not as high as celecoxib
- ❖ **Etodolac (Lodine)** – “ “
- ❖ **Nabumetone (Relafen)** “ “

OPIOIDS

- Opioids used in combo (eg. With APAP) – used for moderate pain. Opioids used alone are for severe pain.
- Codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone are full opioid receptor agonists.
- Opioid AUX label: cannot be refilled w/o a rx, may cause drowsiness, do not operate machinery. Do not share. *If long acting, do not crush/chew*, do not drink alcohol
- Allergy:**
 - Allergy symptoms (not just nausea) – diff breathing, severe drop in BP, serous rash, swelling of face, lips, tongue, larynx
 - if allergic to the following, do not use another:
Morphine, Codeine, Hydrocodone, Hydromorphone, Oxycodone
- Constipation:**
 - Tolerance usually develops to opioid s/e except constipation
 - Will likely require stimulant laxatives (senna, bisacodyl) , osmotic laxatives (MOM). Sometimes docusate (DSS) alone may be enough. Or may use DSS + stimulant laxative
 - Methylnatrexone (Relistor) – SC admin- is a laxative for constipation due to opioids (blocks gut opioid receptors)
 - The pt must have failed DSS + laxative (senna/bisacodyl)

<ul style="list-style-type: none"> • Morphine (long acting: MS Contin, Avinza, Kadian, Oramorph SR, Roxanol) • Morphine/Naltrexone (Embeda) <p>❖ C II</p>	<ul style="list-style-type: none"> • Avinza – NO alcohol, can shorten ER duration. Can sprinkle on applesauce • Kadian – can sprinkle on applesauce • Embeda – if drug altered (for abuse), then naltrexone an opioid blocker is released. Capsule can be sprinkled on applesauce. Injection of crushed capsule can be fatal. 2 week washout period with MAOI 	<p>S/E:</p> <ul style="list-style-type: none"> • GI (constipation, n/v) • CNS effects (sedation, dizziness, Δs in mood, confusion) • Skin rxns (flushing, pruritis, diaphoresis – may need antihistamine)
<ul style="list-style-type: none"> • Fentanyl (Duragesic) • Fentanyl- Sublimaze injection • Actiq SL lozenge • Abstral, Fentora SL pills • Onsolis SL film • Lazanda nasal spray <p>❖ CII Only use for chronic pain mngmnt</p>	<ul style="list-style-type: none"> • Patch: 12.5, 25, 50, 75, 100 mcg/h transdermal patch- ΔQ3 days (<i>may be Q2 days if it doesn't last long enough, but pain is controlled, may risk resp depression if \uparrow dose</i>) • Patch: do not apply >1 patch each time. Caution with fever - notify Dr. Apply to hairless skin (chest, back, flank, upper arm) • Dispose in toilet / cut it up 	<p>S/E: do not switch generic fentanyl, try to stay with same one Use water to remove transdermal gel, do not use soap/alcohol</p> <p>Contraindications: cannot use in opioid naïve pts</p> <p>SL forms are REMS drugs</p>
<ul style="list-style-type: none"> • Hydromorphone (Dilaudid) • Hydromorphone ER (Exalgo) – REMS drug 	<ul style="list-style-type: none"> • Exalgo - contraindicated in opioid naïve pts. & 2 wk washout period req with MAOIs <p>❖ CII</p>	
<ul style="list-style-type: none"> • Oxycodone IR (oxycodone, Oxenta) • CR (OxyContin, OxyContin OP) - REMS • Oxycodone/APAP (Endocet, Percocet, Roxicet) • Oxycodone/ibuprofen (Combunox) <p>❖ CII</p>	<p>Avoid high fat meals with higher doses</p>	<p>Boxed warning:</p> <ul style="list-style-type: none"> • Avoid use with 3A4 inhibitors <p>Oxycontin OP contains polyethylene oxide to deter abuse – substance forms gel when mixed with water.</p> <p>Oxenta – IR form that cannot be crushed into powder – contains nasal irritant</p>
<p>Oxymorphone (Opana, Opana ER, Opana inj)</p> <p>❖ CII</p>	<p>Take one empty stomach No alcohol</p>	<p>MUST use lower doses in elderly, renal or mild liver impairment</p> <p>CI in mod-severe liver dysfxn</p>
<p>Methadone (Dolophine) Liquid – Methadose</p> <p>❖ CII</p>	<p>Starting dose 2.5-10 mg Q8-12</p> <p>40 mg is indicated for detox and maintenance txt of opioid addiction – not FDA approved for pain</p>	<ul style="list-style-type: none"> • Variable T $\frac{1}{2}$ (15-55 hrs) – hard to dose safely • Risk of QT prolongation • Can \downarrow testosterone, sexual dysfxn
<p>Meperidine (Demerol)</p> <p>❖ CII</p>	<ul style="list-style-type: none"> • Short duration of action (pain control for max 3 hrs) • Avoid as agent for chronic pain mngmnt • In combo with other drugs, it is serotonergic and can raise risk of serotonin syndrome 	<p>Caution: Renal impairment elderly at risk of CNS toxicity (seizures)</p> <p><i>Normeperidine (metabolite)</i> is renally cleared and can accumulate and cause CNS tox (seizures)</p>

Opioids used in combination

<ul style="list-style-type: none"> • Hydrocodone/APAP (Lorcet, Lortab, Vicodin, Norco) • Hydrocodone/Ibuprofen (Vicoprofen) 	Hydrocodone is C II, hydrocodone/APAP/ibuprofen is C III watch for APAP max dosing.	
<ul style="list-style-type: none"> • Codeine/ APAP (Tylenol #2,3,4) ❖ Codeine-C II, Codeine/APAP-C III Used as antitussive- cough syrups are C V	Use with caution if 2D6 variants, may have inc conversion of codeine to morphine	S/E: drowsiness, high GI (constipation, nausea)
<ul style="list-style-type: none"> • Tramadol (Ultram, Ultram ER, Ryzolt – ER tabs) • Tramadol/APAP (Ultracet) ❖ Not controlled by DEA, C IV in a few states	Max 400 mg/day <i>Opioid agonist/NRTI/SSRI</i>	<ul style="list-style-type: none"> • ↑seizure threshold • Serotonin syndrome risk if used in combo with others • Dizziness, nausea, constipation, loss of appetite, flushing, insomnia (some pts find it sedating, but most do not) • Resp depression (rare) • Physiological dependence
Tapentadol (Nucynta, Nucynta ER) ❖ CII	<i>Opioid agonist/NRTI</i>	<ul style="list-style-type: none"> • Dizziness, drowsiness, nausea, but LESS GI s.e than opioids • Physiological dependence

OPIOID ANTAGONIST FOR USE IN OVERDOSE

- ❖ **Naloxone (Narcan) - opioid antagonist**
- ❖ Nalmefene (Revex)
- ❖ Morphine + naltrexone (Embeda) – designed to ↓ high from crushing morphine
 1. Will cause an **acute withdrawal rxn** (pain, anxiety, trouble breathing) in pts dependent on opioids
 2. Embeda – avoid alcohol, can cause death
 3. Naltrexone – opioid blocker normally used to treat alcoholism; the IV form (Vivitrol) is used for alcohol & opioid dependence.
 4. Acute OD s/s: **somnolence, resp depression, shallow breathing, cold and clammy skin & constricted (pin point) pupils, coma, death**
- ❖ **Buprenorphine + naloxone** (Suboxone tabs and SL film) – *buprenorphine = opioid agonist*
 1. SL film has slightly higher concn, not bioequiv to tabs
- ❖ Buprenorphine transdermal (Butrans)
- ❖ Buprenorphine (Buprenex Inj)
 1. Buprenorphine are REMS drugs. C III
 2. Suboxone: used as alternative for methadone. Used daily for addiction. **To prescribe suboxone, Dr. must have Drug Addiction Txt Act (DATA) waiver. DEA will start with an X**
 3. S/E: CNS depression (sleepiness, confusion, mental impairment)
 - a. Resp depression if OD
 - b. Buprenorphine reduces pts opioid cravings and withdrawal symptoms. Binds to the mu receptor, so blocks other opioid effects
 - c. **Prolongs QT interval**
 4. Butrans patch counseling: only for ppl with chronic pain.
 - a. Do not place in direct heat, this can lead to OD and death.
 - b. Do not cut the patch, wear 1 patch for 7 days .
 - c. Do not drink alcohol
 - d. Call ambulance if pt becomes extremely sleepy, pupils of eyes become pin point, feel faint/dizzy, breathing becomes much slower than normal.

Opioid Dose Conversions

Drug	IV/IM	PO
Morphine	10	30
Hydromorphone	1.5	7.5
Oxycodone	-	20
Hydrocodone	-	30
Fentanyl	0.1	-
Meperidine	75	300

MUSCLE RELAXANT/SPASTICITY AGENTS

1. **Carisoprodol (Soma)** – CIV (due to dependence, withdrawal, symptoms, diversion, abuse)
2. **Baclofen (Lioresal)**
3. **Cyclobenzaprine (Flexeril, Amrix ER)**
4. **Metaxalone (Skelaxin)**
5. Methocarbamol (Robaxin)
6. **Tizanidine (Zanaflex)** → abuse potential, tolerance
7. Valium (Diazepam) – CIV → abuse potential, tolerance
 - a. CNS s/e: excessive sedation, dizziness, confusion
 - b. AUX labels: may cause dizziness, do not operate machinery

NEUROPATHIC PAIN AGENTS

1. **Pregabalin (Lyrica)** C-V (produces slight euphoria)
 - a. Diabetic neuropathy, neuralgia, fibromyalgia
 - b. s/e: mild euphoria, dizziness, somnolence, edema, wt gain
2. **Duloxetine (Cymbalta)**
 - a. Neuropathy, fibromyalgia, depression, GAD
 - b. s/e: common to all SNRI - ↑BP, HR, sexual side effects (↓ libido, anorgasmia, etc), restless leg, mood changes ; spec to duloxetine (nausea, dry mouth, ↓ appetite)
3. **Gabapentin (Neurontin)**
 - a. Used off-label for neuropathic pain
 - b. s/e: somnolence, fatigue, dizziness
4. Gabapentin ER (Gralise)
 - a. A diff formulation of long acting gabapentin was released for restless leg (Horizant) taken 2 hrs prior to sleep
5. **Amitriptyline (Elavil)**
 - a. Not indicated, but clinical evidence for neuropathic pain
 - b. s/e: uncommon at low doses, but could include: **QT prolongation with OD**, orthostatic hypotn, tachycardia, **anticholinergic** – dry mouth, blurred vision, urinary retention.

FIBROMYALGIA: SNRI

1. Milnacipran (Savella)
 - a. S.E: nausea, ha, constipation, dizziness, ↑HR, BP
 - b. DI : ↑ risk of mydriasis (CI with narrow angle glaucoma)
2. **Pregabalin (Lyrica)**
3. **Duloxetine (Cymbalta)**

TOPICAL AGENTS FOR LOCALIZED PAIN

1. **Lidocaine 5% patches (Lidoderm)** – apply 12 hrs on, 12 hrs off
 - a. Approved for shingles
 - b. S/E: minor topical pain, itching, rash
 - c. Can cut into smaller pieces, do not apply >3 patches at one time
2. **Capsaicin 0.025% and 0.075% (Zostrix, Zostrix HP)**
3. Capsaicin patch (Qutenza 8%)
 - a. S/E: topical burning (dissipates with cont. use)
 - b. Qutenza – given in Dr. office, causes topical burning and req pre-txt with lidocaine (applied for 1 hr and lasts for months)
 - c. Capsaicin counseling: rub in until fully absorbed, apply 3-4x/day. If treating hands, leave on for 30 mins, then wash hands. Never cover with bandage/hot pad, serious burn can occur. (Best results after 2-4 wks)
4. Diclofenac topical (Voltaren gel, Flector patch)
5. Salonpas, etc (methyl salicylate, etc)

[25] MIGRAINE

1. Migraines are chronic headaches that cause significant pain for hours-days
2. Severe pain, nausea, vomiting, sensitivity to light and sound. Some are accompanied by sensory warning symptoms (aura) – flashes of light, blind spots, tingling in arms/legs
3. Migraine causes:
 - a. Caused by changes in trigeminal nerve and imbalance in NT (5-HT). serotonin decreases during a migraine causing VC in blood vessels. Triptans are serotonin receptor agonists that cause VC of cranial blood vessels
4. **TXT:**
 - a. Common type of migraine is a menstrual associated migraine – use hormone therapy to treat (estradiol patch or OC.)
 - b. Children get migraines- ibuprofen or triptans
 - c. Non pharmacologic txt: avoiding triggers, mental relaxation, stress management, cold compresses to head
 - d. **Pharmacologic**
 - i. Advil Migraine (ibuprofen)
 - ii. Excedrin Migraine (ASA/APAP/caffeine)
 - iii. Triptans
 - iv. Hydrocodone or opioid combos or tramadol

ACUTE TXT

- **Triptans** are commonly used. Some pts find better relief with NSAIDs or Excedrin Migraine. Others use NSAID and triptans together
 - ❖ **Sumatriptan (Imitrex)**
 - ❖ Sumatriptan Needleless inj (Sumavel DosePro)
 - ❖ **Sumatriptan SC inj (Imitrex STATdose)**
 - ❖ **Sumatriptan nasal spray (Imitrex nasal spray)**
 - ❖ Sumatriptan + naproxen (treximet)
 - ❖ **Rizatriptan (Maxalt, Maxalt-MLT)** good for n/v, dysphagia
 - ❖ **Eletriptan (Relpax)**
 - ❖ Naratriptan (Amerge)
 - ❖ Almotriptan (Axert)
 - ❖ Frovatriptan (Frova)
 - ❖ Zolmitriptan (Zomig, Zomig [ZMT](#), Zomig NS) good for n/v, dysphagia

Common Migraine Triggers

1. Hormonal Δ 's in women – fluctuations in estrogen trigger HA. Some women will use monophasic BC to keep estrogen levels constant. For women with migraines, ACOG recom POP pills
 2. Foods- esp alcohol (beer, wine), aged cheeses, chocolate, overuse of caffeine, MSG, salty foods
 3. Stress
 4. Sensory stimuli – bright lights, sun flare, loud sound
 5. Δ 's in wake- sleep pattern (too much/little sleep)
 6. Δ 's in environment – water/barometric pressure
- e. **PPX:** if a pt has >1 migraine/mth or if want ppx :
 - i. To dec migraine freq: antidepressants, anticonvulsants, vitamins, natural products
 - ii. Try agent at reasonable dose for 2-6 mths. Ppx agents can \downarrow freq by 50%, just need to find right one
 - iii. Natural Products = Feverfew, willow bark (a salicylate), butterbur, guarana (a caffeine product), fish oils, Mg, Coenzyme 10, riboflavin

1. MOA: 5HT₁ agonists. Causes VC, inhibit neuropeptide release, and dec pain transmission
2. S/E: somnolence, nausea, paresthesias, dizziness. **Triptan sensations** (pressure in chest/heaviness or pressure in neck region)
3. CI: rare cerebrovascular and CV events can occur \therefore are CI in pts with cerebrovascular disease or uncontrolled HTN
4. DOA: **longest acting, slower onset** = frovatriptan & naratriptan
Shorter acting, fast onset = almotriptan, eletriptan, rizatriptan, sumatriptan, zolmitriptan.
5. DI: FDA warning about combining triptans w. serotonergic drugs (report restlessness, sweating, confusion, hallucinations)

OTC MIGRAINE AGENTS

- ❖ Advil Migraine (Ibuprofen)
- ❖ Excedrin Migraine (APAP/ASA/caffeine)
- ❖ ASA is not an option due to nausea

LESS COMMONLY USED MEDICATIONS:

- ❖ **APAP/Butalbital/Caffeine (Fioricet) C III** also comes as (Fioricet with codeine)
 - Contains a barbiturate- if using regular and long term, must taper pt off or else will get worsening HA, tremors, delirium, seizures

MIGRAINE PROPHYLAXIS

1. 1st line:

- ❖ **Propranolol (Inderal)** → DOC if s.e are tolerated: fatigue, ↓ HR, possible depression since its most lipophilic
non selective BB – do not use in COPD/asthma
- ❖ **Timolol (Blocadren)** → non selective BB – do not use in COPD/asthma
- ❖ **Amitriptyline (Elavil)** → dry mouth, sedation, constipation, urinary retention, blurry vision, wt gain, QT prolong.
- ❖ **Divalproex (Depakote)** → avoid in women of child bearing age (teratogenic), liver tox, pancreatitis, sedation, wt gain
- ❖ **Sodium valproate**
- ❖ **Topiramate (Topamax)** → nephrolithiasis, open angle glauc, depression, wt loss

- ❖ ASA/Butalbital/Caffeine (Fiorinal) **C III** also comes as (Fiorinal with codeine)
 - If using codeine, counsel on nausea, constipation
- ❖ Butorphanol (Stadol NS) **C IV** intranasal spray. Onset is 15 mins

Ergotamine products: **Preg Cat X. BBW** : *do not use with strong/med 3A4 inhibitors*

- ❖ Ergoloid mesylates (Ergomar, Ergostat)
- ❖ Ergotamine/caffeine (Cafergot)
- ❖ Dihydroergotamine (DHE-45, Migranal NS)
 - S/E: n/v, muscle pain, tingling pain, wkness in legs, tachy, bradycardia

2. 2nd line:

- ❖ Other BB
- ❖ ACEi
- ❖ Antidepressants
- ❖ Natural products
- ❖ BC pills (for premen migraines)
- ❖ Botulinum toxin A (Botox inj)

[26] RHEUMATOID ARTHRITIS (RA) & SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

RHEUMATOID ARTHRITIS (RA)

[25]

1. An autoimmune disease that causes chronic inflammation of joints & other organs (kidneys, eyes, heart, lungs)
[Osteoarthritis (OA) is the most common joint disorder, which is due to aging and wear and tear on a joint.]
2. Typically presents first in hands and feet. The inflammation (caused by macrophages, cytotoxins, & free radicals)
3. **Clinical presentation:** morning fatigue, fever, wkness, loss of appetite, joint & muscle pain
 - a. Any synovial joint can be involved, but the finger joints are most often affected. Wrist, knees, toe joints are also freq involved
4. TXT:
 - a. Non pharmacological: rest, physical therapy, occupational therapy, exercise, diet, wt control, possible surgical intervention (joint replacement)
 - b. **Goal: DMARD within 3 mths of dx.** Pts may req bridging therapy or in some cases long term use of NSAIDS/Steroids
 - c. Milder symptoms – old standard non-biological DMARD (Methotrexate, hydroxychloroquine, sulfasalazine) - can also be used in combo
 - d. Severe disease – newer biological DMARDS (etanercept, adalimumab, infliximab) - can also be used w/ MTX

Diagnosis – criteria 1-4 must be present for ≥ 6 wks. 4 or more criteria must be present

1. Morning stiffness around joints >1 hr
2. Soft tissue swelling (arthritis) in >3 joints
3. Swelling of hand, foot, or wrist joints
4. Symmetric involvement
5. SC nodules
6. (+) serum rheumatoid factor (70% of pts)
7. Radiographic erosions/periarticular osteopenia in hand/wrist joints

AGENTS USED FOR PAIN & INFLAMMATION

1. NSAIDS – **Ibuprofen (Advil, Motrin)**, etc
 - a. OTC (200-400 Q6-8) for mild-moderate pain
 - b. RX (600-800 TID) for moderate pain/inflammation.
 - c. BBW: see pain section – CV, GI. Pregnancy
2. Cox 2 inhibitors – **Celecoxib (Celebrex)**
 - a. Lower GI risk but higher MI/stroke risk
 - b. CI with sulfa allergy, same BBW as NSAIDS
3. Steroids – **Prednisone (Dfdrieltasone)**
 - a. Initial dose 5-60 mg QD (some use alt day therapy to dec adrenal suppression)
 - b. Indicated for acute infl/pain. If used long term, assess bone density & consider bisphosphonate, Vit D & Ca
 - c. If used longer >2 wks, must taper to avoid withdrawal symptoms
 - d. S/E: **short term-** fluid retention, stomach upset, emotional instability (euphoria, mood swings, irritability), inc appetite, wt gain, hyperglycemia, HTN
Long term – adrenal sup/cushings, impaired wound healing, HTN, hyperglycemia, cataracts, osteoporosis (if taking >7.5 mg for >3 mths, will lose 8% of bone density) hypokalemia, growth sup in children, muscle wasting, dermal thinning, bruising, menstrual irreg.

NON-BIOLOGICAL DISEASE MODIFYING ANTI-RHEUMATIC DRUGS (DMARDS)

Methotrexate (Rheumatrex) <i>Gold standard for RA, well tolerated in many pts</i>	7.5-22 mg/wk Low WEEKLY dose for RA (never dosed QD for RA) S/E: n/v/d/GI upset – take with food. Anorexia, reddening of skin, ↓ plt Contraindic: Pregnancy (Cat X) , chronic liver disease, blood dyscrasias	BBW: <ul style="list-style-type: none"> Fetal death/congenital abnormalities Hepatotoxicity Bone marrow suppression Malignant lymphomas Fatal dermatologic rxns Renal damage (w/ high doses)
Hydroxychloroquine (Plaquenil)	<i>[corneal deposits – amiodarone also causes this, it can also cause hyper/hypothyroidism, mainly hypo]</i>	S/E: ↓ visual acuity, photophobia, blurred vision, corneal deposits (can see white spots), n/v, rashes, alopecia, ↓ plts Monitoring: eye exam within 1 st yr of txt
Sulfasalazine (Azulfidine, Azulfidine EN, Sulfazine, Sulfazine EC)	Take with food and water to prevent crystalluria Impairs folate abs. may give 1 mg/day folate suppl.	Contradinc: sulfa or salicylate allergy Monitoring: can cause yellow-orange coloration of skin/urine Met. to sulfapyridine and 5-ASA
Minocycline (Minocin)		S/E: ↑ LFTs, photosensitivity Monitoring: do not use in pregnancy or children <8 yo
Leflunomide (Arava) Can use +/- MTX	<ul style="list-style-type: none"> Must have preg test before starting med and use 2 forms of BC Must wait 2 yrs after cessation of drug to get pregnant <i>[Isotretinoin, MTX, Leflunomide → req 2 forms of BC (estrogen/pill + another form ; cannot use POP due to strict schedule of 3 hrs)]</i>	BBW: women of child bearing age should not receive leflunomide until preg excluded S/E: hepatotox, URI, alopecia CI : Pregnancy (Cat X)

BIOLOGIC DMARDS

Etanercept (Enbrel, Enbrel Sureclick autoinjector) <i>Usually 1st line for biologics</i>	<ul style="list-style-type: none"> TNFα inhibitor SC Q week <i>-give Med Guide with new rx & refills</i>	BBW: serious infxn and malignancies (lymphoma) S/E: infxn, injection site rxn CI: sepsis (severe infxn)
Adalimumab (Humira, Humira pen) <i>Usually 1st line for biologics</i>	<ul style="list-style-type: none"> TNFα inhibitor SC QOD	Monitoring: signs of infxn, WBC, s/s HF, LFTs
Infliximab (Remicade) –given with MTX	<ul style="list-style-type: none"> TNFα inhibitor IV week 0,2,6, Q8 wks <u>Must be given in Dr. office</u> due to infusion rxn : hypotn, fever, chills, pruritus Delayed hypersen rxn 3-10 days after admin – fever, rash, myalgia, HA	Usually, MTX is used 1 st line, then these agents are add on. <ul style="list-style-type: none"> Never use combo biologics. Do not use live vaccines <i>ALL req. TB test before use & annually –can activate latent TB</i>
Rituximab (Rituxan) – given with MTX	<ul style="list-style-type: none"> Anti- CD 20- mab Need to premedicate with steroid	BBW: infusion related rxns <ul style="list-style-type: none"> Progressive multifocal leukoencephalopathy (PML) Tumor lysis syndrome – leading to acute renal failure Fatal mucocutaneous rxns (SJS, TEN)

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

1. A systemic autoimmune disease that can affect any part of the body, has periods of illness (flares) and periods of remission. Hallmark of SLE = dev of auto antibodies by B cells to cellular components
2. Often affects the heart, joints, lungs, skin, BV, liver, kidney, nervous system. – particularly in women age 15-45 yo
3. Clinical presentation: fatigue, fever, anorexia, wt loss, muscle aches, **butterfly rash (>50% of SLE pts)**, photosensitivity, lupus nephritis (>50% SLE pts)
4. Txt:
 - a. **Non-pharmacologic:** rest & proper exercise (managing fatigue), smoking cessation (smoking can be a trigger for the disease), sunscreens (photosensitivity)
 - b. **Drug therapy:** IS, cytotoxic drugs, antiinflam.
 - c. Goal of therapy: to suppress immune system to prevent flares

Drug induced Lupus:

1. **Procainamide**
2. **Hydralazine**
3. **Isoniazide**
4. **Quinidine**
5. **Chlorpromazine**
6. **Methyldopa**
7. **Minocycline**

AGENTS USED IN LUPUS:

1. **Antimalarial agents**
 - a. Hydroxychloroquine (Plaquenil) – the safer option. Both take 6 mths to see maximal effect
 - b. Chloroquine
2. **Corticosteroids**
 - a. Prednisone (or methylprednisolone IV if life threatening)
 - b. Used acutely to control flares at higher doses. Taper to lower doses for chronic suppressive therapy
3. **Cytotoxic agents** – used in severe disease
 - a. Cyclophosphamide
 - i. Bone marrow sup, infxn, hemorrhagic cystitis, teratogenesis
 - b. Azathioprine
 - i. Bone marrow sup, infxn, malignancy, hepatotox
 - c. Mycophenolate mofetil (Cellcept)
 - i. BM sup, hepatotox, malign, n/v
4. **Biologics**
 - a. Belimumab (Benlysta) – higher risk of infxn, depression, anaphylaxis, infusion rxn (premedicate)
5. Can rarely cause lung problems/infxn (pneumocystitis carinii pneumonia), skin rxns, diarrhea, mouth sores (ulcerative stomatitis)

METHOTREXATE

1. Pts receiving MTX **for RA or psoriasis – dosage is usually Q WEEK, NOT QD** (pts may be told to divide Qweek dose in half and take it 2x / week)
2. MTX has birth defects and death in unborn babies (Cat X). do not use if breastfeeding
3. If you have kidney problems or excess body water (ascites, pleural effusion) – closely monitor
4. Liver needs to be tested on a regular basis
5. Can rarely cause severe bone marrow suppression & stomach disease (bleeding) when used at the same time as NSAIDs – NSAIDs should not be used with high dose MTX
 - a. If using low dose ASA (81-325) for cardioprotection, continue unless otherwise told

ETANERCEPT

1. Give MedGuide with new RX and Refills
2. **DO not get live vaccines.**
3. **May lower ability to fight infxns. Get tested for TB before starting therapy and annually (acti latent)**
4. **Can cause liver damage** – watch for s.s : tired, skin or eyes look yellow, poor appetite, vomiting, pain on side of stomach
5. Can worsen CHF, cause URI
6. Can cause inj site rxns – symp go away in 3-5 days
7. **SC injection under skin** if thigh, abdomen, upper arm once or weekly
8. **Store med in refrigerator. Let warm to RT before injecting**

[27] Gout

1. Disease that presents with recurrent attacks of acute inflam. arthritis. Typically it occurs in 1 joint, the metatarsophalangeal (big toe).
2. Causes: Uric acid is an end product of purine metabolism. Under normal cond. Uric acid is excreted 2/3 renally, 1/3 by GI tract. When uric acid builds up, the pt may 1) remain asymptomatic – not treated 2) have severe, painful gout attacks
3. **Risk factors:** male, over weight (2-3x ↑ risk), excessive alcohol consumption (esp. beer), HTN, renal insuff, adv age, meds. Total protein intake is not assoc with ↑ uric acid levels (studies show)
4. Lab: normal uric acid (**2 - 7.2**) ; if a case has elevated uric acid levels, but does not state that a gout attack has occurred- DO NOT treat.
5. Txt/ppx
 - a. Drugs used to treat acute attack: colchicine, NSAIDs, steroids
 - b. Ppx: allopurinol, oxypurinol, febuxostat

Drugs that ↑ Uric Acid

1. Diuretics (Loops, thiazides)
2. Niacin
3. ASA
4. CSA
5. Ethambutol
6. Levodopa
7. Pyrazinamide

ACUTE GOUT ATTACK TREATMENT

❖ Colchicine (Colcris)

- ❖ Colchicine + probenecid (Colbenemid)
 - a. **Dosing:** 1.2 mg PO (0.6 mg x2) followed by 0.6 mg (1 tab) 1 hr after [do not exceed 3 doses]
Wait until 3 days before initiating another course
Do not take 2nd dose if have stomach upset, n/d
 - b. **S/E:** n/v, abd pain, diarrhea (80%)
rare = myelosupp, neuromyopathy, death
 - c. **DI:** substrate of 3A4 & PGP – fatal toxicity if combined with strong 3A4 inhibitors & PGP inh (eg. CSA)
 - d. Myopathy & rhabdo have occurred with use with statin/fibrate – try not to use gemfibrozil

❖ Indomethacin (Indocin)

- ❖ Naproxen (Naprosyn)
- ❖ Sulindac (Clinoril)
- ❖ Celecoxib (Celebrex) – used but not FDA approved
 - a. All NSAIDS cause nausea – take with food
 - b. Avoid in renal disease (uric acid is renally cleared and gout pts may have renal insuff.)
 - c. Indomethacin was 1st NSAID approved & is DOC. – but it is more toxic than ibuprofen (↑ GI tox) and has psychiatric s/e (confusion, depression, psychosis)
- ❖ Prednisone (PO)
- ❖ Methylprednisolone (Solu-Medrol) – intra-articular inj
- ❖ Triamcinolone – intra-articular inj
 - d. Prednisone PO – taper is not req. if txt is short term (5-7 days)
 - e. Methylpred, triam – intra-articular inject → systemic s.e unlikely
 - f. **s/e:** acute steroid use : ↑ BP, BG, ↑ appetite, nervousness, insomnia, edema

GOUT PPX

Xanthine Oxidase inhibitors – blocks uric acid production

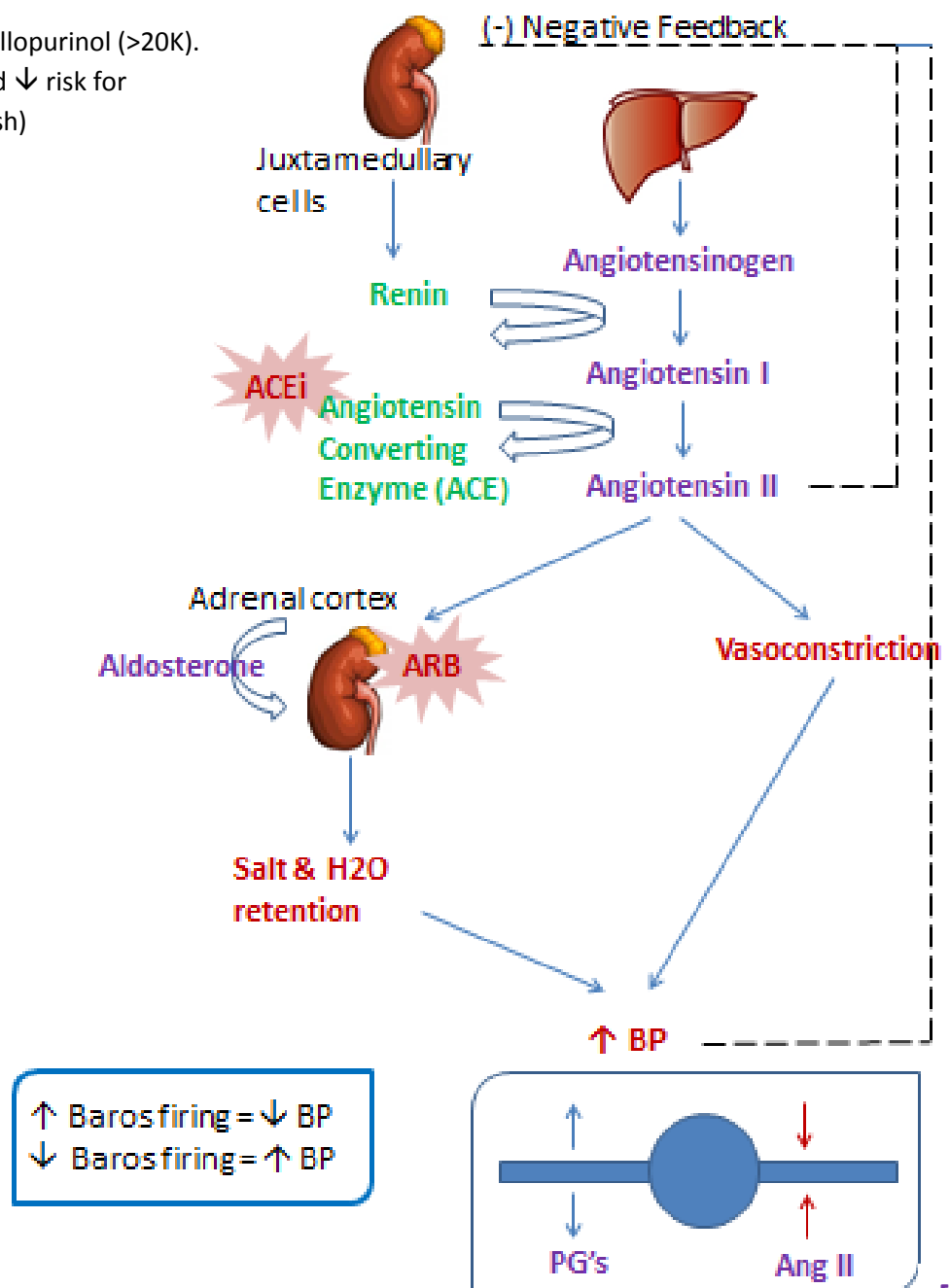
- ❖ **Allopurinol (Zyloprim)** – 50-200 mg QD (ppx for hyperuricemia due to cancer drugs is at higher doses & can be divided)
 - **S/E:** precipitate acute attacks, nausea, skin rash (skin rash may seem benign, but can be serious – SJS, TEN)
 - Take QD *with meals* (for stomach upset). Takes several wks to work. Pt may experience more gout attacks for several mths after starting. Notify dr. if get a rash.
- ❖ Febuxostat (Uloric) – for resistant cases & in renal disease
 - Much more expensive than allopurinol (>20K). safer in renal impairment and ↓ risk for hypersensitivity rxns (skin rash)

Uricosuric- inh. reabs of uric acid at PCT

- ❖ Probenecid
 - May dec renal clearance of other meds (ASA, MTX, theophylline, PCN)
- ❖ Sulfipyrazone
 - Req adequate renal fxn. Not commonly used.

Uricase- breaks down uric acid

- ❖ Pegloticase (Krystexxa) – IV med
 - For resistant cases only, costly
 - **S/E:** risk severe infusion rxns (give in medical setting only) . Can precipitate an attack.



[28] HYPERTENSION

1. Types of HTN:

- Essential HTN – not known to be caused by an identifiable factor
- Secondary HTN – linked to a specific cause (renal/adrenal disease, drug induced)

2. **Drug induced HTN** – corticosteroids, excessive alcohol (>1-2 drinks/day), NSAIDs, ACTH, amphetamines, appetite suppressants, caffeine, CSA, erythropoietin, estrogen (eg: BC with higher doses), oral decongestants (pseudoephedrine), thyroid hormone (if too much), duloxetine & venlafaxine (at higher doses), chemo drugs (bevacizumab-Avastin, sorafenib-Nexavar)

3. Classification of BP

- (Normal) <120/80
- (Pre-HTN) 120-139 / 80-90
- (Stage 1) 140-159 / 90-99 → consider thiazide. May consider ACEi/ARB, BB, CCB, combo
- (Stage 2) ≥ 160 / ≥ 100 → start with 2 drug combo (usually thiazide + ACEi, ARB, BB, or CCB)
- BB are not generally 1st line for CAD prevention

4. Lifestyle modification:

- DASH diet – high in fruits & veg. low fat dairy with red. Saturated and total fat
- Reduce Na⁺ - healthy adults should be ≤ 2.4 g/day. If hypertensive, <1.5 g/day
- Alcohol – 1 drink/day (women) 2 drinks/day (men)

DIURETICS - *Diuretics* ↓ *Li clearance, high risk of Li toxicity- should avoid use.*

- Counseling: may make you feel dizzy & lightheaded when getting up from a sitting/lying position. K⁺ suppl. may be needed. Will cause you to urinate more throughout the day.

Thiazides – inhibit Na reabsorp at distal tubules. Also

↑ excretion of K and H⁺

- ❖ Chlorothiazide (Diuril)
- ❖ Chlorthalidone (Thalitone)
- ❖ **Hydrochlorothiazide** (Microzide-cap, Oretic, Esidrix)
- ❖ Indapamide (Lozol)
- ❖ Metolazone (Zaroxolyn)
- ❖ Methylclothiazide

- S/E:** HYPO K⁺, Na⁺, Mg, HYPER Ca⁺, ↑UA, elevated lipids, ↑BG, photosensitivity, rash
- Contraindications:** hypersens to sulfonamide drugs. Sulfa Allergy – may not cross react, but 1st dose should be given under supervision
- May not be as effective if CrCL < 30, except metolazone may work in pts with reduced renal fxn

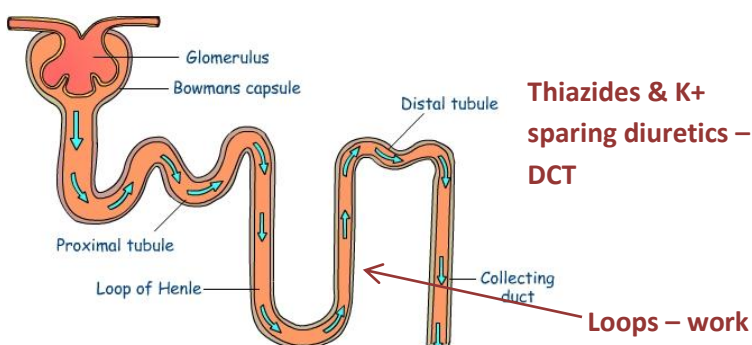
Loop diuretics – inhibit reabs of Na & Cl⁻ from the

ascending loop of Henle & distal renal tubule. Causes ↑ excretion of water, Na, Cl⁻, Mg, Ca

Used more for edema, occasionally for BP if ↓ renal fxn

- ❖ **Furosemide (Lasix)** - oral loop equiv = 40 mg
- ❖ Bumetanide (Bumex) - oral loop equiv = 1 mg
- ❖ Torsemide (Demadex) - oral loop equiv = 20 mg
- ❖ Ethacrynic Acid (Edecrin)

- S/E:** HYPO K⁺, Na, Mg, Cl, Ca, ↑ UA, BG, orthostatic hypotn, metabolic alkalosis, photosensitivity, ototoxicity (MORE with ethacrynic acid)
[loops can inc ototox potential of aminoglycosides; Do not use ethacrynic acid with other loops due to ↑ ototox]
- Contraindications:** caution in pts with sulfa allergy (except ethacrynic acid)
- Monitoring:** renal fxn, fluid status, BP, electrolytes, hearing with high doses/ rapid IV admin (IV admin is light sensitive-use amber bottle)



K⁺ sparing Diuretics /Aldosterone receptor Antagonists – compete w/ Aldosterone for receptor sites in distal renal tubules. ↑ excretion of Na, Cl, water (conserves K⁺ and H⁺)

- ❖ Amiloride (Midamor)
- ❖ Triamterene (Dyrenium)
- ❖ **Triamterene + HCTZ (Maxzide, Dyazide)**
- ❖ **Spironolactone (Aldactone)** – *non selective aldo antag (also blocks androgen & progesterone receptors)*
- ❖ Eplerenone (Inspra) – *selective aldo antag*

1. BBW: spironolactone – tumor risk. Amiloride & triamterene – hyperkalemia, potentially fatal.
2. S/E: **HYPER K⁺, ↑Cr** . For Spironolactone = gynecomastia, breast tenderness, impotence, hyperchloremic met. acidosis
3. Contraindications: **Anuria, K > 5.5, SCr >2.5 CrCl <30**

RAAS Inhibitors

- All RAAS inhibitors ↓ vasoconstriction, ↓ aldosterone release & benefit renal protection & HF.
- *Angioedema is more common in black pts.* It is more likely caused by ACEi/ARBs & if a pt had angioedema with either class of agents, all others are contraindicated. Report s/s of : swelling of lips, mouth, tongue, or neck

ARBs – block Ang II from binding to AT1 receptor on vascular smooth muscle

- ❖ **Valsartan (Diovan)**
 - ❖ **Losartan (Cozaar)**
 - ❖ **Irbesartan (Avapro)**
 - ❖ **Candesartan (Atacand)**
 - ❖ **Olmesartann (Benicar)**
 - ❖ **Telmisartan (Micardis)**
 - ❖ Eprosartan (Teveten)
 - ❖ Azilsartan (Edarbi)
1. **BBW:** can cause injury & death to developing fetus. d/c when preg is detected. Preg Cat C (1st trim), D (2,3rd trim) . Valsartan is Preg D.
 2. **S/E:** HyperK⁺, angioedema, hypotn, headache, dizziness
 3. **CI:** angioedema & bilateral artery stenosis

Renin Inhibitor – directly inhibits renin (resp for conversion of angiotensinogen to ang I)

- ❖ **Aliskiren (Tekturna)**
1. Avoid high fat foods. +/- food
 2. BBW: can cause injury & death to developing fetus. d/c when preg is detected. Preg Cat C (1st trim), D (2,3rd trim)
 3. S/E: HyperK⁺, angioedema, hypotn.
 4. CI: angioedema & bilateral artery stenosis
 5. **DI:** aliskiren is a 3A4 substrate. Atorvastatin ↑aliskiren levels. Aliskiren ↓ furosemide levels

ACEi – inhibits ACE from converting Ang I to Ang II (a potent VC) ✓Preload ✓Afterload

- ❖ **Benazepril (Lotensin)**
 - ❖ Captopril (Capoten) – **take 1 hr before meals, TID**
 - ❖ **Enalapril, Enalaprilat IV inj (Vasotec)**
 - ❖ Fosinopril (Monopril)
 - ❖ **Lisinopril (Prinivil, Zestril)**
 - ❖ **Quinapril (Accupril)**
 - ❖ **Ramipril (Altace)**
 - ❖ Moexipril (Univasc)
 - ❖ Perindopril (Aceon)
 - ❖ Trandolapril (Mavik)
1. **BBW:** can cause injury & death to developing fetus. d/c when preg is detected. Preg Cat C (1st trim), D (2,3rd trim)
 2. **S/E:** Cough, HyperK⁺, angioedema, hypotn.
Captopril has more SEs (taste perversion, rash)
 3. **CI:** angioedema & bilateral artery stenosis

Beta Blockers

- BB can cover up symptoms of hypoglycemia (shakiness, anxiety) but not sweating/hunger – mainly occurs in non-selective agents
- BB can enhance the effects of insulin & oral hypoglycemic (sulfonylureas)
- Use with caution with other drugs that slow HR (digoxin)

β -1 selective blockers (AMEBBA – atenolol, metoprolol, esmolol, bisoprolol, betaxolol, acebutolol)

- ❖ Acebutolol (Sectral) –ISA (*B1 selec, B2 at high doses*)
- ❖ **Atenolol (Tenormin)**
- ❖ Betaxolol (Kerlone)
- ❖ Bisoprolol (Zebeta)
- ❖ **Metoprolol tartrate (Lopressor)**
- ❖ **Metoprolol succinate (Lopressor XL, Toprol XL)**

1. S/E : \downarrow HR, hypotn, fatigue, dizziness. Less common – depression, \downarrow libido (*1° for propranolol but any can cause it*)
2. CI: severe bradycardia, 2nd or 3rd degree heart block
3. Caution in those with DM who have recurrent hypoglycemia, asthma, COPD

β -1 selective blocker & Nitric Oxide

- ❖ **Nebivolol (Bystolic)**

1. S/E: HA, fatigue, dizziness, diarrhea, nausea ; Nitric oxide causes peripheral VD

β -1, β -2 blockers ; ISA =(CAPP – acebutolol, carteolol, penbutolol, pindolol)- these do not \downarrow HR as much as others

- ❖ **Propranolol (Inderal LA, InnoPran XL)**
- ❖ Carteolol (Cartrol)
- ❖ Nadolol (Levatol)
- ❖ Penbutolol (Levatol)
- ❖ Pinodolol (Visken)
- ❖ Timolol (Blocadren)

Non selective α & β blockers

- ❖ **Carvedilol (Coreg, Coreg CR)** →take with food
 - ❖ **Labetalol (Trandate, Normodyne)** 200 – 2400 mg/d
1. S/E: same as above. Preg Cat C

CCB

- Covera HS, Adalat CC, Sular – have capsular shells that can be seen in feces
- Clevidipine – (for inpt DPH CCB) CI in soy/egg allergy
- **Dihydropyridines (amlodipine, nifedipine)**
 1. 1° used for HTN, angina
 2. Cause VD, which can lead to reflex tachy, HA, flushing, periph edema

DHP – CCB → inhibits Ca from entering the ‘slow’ channels (voltage sensitive areas of vascular SM), resulting in peripheral VD and \downarrow periph vascular resistance

- ❖ **Amlodipine (Norvasc)**
 - ❖ **Felodipine (Plendil)**
 - ❖ **Nifedipine IR (Procardia) , ER (Adalact CC, Procardia XL, Afeditab CR)**
 - ❖ Nisoldipine ER (Sular)
 - ❖ Nicardipine IR (Cardene- TID), ER (Cardene SR)
1. S/E: **Peripheral edema**, reflex tachy, HA, flushing
 2. Do not use SL nifedipine, may inc risk of MI

- **Non dihydropyridines (diltiazem, verapamil)**

1. 1° used for arrhythmias to control/slow HR, sometimes HTN, angina
2. Negative inotropes (\downarrow contraction force)
3. Negative chronotropes (\downarrow HR)
4. Diltiazem & verapamil are 3A4 Inhibitors & substrates
5. S/E: \downarrow HR, constipation (esp verapamil), gingival hyperplasia

Non DHP – CCB → inhibits Ca from entering the ‘slow’ channels (voltage sensitive areas of vascular SM) & **myocardium**, result in coronary VD

- ❖ **Diltiazem** (Cardizem, Dilacor, Dilt-CD, Cartia, Tiazac, Taztia)
 - ❖ **Verapamil** (Calan and SR, Isoptin SR, Verelan PM, Covera HS)
1. S/E: edema, AV block, bradycardia, hypotn, arrhythmias, HF, HA, constipation (more with verapamil), gingival hyperplasia

Centrally Acting α_2 Adrenergic Agonists

- Clonidine is commonly used for resistant HTN & in pts who cannot swallow (dysphagia, dementia) since it comes as a patch. Δ ed Qweek, so good for adherence
 - Sometimes it's used off label to treat opioid withdrawal to block nervousness, anxiety, help with sleep
 - Do not stop abruptly, it will cause withdrawal syndrome (high BP, anxiety, H, tremors) – taper over 2-5d

Centrally acting α_2 Agonists → stimulates α_2 in brain which results in reduced sympathetic outflow from CNS

- ❖ **Clonidine (Catapres, Catapres TTS patch, Duraclon** Inj, Clonidine ER susp)
 - ❖ Guanfacine (Tenex)
 - ❖ Methyldopa (Aldomet)
1. S/E: bradycardia, dry mouth, drowsiness, fatigue, lethargy, depression, psychotic rxns, nasal stuffiness, impotence, & exacerbation of Parkinson's. skin irritation with patch
 2. Methyldopa – above s/e + hypersensitivity rxns, hepatitis, myocarditis, hemolytic anemia, post coombs test, lupus like syndrome.
 3. Rebound HTN if stopped abruptly.

Direct vasodilators – VD of arterioles w/ little effect on veins

❖ **Hydralazine (Apresoline)** ✓ *Afterload*

1. S/E: **Lupus like syndrome** (report fever, joint/muscle ache, fatigue), reflex tachy

❖ Minoxidil

1. S/E: fluid retention, tachycardia, aggravation of angina, pericardial effusion, hirsutism (used for hair growth - Rogaine)

α Blockers – binds to α_1 which results in VD of arterioles & veins. Used mostly for BPH. Not 1st line for HTN

❖ Prazosin (Minipress)

❖ **Terazosin (Hytrin)**

❖ **Doxazosin (Cardura)**

1. S/E: orthostatic hypotn, syncope with 1st dose, dizziness, fatigue
2. Caution w. concurrent use with PDE5 inh (additive effect on BP, dizziness)

Combo Drugs

Lotrel	Amlodipine + benazepril	Micardis HCT	Telmisartan + HCTZ
Exforge	Amlodipine + valsartan	Diovan HCT	Valsartan + HCTZ
Azor	Amlodipine + olmesartan	Benicar HCT	Olmesartan + HCTZ
Lotensin HCT	Benazepril + HCTZ	Tenoretic	Atenolol + chlorthalidone
Prinzide, Zestoretic	Lisinopril + HCTZ	Ziac	Bisoprolol + HCTZ
Avalide	Irbesartan + HCTZ	Dyazide, maxzide	Triamterene + HCTZ
Hyzaar	Losartan + HCTZ		

Hypertensive Urgency

- BP > 185/ 110 w.o acute organ damage
- Txt: PO meds
 - Captopril (Capoten) – hypotn, \uparrow K, angioedema (shortest T $\frac{1}{2}$ acei)
 - Clonidine (Catapres) – hypotn, drowsiness, sedation, dry mouth
 - Labetolol (Normodyne, Trandate) – hypotn, heart block, bronchoconstriction
 - Do **not** use nifedipine SL!

Hypertensive Emergency

- BP > 185 / 110 **with** organ damage (encephalopathy, MI, unstable angina, PE, eclampsia, stroke, aortic dissection)
- Txt: IV meds
 - Clevidipine (Cleviprex)
 - Nitroprusside (Nipride)
 - Nicardipine (Cardene)
 - Fenolopam (Corlopam)
 - NTG – IV will absorb into plastic, keep in glass bottles and do not use tubing.
 - Enalaprilat (Vasotec IV)
 - Hydralazine
 - Labetalol, Esmolol

[29] DYSLIPIDEMIA

1. Targeting different lipids:
 - a. LDL → Statins (most effective)
 - b. HDL → Niacin (rx strength), Fenofibrates
 - c. TG → Fenofibrates or Lovaza (omega-3 fish oils)
2. May drug classes for cholesterol are potentially hepatotoxic (statins, niacin, potentially fibrates & ezetimibe)

3. Natural Products

- a. Red yeast rice : produce of yeast grown on rice that contains naturally occurring HMG-CoA reductase inhibitors, avail in capsules – myopathy & myalgias have been reported
- b. Garlic – very small benefit on cholesterol
- c. Fish oils (to ↓ TG) & plant sterols may provide addt benefit

LDL = CH – HDL – (TG/5)

CHD risk equiv: 1)DM 2) PAD, CAD 3) Abd aortic aneurysm 4) FH risk >20%

Statins – inhibit HMG-CoA reductase (an enzyme converting HMG-CoA to mevalonate – the rate limiting step in chol prod.)

☀ = take at bedtime

- ❖ **Atorvastatin (Lipitor)** → equiv dose = 10 mg
- ❖ Atorvastatin + amlodipine (Caduet)
- ❖ **Simvastatin (Zocor)** ☀ → equiv dose = 20 mg
- ❖ **Simvastatin + ezetimibe (Vytorin)**
- ❖ **Rosuvastatin (Crestor)** → equiv dose = 5 mg
- ❖ **Pravastatin (Pravachol)** → equiv dose = 40 mg
- ❖ **Lovastatin** (Mevacor (IR) –with dinner, Altoprev (ER) ☀) → equiv dose = 40 mg
- ❖ Fluvastatin (Lescol, Lescol XL) ☀ → equiv dose = 80 mg
- ❖ Pitavastatin (Livalo) → equiv dose = 2 mg
 - Most potent statin. CI with CSA

Statin potency: F-PL-SARP (low → high)

“families play SARP”

Fluva – Prava – Lova – Simva – Atorva – Rosuva - Pita
80 mg 40mg 40 mg 20 mg 10 mg 5 mg 2mg

1. **S/E:** myalgias, arthalgias, myopathy, rhabdo, ↑ LFTs
2. **Monitoring:** LFT at baseline and at 3 mths; notify Dr. of s/s of liver damage
3. **Renal:** use lower doses if CrCl <30, except with Lescol & Lipitor
4. Preg Cat X
5. **Can take at any time:** PLLS- **Pravachol, Lipitor, Livalo, Crestor**
6. Simvastatin & lovastatin – undergo extensive 1st pass met via 3A4. Atorvastatin undergoes less 1st pass.
7. Inc risk of muscle damage with amiodarone & other 3A4 inh (azoles, grapefruit, CSA, diltiazem, verapamil, macrolide, protease inh)
8. Rosuvastatin – may ↑ INR. CSA may ↑ rosuvastatin (DNE 5 mg rosuva). Gemfibrozil combo should be avoided (DNE 10 mg rosuva)

Ezetimibe (Zetia) + simvastatin (Vytorin) – intestinal chol. Absorption inhibitor

1. Used alone or in combo w. statin or fenofibrate for addt ↓ LDL
2. **S/E:** well tolerated, may cause URI, diarrhea, arthralgias, myalgias, pain in extremities
3. **DI:** no contraindications; when Ezetimibe + CSA, both concn can ↑. Concomitant bile acid resins ↓ ezetimibe. Separate doses by 4-6 hrs.

Omega-3 Acid Ethyl Esters (Lovaza)

1. ↓ TG up to 45%, ↑ LDL up to 44% - must monitor
2. **For TG:** use when TG >500 in addition to a low fat diet
3. Start 2 cap QD can ↑ to 4 QD (can also split to BID) +/- food, but food may be more comfortable
4. **S/E:** eructation (burping), dyspepsia, nausea, indigestion (stom upset)
5. **DI:** may prolong bleeding time. Monitor INR

Bile Acid Sequestrants/Bile Acid Resins

- These bind bile acids in the intestine & cause more bile acids to be excreted in the stool. This reduces the amt of bile acids returning to the liver & forces the liver to produce more bile acids to replace those lost. To produce more bile acids, the liver converts more cholesterol into bile acids, which lowers the level of chol. in the blood.

❖ Cholestyramine (Questran)

❖ **Colesevelam (WelChol)** – also approved for DM II (↓A1C 0.5%) – take with meals & liquid

❖ Colestipol (Colestid)

1. S/E: **constipation** (may need dose reduction/laxative), **abd pain, cramping, gas, bloating** (less GI s/e with WelChol)
These meds ↓ folate, suppl in women & Children
2. CI: bowel obstruction, TG >500, hx of hyperTG induced pancreatitis
3. WelChol Preg B, others Cat. C
4. Questran & Colestipol, separate all drugs by 1 hr before and 4-6 hrs after (statins, fibrates, etc)
5. WelChol has less DI than other
 - a. Take 4 hrs before WelChol: phenytoin, levothyroxine, glyburide, OC, (*Niaspan* for all bile acid resin)

Fibrates

- Activates the Peroxisome proliferator receptor alpha (PPARα) –this enhances elimination & ↓ synthesis of VLDL (causing ↓ TG) and ↑ HDL. When TGs are high, reducing TGs may ↑ LDL

❖ **Fenofibrate, Fenofibric Acid (TriCor, Trilipix, Antara, Lofibra, Fenoglide, Triglide)**

❖ **Gemfibrozil (Lopid)** – take 30 min before bfast & dinner

1. S/E: ↑ LFTs, ↑CPK, myopathy, abd pain, dyspepsia, constipation, rhinitis, cholelithiasis –rare (gallstones in gallbladder)
2. CI: severe renal/liver/gallbladder disease . Preg C
3. DI: when used in combo with statins, fenofibrates ↑ risk of myopathies (esp gemfibrozil)
 - a. Only **Trilipix** has the indication for use with statin
 - b. Fibrates ↑ effects of sulfonylureas & warfarin
4. Antara, Tricor, Triglide, Trilipix: take +/- food
5. Fenoglide, Lofibra, Lipofen: take QD with food

Niacin

- ↓ rate of hepatic synthesis of VLDL (↓TG), and LDL. May also ↑ rate of chylomicron TG removal

❖ Immediate release (crystalline) niacin (Niacor) – **OTC**

❖ **ER Niacin (Niaspan)** 

❖ ER Niacin + lovastatin (Advicor) **ER Niacin + simvastatin (Simcor)**

❖ CR Niacin (Slo-Niacin) – **OTC**

❖ Do NOT use flush free niacin ; ineffective (Inositol hexaniacinate or hexanicotinate)

1. ↑HDL 15-35%, ↓TG 20-50%

2. **Con w. niacin is the poor tolerability due to flushing/itching.** Extended release forms (CR, SR) have less, but still signif

- a. Can pretreat with up to 325 mg ASA (or 200 mg ibuprofen) 30 min before dose for a few wks
 - b. Avoid alcohol, hot beverages, spicy food around time of dose
3. **Slo-Niacin (OTC) is more hepatotoxic. The best clinical choice is Niaspan (↓s.e, w/o inc liver damage) – more expensive**
 4. S/E: **flushing, pruritis, diarrhea, GI distress, hyperglycemia, hyperuricemia, hepatotox, ortho hypotn**
 5. Niaspan approved with use with simva & lovastatin, but risks must outweigh benefits due to inc risk of rhabdo.
Separate dose from bile acid resins by 4-6 hrs
 6. *Niaspan*: take at bedtime after low fat snack. *Others*: take with food (max 2 g/day vs niacin is max 6g/day)

[30] HEART FAILURE

Oxygen poor blood → R. atrium → Tricuspid valve → R. ventricle → Pulmonary valve → Pulmonary artery → Lungs → Pulmonary veins → oxygen rich blood → L. atrium → Mitral valve → L. ventricle → aortic valve → Aorta → body → vena cava

Pathophysiology:

1. Heart sounds: S1 (lub) = tricuspid & mitral valves closing in the R & L Atrium. S2 (dub) = pulmonary & aortic valves closing in R & L Ventricle.
2. Each time the L. ventricle closes, it ejects a volume of blood (CO). $CO = SV \times HR$
3. Heart failure occurs when the L. vent (R. vent or both) does not fill with or eject blood properly, so the heart fails to pump suff. Amt of blood to meet the body's metabolic needs
4. In the early stages of HF, the heart responds to the ↓ output by growing thicker muscular walls to pump harder. Over time, due to the smaller ventricle b/c of the expanded muscle, the walls weaken and this ↓s CO.
5. In an attempt to compensate & inc CO, the body tries to maintain MAP thru constricting arterial vessels by activating sympathetic NS (releases renin, ↑ ang II, ↑ ADH, ↑ aldosterone, ↑ renal abs of Na and water).
6. This ↑ in blood volume is harmful bc it ↑ venous pressure & causes pulm and systemic edema. The excess fluid causes the body to become congested and class symptoms of HF appear (SOB, fatigue, pulm congestion, periph edema)

Drugs that cause / worsen HF

1. Chemotherapeutic agents (esp **anthracyclines**)
– doxorubicin, daunorubicin, trastuzumab (Herceptin), imatinib (Gleevec), docetaxol (Taxotere)
2. **Amphetamines** & other sympathomimetics
3. **Negative inotropic drugs** (verapamil, diltiazem)
4. **Class I antiarrhythmic agents** (mexiletine, tocainide, procainamide, quinidine, disopyramide, flecainide, propafenone) – do not use
5. **Immunomodulators** (interferons, etanercept, rituximab)
6. **NSAIDs** (incl. Cox 2 inh)
7. **Triptan** migraine drugs (CI w. hx of CV disease / uncontrolled HTN) & ergot derivs
8. **Thiazolidinediones** (pioglitazone & esp rosiglitazone)

S/S of HF

1. Dyspnea at rest/on exertion
2. Wkness / fatigue
3. SOB
4. Orthopnea
5. Jugular venous distention (JVD)
6. Bibasilar rales
7. Edema
8. Ascites
9. S3 gallop
10. EF <40% (if systolic dysfxn) >40% (in diastolic dysfxn)

Non Pharmacologic txt:

1. Monitor body wt daily
2. Limit Na to < 2 g/day. If also have HTN, <1.5 g /day
3. Consider MVI due to dietary restrictions
4. Use fish oils (1g/day) or omega 3 polyunsat fat
5. Avoid ephedra (ma huang) or ephedrine (due to inc morbidity & mortality)
6. Avoid NSAIDs
7. Pneumococcal vacc & influenza
8. BMI <30

Pharmacotherapy:

1. Cornerstone of therap = ACEi + BB
2. Other agents that shown positive impact on mortality:
ARBS, Aldosterone antagonists, combo hydralazine + nitrate
3. Diuretics (mainly loop)
4. Digoxin can be used to treat symptoms of HF

HF Classification

ACC/AHA Staging (What the Dr. sees)	NYHA Fxnal class (how the pt is feeling)
A. No structural heart disease No symptoms	No corresponding categ.
B. Structural heart disease No S/S (low EF, LVH, prev MI)	1. No limitations of physical activity
C. Structural heart disease + symptoms (SOB, fatigue)	2. Slight limitation of phys activity Comfortable at rest, but ordinary activ results in fatigue 3. Marked limitation of phys active Comfortable at rest, but minimal exertion (bathing/dressing) causes symptoms
D. Advanced structural heart disease + symptoms at rest	4. Unable to carry on any phys activ w/o discomfort. Symptoms present at rest

With these drugs, treat to target dose for symptom control, not to ↓ BP

ACEi approved for HF

1. Captopril (Capoten)
2. Enalapril, Enalaprilat inj (Vasotec)
3. Fosinopril (Monopril)
4. Lisinopril (Prinivil, Zestril)
5. Ramipril (Altace)
6. Trandolapri (Mavik)

Hydralazine/Nitrates - hydralazine is an arterial VD (↓ Afterload), Nitrates are venous VD (↓ Preload)

- BiDil is indicated in blk pts with Class III, IV HF who are symptomatic on optimal ACEi & BB. These drugs are also used in pts intolerant of ACEi/ARB (as adjunctive therapy). Do not use nitrates alone, hydralazine is also used to improve efficacy & reduce nitrate tolerance

ARBs for HF (those mentioned in guidelines)

1. Candesartan (Atacand)
2. Losartan (Cozaar)
3. Valsartan (Diovan)

1. Isosorbide dinitrate/hydralazine (BiDil) – no nitrate tolerance (so don't have to worry about nitrate free dosing period like other nitrates)
 - a. **S.E:** Lupus like syndrome (report fever, joint/muscle aches, fatigue), dizziness, reflex tachy

Aldosterone receptor Antagonists - ↓ cardiac remodeling, ↓ Na/water retention, ↓ morb & mortality, used in class III & IV HF

1. Spironolactone – non selective (also blocks androgen & progesterone receptors)
2. Eplerenone (Inspra) - selective (has less s/e)
3. Triple therapy of ACE, ARB, aldosterone antag is not recom due to high risk of hyperK+

2. Hydralazine (Apresoline)
 - a. **S.E:** Lupus like syndrome (report fever, joint/muscle aches, fatigue), dizziness, reflex tachy
3. Isosorbide mononitrate (Imdur, Ismo, Monoket) dinitrate (Isordil)
 - a. **S.E:** HA, dizziness, tachyphylaxis (need 10-12 hr nitrate free interval)
 - b. **CI** with PDE5 i

Beta Blockers – inhibits SNS and ↓ cardiac remodeling & ↓ M&M. Used in class II-IV, avoid BB with ISA bc these can worsen survival

1. Bisoprolol (Zebeta) – benefit in trials but no FDA indication
2. Metoprolol, Metoprolol succinate (Lopressor, Toprol)
3. Carvedilol (Coreg, Coreg CR) – non selective α, β blocker. – do not use for pts with asthma/COPD; *take with food (due to dizziness), sprin on aplesce*

Drugs that ↓ HR:

Digoxin
verapamil, diltiazem
BB

Diuretics – Loops (for HF, renal disease) – don't work well when kidneys are good, not gen. used for HTN

1. Furosemide (Lasix) oral loop dose equiv = 40 mg
2. Bumetanide (Bumex) oral loop dose equiv = 1 mg
3. Torsemide (Demadex) oral loop dose equiv = 20 mg
4. Ethacrynic acid (Edcrin) – prob don't pick

<u>Loops</u>	<u>Thiazides</u>
↓↓↓ K	↓ K
↓ Ca++	↑ Ca++
Give ½ BF, ½ lunch (don't give full dose in morning- too dizzy)	used for HTN, first will cause diuresis then will cause VD

Digoxin (Lanoxin, Digitek)– leads to symptom improvement, ↑ exercise tolerance, ↑ QOL. Inhibits NA/K ATPase, acts as a positive inotrope (↑ contractility & CO) and negative chronotrope (↓HR)

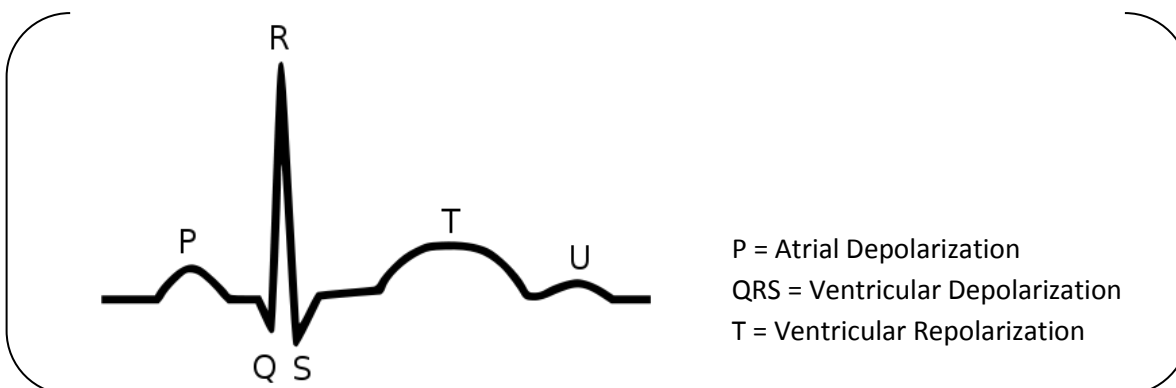
1. **Dosing:** 0.125-0.25 mg QD, LD not needed for HF (therapeutic range = 0.5-0.9 ng/mL higher for A.fib)
2. **↓ Renal fxn:** can be given 0.125 mg QOD or even less freq
3. **S/E:** dizziness, HA, d/n/v, rash, mental changes
4. **Toxicity:** n/v, loss of appetite, bradycardia. Blurred or 'yellow' vision/halo, abd pain, confusion, delirium, prolong PR interval, bidirectional vent tachycardia
5. **Antidote:** Digibind or DigiFab
6. ↑ Digoxin levels w/: amiodarone, quinidine, verapamil, erythromycin, clarithromycin, azoles, CSA, PIs, *HYPO K*, *HyperCa*
7. ↓ levels of digoxin with: St John's Wort, bile acid resins

ACUTE DECOMPENSATED - INPATIENT HEART FAILURE TXT

❖ For pts with low BP & CO, **IV inotropic drugs** (dobutamine, milrinone – are reasonable to maintain systemic perfusion)

❖ **Vasodilators**

1. **Nesiritide (Natrecor)** – B- type natriuretic peptide that binds to vascular SM and ↑cGMP resulting in SM relaxation.
 - a. S/E: hypotn, ↑SCr
 - b. CI: SBP <90
2. **NTG**- venous VD, dilates coronary arteries & improves collateral BF to ischemic regions.
 - a. S/E: hypotn, HA, lightheadedness, tachycardia, tachyphylaxis
 - b. CI: SBP <90, PDE5i, ↑ intracranial press
3. **Nitroprusside (Nipride)** – arterial & venous VD, has pronounced effects on BP
 - a. S/E: hypotn, HA, tachycar, cyanide tox
 - b. Must be protected from light- use alum. foil (blue color = degraded to cyanide)



[31] ANTICOAGULATION

Unfractionated Heparin (UFH)

- ❖ Heparin
 - S/E: HIT, HyperK+, osteoporosis (with long term use)

LMWH

- ❖ Enoxaparin (Lovenox)
 - S/E: thrombocytopenia, anemia
- ❖ Dalteparin (Fragmin)
- ❖ Tinzaparin (Innohep)

Fondaparinux (Arixtra)

Direct Thrombin Inhibitor – used in pts with hx of HIT

- ❖ Lepirudin (Refludan) - IV
- ❖ Argatroban (Novastan) - IV
- ❖ Bivalirudin (Angiomax) -IV
- ❖ Dabigatran (Pradaxa) – PO
 - S/E: gastritis like symptoms, bleeding (more GI bleeding)
 - DI: avoid use with rifampin & other PGP inducers

Factor Xa Inhibitor

- ❖ Rivaroxaban (Xarelto)
 - DI: avoid with PGP & 3A4 inducers ; if used, consider inc dose to 20 mg

Warfarin

1. Racemic mixture of R & S enantiomers, S is 3-5x more potent
2. S/E: skin necrosis, purple toe syndrome, Preg X
3. DI: 2C9 inducers : phenobarb, phenytoin, primidone, rifampin (large ↓ INR), st johns
4. 2C9 inhibitors: amiodarone, Bactrim, azoles, macrolides, metronidazole
5. Natural products that ↑ bleeding risk: ginkgo biloba, bromelains, danshen, dong quai, vit E, evening primrose, HD fish oil, garlic, ginseng, glucosamine, grapefruit, willow bark (Coenzyme Q10 ↓ effectiveness)
6. SSRI, SNRI also inc bleeding risk w/o change in INR

Atrial Fibrillation Antithrombotic therapy

1. Pts with A. fib for ≥48 hrs should get anticoagulation for 3 wks before & 4 wks after cardioversion (electrical/pharmacological)
2. Pts staying in A.fib will need chronic AC for stroke prevention
3. CHADS₂ score:
 - a. Chad score 0= **Aspirin 81-325mg QD**
 - b. Chad score 1=**Aspirin 81-325mg QD -or- Warfarin 5mg QD/ dabigatran/ rivaroxaban**
 - c. Chad score 2= **Warfarin 5mg QD** (target INR 2-3)/ **dabigatran /rivaroxaban**

CHADS₂ score (all 1 point except stroke/TIA)

CHF (EF<35%)

HTN

Age >75

Diabetes

(2) Prior Stroke or TIA

Drug	Dosing		PK	
Warfarin ❖ Inhibits VKORC1 therefore ↓ regeneration of Vit K epoxide - Inhibits activated clotting factors 2a,7a,9a,10a, protein C & S	Warfarin initiation: <ul style="list-style-type: none"> 5 -10 mg for 1-2 days, then adjust based on INR 2.5 mg (if elderly, malnourished, liver disease, high bleeding risk, CHF exacerbation, or interacting drugs) 	DVT TXT = 3-6 months = 4-6 weeks DVT PPX	T ½ = 20-60 hrs (avg 40 hrs) BA: 100% Protein bound: 99% Metabolism: via 2C9* , 3A4, 2C19, 1A2 Monitoring: (after 2-3 doses. if long term then monthly) – INR <ul style="list-style-type: none"> DVT/PE, A.Fib, certain valves (bioprosthetic valves) = 2-3 Mechanical, caged ball valves = 2.5-3.5 Prophylaxis = 1.5-2 	Antidote: Vit K -- PO is preferred over IV and SC <ul style="list-style-type: none"> 5-9 no bleeding=1-2.5 mg PO ≥9 no bleeding=2.5-5 PO Bleeding=10 mg IV slow + FFP (15 ml/kg) <i>slow infusion 10 mg in 50 cc NS over 1 hr to prev. anaphylaxis 1st line PO >IV>SC</i>
Pts with 2C9*2 or 2C9*3 allele or polymorphism to VKORC gene ↑ risk of bleeding		Management of signif elevated INR w/ or w/o bleeding: PO Vit K onset = 6-12 hrs - do not give via IM or SC route <ul style="list-style-type: none"> <u>INR 5-9</u> → omit 1-2 doses, reduce dose to 10-20%. Alternatively, consider Vit K 1-2.5 mg PO (if at ↑ risk of bleeding) <u>INR >9</u> → hold warfarin, give Vit K 1 2.5-5 mg PO, resume when INR is therapeutic <u>Serious bleeds, any INR</u> → hold warfarin, give Vit K 10 mg IV slow + fresh frozen plasma (15 ml/kg ; ~250 ml/unit) or prothrombin complex concentrate (PCC) or recombinant factor VIIa <u>Life threatening bleed, any INR</u> → hold warfarin, give FFP, prothrombin complex concentrate or recombinant factor VIIa + Vit K 10 mg IV slow; repeat as needed 		
Heparin (UFH) ❖ Binds to antithrombin and accelerates its effects (mainly inhibits factor 2a, 10a– little effect on 9a, 11a, 12a)	DVT, PE, A fib : <ul style="list-style-type: none"> Initial bolus = 80 Units/kg (max 10,000 U) Initial infusion rate = 18 Units/kg/hr (max 2000 U/hr) NSTEMI, STEMI, unstable angina : <ul style="list-style-type: none"> Initial bolus = 60 units/kg (max 5,000 U) Initial infusion rate = 12 Units/kg/hr (max 1,000 U/hr) 	DVT PPX : <ul style="list-style-type: none"> 5000 SC TID If <50 kg or >75 yo = 5000 SC BID 	T ½ = 1-2 hrs Elim: 1° through endothelial cells and macrophages <i>*no renal/liver adjustment</i> Monitoring: <ol style="list-style-type: none"> Heparin Assay (goal 0.3-0.7 units/ml) → draw 6 hrs after 1st dose and after dosage Δ aPTT (goal depends on reagent used) 	Antidote: Protamine sulfate (1 mg protamine neutralizes 100 heparin units – max 50 mg) → use heparin dose over last 3-4 hrs ; give as slow IV push not to exceed 50 mg over 10 mins 5-14 d after starting heparin agent is when HIT (IgG mediated) most likely to occur (plt drop >50% or plt <150)

<p>Enoxaparin (LMWH)</p> <ul style="list-style-type: none"> ❖ Binds to antithrombin (AT) which inhibits Xa, very little effect on II a • 3x Less likely to produce HIT <p>30mg/0.3 ml 40mg/0.4 ml 60mg/0.6 ml 80mg/0.8 ml 100 mg/ml 120mg/0.8 ml 150mg/ml</p>	<ul style="list-style-type: none"> - DVT/PE = 1 mg/kg SQ BID or 1.5 mg/kg SQ QD - Unstable angina/NSTEMI : 1 mg/kg SQ BID - STEMI <75 yo : 30 mg bolus + 1 mg/kg BID - >75 yo = 0.75 mg/kg BID <p><u>Renal impairment, CrCl < 30:</u></p> <ul style="list-style-type: none"> • DVT PPX: 30 mg QD • DVT TXT/Unstable angina : 1 mg/kg QD 	<ul style="list-style-type: none"> - DVT PPX (abd surgery/medical pts): 40 mg QD - DVT PPX (knee/hip surgery) : 30 mg BID <p><u>Obese pts:</u></p> <ul style="list-style-type: none"> • VTE PPX (BMI >40) : Inc dose by 30% (40 mg BID) • TXT : weight based dosing (no max dose) 	<p>T ½ = 3-6 hrs BA = 90%</p> <p>Elimination: Renally; Adjust for renal failure</p> <p>Monitoring:</p> <ul style="list-style-type: none"> - LMW Heparin Assay (anti-Xa) (goal 0.5 – 1.0) → draw 4 hrs after 2nd or 3rd dose for ss 	<p>Antidote:</p> <p>Protamine sulfate --use 1 mg protamine sulfate for 1 mg enoxaparin If LMWH given within 8 hrs, give 1 mg per 100 anti-Xa units (1 mg enoxaparin = 100 anti Xa units)</p>
<p>Fondaparinux (Anixtra)</p> <ul style="list-style-type: none"> ❖ Synthetic heparin that inhibits AT and inhibits Xa (not a LMWH) <p><i>(not long enough to reach factor II)</i></p> <p>Use in pts for hx of HIT</p>	<p>DVT/PE TXT:</p> <ul style="list-style-type: none"> • <50 kg = 5 mg SC QD • 50-100 kg = 7.5 mg SC QD • >100 kg = 10 mg SC QD <p>ACS : 2.5 mg QD</p>	<p>Thromboprophylaxis: 2.5 mg QD</p>	<p>T ½ = 17 hrs BA = 100% Excretion= urine</p> <p>Contraindicated in pts with:</p> <ol style="list-style-type: none"> 1. CrCl <30 2. Body wt <50 kg (for ppx) 	<p>Antidote: None, can use Recombinant factor VIIa (does not bind to protamine sulfate)</p> <p>[For surgery, hold ~ 3 days]</p>
<p>Argatroban</p>	<p>Initiate at 1 mcg/kg/min</p> <p><u>Hepatic impairment:</u> Initiate at 0.5 mcg/kg/min or use lepirudin</p> <p><u>Renal impairment:</u> No Δ, not renally elim.</p>		<p>T_{1/2} = 45 min</p> <p>Monitoring: aPTT: goal depends on reagent used;</p> <ul style="list-style-type: none"> • UH=45-70 sec. <p>check aPTT Q 2 hrs until consecutive values in range, then at least QD</p>	<p>If using argatroban to cont. anticoagulation b/c of HIT:</p> <ul style="list-style-type: none"> • do not use warfarin until plt >100 K • overlap warfarin for at least 5 days (for doses < 2 mcg/kg/min, target INR >4 b/c argatroban falsely elevates INR)

Lepirudin (Refludan) - Direct Thrombin Inhibitor – IV Use in pt with hx of HIT	Initiate at 0.075 mg/kg/hr <u>Renal impairment</u> (CrCl \leq 60 or SCR >1.5): Use argatroban	T_{1/2} = 60-80 min Monitoring: aPTT: goal depends on reagent used; <ul style="list-style-type: none"> UH=45-70 sec. check aPTT Q 4 hrs until consecutive values in range, then at least QD	If using lepirudin to cont. anticoagulation b/c of HIT: <ul style="list-style-type: none"> do not use warfarin until plt >100 K before initiating warfarin, dec lepirudin until aPTT is ~45 sec overlap warfarin for at least 5 days
Dabigatran (Pradaxa) Direct Thrombin Inhibitor – PO	150 mg BID; 75 mg BID if CrCl 15-30 Once bottle is opened, it must be used within 4 mths. Keep in original package.	No lab monitoring req.	[for surgery, hold for: CrCl >50 = 1-2 days CrCl <50 = 3-5 days
Rivaroxaban (Xarelto) Factor Xa inhibitor PPX for DVT in pts with knee/hip sx PPX for stroke w/ A. fib	A.Fib CrCl > 50 : 20 mg QD CrCL 15-50 : 15 mg QD CrCL <15 : avoid PPX DVT : 10 mg QD x 35 days if hip sx, 12 days if knee sx		No antidote

[32] CHRONIC ANGINA

1. **Stable angina** is predictable CP (brought on by exercise, or stress). The pain comes on slowly, gets worse over the next few mins and subsides. The pain usually lasts 5-15 mins and goes away with NTG use or rest.
This is caused by the heart muscle needing more oxygen. The most common cause is CHD (narrowed by atherosclerosis)
2. **Prinzmetal's (variant or atypical) angina** – present in pt with normal coronary arteries but symptoms result bc of vasospasms in the arteries
3. **Silent ischemia** – transient ischemic attacks w/o symptoms of angina. Often detected during an exercise testing (ST elevation or depression)
4. **Unstable angina** (part of acute coronary syndrome) – severe, crushing CP due to ischemia, acute medical care is needed

PHARMACOLOGIC THERAPY FOR CHRONIC STABLE ANGINA

1. Antiplatelet agent (ASA, if CI then clopidogrel)
2. Plus antianginal agent (BB, CCB, nitrates, sometimes ranolazine (Ranexa))

Antiplatelet Agents

- ❖ **Aspirin (Bayer, Ascriptin, Bufferin)** 75-162 mg QD
 - **S/E:** dyspepsia, heartburn, GI upset, GI bleed, renal impairment, hypersensitivity
 - EC products must be chewed if pt is having ACS
- ❖ **Clopidogrel (Plavix)** 75 mg QD [used if CI to ASA]
 - **BBW:** effectiveness depends on the activation to an active metabolite mainly by 2C19. PM exhibit higher CV events than normal 2C19 fxn. 2C19*1 allele = fully fxnal metabolism, 2C19*2*3 = non fxnal
 - **S/E:** bleeding, bruising, rash, TTP (rare – thrombotic thrombocytopenia purpura; Report: fever, wkness, skin paleness, purple skin patches, yellowing of skin/eyes, neurological changes)
 - **DI:** 2C19inhibitors (cimetidine, fluconazole, ketoconazole, viroconazole, fluoxetine, fluvoxamine) omeprazole is a moderate 2C19 inh.

Antianginal Therapy

- ❖ BB – 1st line, do not use ISA
 - Inhibits catecholamine effects, ↓ HR(neg chrono), ↓contractility (neg inotropic)
 - *Avoid use in Prinzmetal's angina*
- ❖ CCB – preferred agent for Prinzmetal's (variant) angina
 - VD, ↓SVR, Non-DHP ↓ contractility & HR
- ❖ Nitrates
 - ↓ cardiac demand by ↓ LVP and preload. Causes VD of veins & arteries
 - Call 911 if CP doesn't go away with 1st dose of SL or spray
 - For long acting nitrates – req. nitrate free interval
 - **S/E:** HA, flushing, hypotn, tachy, dizziness
- ❖ **Ranolazine (Ranexa)**
 - ↓ intracellular Na and Ca, may ↓ myocardial demand
 - **S/E:** dizziness, constipation, QT prolongation
 - 3A4 substrate

Nitroglycerine formulations

1. **Nitroglycerine SL tabs (Nitrostat)**
2. **Nitroglycerine SL Spray (Nitromist, Nitrolingual Pump spray)** 0.4 mg per spray
3. Nitroglycerine ointment 2% (Nitro-Bid) → dosed BID, 6 hrs apart, 10-12 hrs dose free interval
4. Nitro transdermal patch (Nitro-Dur, Minitran) → 12-14 hrs on, 10-12 hrs off (to prevent tolerance)
5. Nitro ER caps (Nitro-time)
6. Nitro IV
7. **Isosorbide mononitrate tabs/caps (Ismo, Monoket)** → BID, at least 7 hrs apart (9am, 4 pm)
8. **Isosorbide mononitrate ER (Imdur)** → QD or BID (same as above)
9. Isosorbide dinitrate (Isordil IR and SL) → BID-TID, 7am, 12pm, 5pm for 14 hr dose free interval
10. Isosorbide dinitrate SR (Dilatrate SR) → SR/ER needs 18 hr dose free interval

Counseling

NTG SL or Spray

1. Call 911 if pain persists after 1 dose of SL NTG (can take up to 3 doses at 5 min intervals while waiting for ambulance)
2. NTG tabs should be kept in original container ; prev. recom to replace Q6 mths is no longer valid for new reformulations – keep until manuf expiration date
3. If tablets get powdery, then get a new bottle
4. You may feel slight burning/stinging in your mouth. This does not happen all the time, do not take another if you do not feel the burning
5. NTG Pump: spray 5 times to prime the 1st time used or if have not been used in >6 wks.
 - a. Do not shake. Use 1 spray Q 5 mins (max 3 sprays in 15 mins)
 - b. On or under the tongue
6. Nitrostat SL tabs: 0.3, 0.4, 0.6 mg . place 1 tab under the tongue and allow it to dissolve, do not chew/swallow
7. If pt recently used PDE5i, avoid use of NTG

NTG Patch

1. Apply to upper arm / chest. Keep above knees/elbows
2. Do not apply immediately after shower, allow skin to dry
3. Use 1 patch QD for 12-14 hrs, off for 10-12 hrs to dec tolerance

Isosorbide Mononitrate

1. Usually dosed BID or as directed. Take when 1st wake up and 2nd dose 7 hrs later
2. **S.E**: HA, dizziness, lightheadedness, redness – will dec as your body gets used to it
3. Do not use with PDE5i

Ranolazine

1. Used to treat chronic stable angina (dec number of times you get CP)
2. Do not eat/drink grapefruit, can cause QT prolongation (hypoK, hypo Mg may also inc risk of QT prolongation)

[33] ACUTE CORONARY SYNDROMES

- A set of clinical disorders that results from an imbalance between myocardial O₂ demand and supply (primary reason is due to an occlusive plaque/clot in the artery)
 - This can lead to an infarction that is detectable by looking at biochemical markers (**Troponins** I or T and creatine kinase myocardial band(**CK-MB**), & **CPK**)
1. **ACS encompasses: 1) Unstable Angina 2) NSTEMI 3) STEMI**
 2. **S/S of ACS:** severe CP (usually is not relieved with NTG) , may radiate to left shoulder, arm, jaw, back, neck, diaphoresis, n/v, numbness, SOB, dyspnea

Diagnosis:

UA: CP, (-) cardiac enzymes,
No ECG changes

NSTEMI : CP, (+) cardiac
enzymes

STEMI : CP, (+) cardiac
enzymes, ST segment changes

TXT for UA / NSTEMI = MONA + GAP-BA

1. **Morphine** → causes arteriolar & venous dilation.
Prompts ↓ in myocardia O₂ demand; pain relief
 - a. s/e: hypotn, bradycardia, n/v, sedation, resp depression (antidote: Naloxone (Narcan))
2. **Oxygen** → if cyanosis or resp distress. SaO₂>90%
3. **Nitrates** → dilates coronary arteries & improves BF, ↓ oxygen demand by ↓ preload
 - a. NTG SL or spray followed by IV for immediate relief of CP. Do not use if BP <90 or HR <50
 - b. Do not give if within 24 hr of sildenafil use, 48 hrs of tadalafil use
4. **ASA** → inhibits plt aggregation by inhibiting TxA₂
 - a. Use ASA immediately & indefinitely
 - b. Chew non enteric coated 162-325 mg & cont 75-162 mg QD. If intolerant of ASA, load clopidogrel & cont with 75 mg QD
5. **GP IIb/IIIa antagonist** → blocks fibrinogen binding to GPIIb/IIIa receptors on plts – dec plt aggregation
 - a. (abciximab, eptifibatide, tirofiban) Can be used in medical management or for those going for an intervention
6. **Anti-coagulants** → clotting factor inhibitors
 - a. Used to prev. futher clotting. Heparin, LMWH (enoxaparin, dalteparin), fondaparinux, bivalrudin
7. **P2Y₁₂ inh** → inhibits P2Y₁₂ on plt receptor
 - a. Clopidogrel, prasugrel, ticagrelor – LD followed by MD unless undergoing CABG
8. **BB** → cardioprotective
 - a. Should be initiated within 24 hrs who do not have the following: signs of HF, low CO, risk of cardiogenic shock
9. **ACEi** → dec preload & afterload, prev cardiac remodeling
 - a. Should be admin within 24 hrs for pts with pulm congestion or LV EF <0.4 ; do not use IV acei due to risk of hypotn

GP IIb/IIIa ANTAGONIST (reversibly block plt aggregation)

- ❖ **Abciximab (ReoPro)**
- ❖ **Eptifibatide (Integrilin)**
- ❖ Tirofiban (Aggrastat)

1. CI: thrombocytopenia (plt < 100,000) , recent (within 6 wks) major surgery, hx of CVA within 2 yrs (abciximab), severe uncontrolled HTN, hypersensitivity to murine proteins (abciximab), renal dysfxn (eptifibatide, tirofiban)
2. **S/E: thrombocytopenia** (esp abciximab), **hypotn**
3. **Plt fxn returns after 24-48 hrs after d/c abciximab, 4-8 hrs for eptifibatide & tirofiban**

P2Y₁₂ INHIBITORS

- ❖ **Clopidogrel (Plavix)** – **Prodrug- irreversibly binds to receptor** LD: 300-600 mg MD 75 mg QD
 - ❖ Prasugrel (Effient)- **prodrug – irreversibly binds to receptor** LD: 60 mg MD: 10 mg QD
 - ❖ Ticagrelor (Brilinta) - **not a prodrug – reversible binding (faster onset & offset)** LD: 180 mg MD: 90 mg **BID**
1. Clopidogrel **BBW:** 2C19 Poor metabolizers
 2. Prasugrel, Ticagrelor **S/E: bleeding** (pras> clop) , **TTP** (thrombotic thrombocytopenic purpura)
 3. Ticagrelor **S/E: dyspnea**
 - a. **Do not use ASA MD >100 mg (this reduces effectiveness of ticagrelor)**

THROMBOLYTICS

- Cause fibrinolysis by binding to fibrin in a thrombus & converting the plasminogen to plasmin. (Plasmin then degrades the fibrin mesh into soluble end products leading to clot dissolution.)
 - Recommended when a hosp cannot perform PCI within 90 mins from symptom onset [door to balloon]
 - Thrombolytics should be initiated within 30 mins upon arrival (GL still found it beneficial after 12 hrs from symptom onset for STEMI) [door to needle]
- ❖ Alteplase (t-PA, rt-PA, Activase)
 - ❖ Reteplase (r-PA, Retevase)
 - ❖ Tecteplase (TNK-tPA, TNKase)
 - ❖ Streptokinase (Streptase)
 1. **S/E:** hypotn, intracranial hemorrhage, fever
 2. **CI:** severe uncontrol HTN (SBP >185 or DBP >110), pregnancy, (strepto, anistreplase – prior exposure in past yr)

What to stop/cont when going for CABG

1. **Continue:**
 - a. ASA
 - b. UFH (stop enox-12-24 hrs, fondaparinux-24 hrs, bivalirudin-3 hrs before & dose with UFH)
2. **Discontinue:**
 - a. clopidogrel/ticagrelor (5 days before)
 - b. prasugrel (7 days before), GPIIb/IIIa (4 hrs before)

Long Term Management in pts s/p MI (Secondary Prevention)

1. ASA indefinitely, use 162-325 mg for:
 - a. 1 mth with bare metal stent
 - b. 3 mths with sirolimus-eluting stent
 - c. 6 mths with paclitaxel-eluting stent
 - d. Then cont ASA with 75-162 mg QD indefinitely (use this dose if no stent was placed)
2. Clopidogrel or prasugrel x 1 mth – 1 yr. Consider cont beyond 15 mths for pts with drug eluting stent
3. NTG SL or Spray PRN
4. BB QD
5. ACEi QD
6. Statin if LDL > 100
7. Anticoag if A.Fib or LV thrombus

[34] ANTIARRHYTHMICS

Additive QT Prolongation

1. **Class Ia and Class III antiarrhythmics** (amiodarone, disopyramide, dronedarone, procainamide, quinidine, sotalol)
2. ABX- **Quinolones** (cipro, levo, moxi, norflox, gemi, sparfloxacin), **Macrolides** (azith, clarith, telith, erythromycin), amantadine, foscarnet
3. **Azoles** (flucon, itracon, ketocon, posicon, voriconazole)
4. Anticancer (arsenic, dasatinib, lapatinib, nilotinib, sunitinib, tamoxifen)
5. PI (saquinavir/ritonavir, atazanavir, lopinavir/ritonavir)
6. Antidepressants – **TCAs** (amitriptyline, nortriptyline, doxepin, desipramine), **SSRIs** (citalopram, fluoxetine, paroxetine, sertraline) **SNRIs** (venlafaxine, desvenla), trazodone
7. Antiemetics – **5HT3 blockers** (dolasetron, ondansetron, granisetron, palonosetron), droperidol
8. **Antipsychotics** – chlorpromazine, thioridazine, pimozide, haloperidol, ziprasidone, risperidone, paliperidone, iloperidone, asenapine, lurasidone
9. Alfuzosin, apomorphine, chloroquine, galantamine, **methadone**, pentamidine

PHARMACOLOGIC TXT : rate control is often 1st line (found to be as effective as rhythm control with cardioversion & antiarrhythmic drugs)

- Drugs used for rate control = BB, Non-DHP, digoxin (all which ↓ HR)
- Before starting meds, always check pts electrolytes (Mg, Ca, Na, K) & run a toxicity screen
- [torsades de pointes – DOC

Vaughan-Williams Classification of Antiarrhythmics

Ia – “Double Quarter Pounder”

Quinidine, Procainamide, Disopyramide

Ib – “Mayo Lettuce Tomatoes Pickles”

Mexiletine, Lidocaine, Tocainide, Phenytoin

Ic – “More Fries Please”

Moricizine, Flecainide, Propafenone

II – BB (eg. esomolol, propranolol)

III – Amiodarone, Dofetilide, Dronedarone, Ibutilide, Sotalol

IV – Verapamil, Diltiazem

Class IA Antiarrhythmics – blocks Na⁺ channels ; ↓ conduction velocity; (has additive QT prolongation)

❖ Quinidine

1. Take with food/milk to ↓ GI upset
2. BBW: quinidine may ↑ mortality in A.fib/flutter
3. S/E: diarrhea (35%), stomach cramp (22%), cinchonism (tinnitus, blurred vision, HA, nausea), QT prolongation
4. DI: major 3A4 substrate; Strong 3A4, 2D6, PGP inhibitor (will ↑ digoxin, warfarin)

Class I antiarrhythmics are sodium channel blockers. They are subclassified by the duration to which they bind and block cardiac sodium channels. Ia = intermediate. Ib = short. Ic = long.

❖ Procainamide

1. Has an active metabolite (N-acetyl procainamide NAPA) ; take on empty stomach
2. BBW: fatal blood dyscrasias (agranulocytosis)
 - a. Long term use leads to positive antibody test which may result in drug induced lupus erythematosus-like syndrome
3. S/E: lupus like syndrome, QT prolongation, hypotn, agranulocytosis
4. DI: 2D6 substrate

❖ Disopyramide (Norpace, Norpace CR)

1. Take on empty stomach
2. S/E: anticholinergic s/e (xerostomia, constipation, urinary retention)
3. 3A4 substrate

Class IB Antiarrhythmics – Blocks Na channels

- ❖ Lidocaine (Xylocaine)
- ❖ Mexiletine (Mexil)
 1. S/E: CNS (hallucinations, confusion, seizures), hypotn, dizziness, sedation
 2. Lidocaine – 3A4, 2D6 substrate. Strong inhibitor of 1A2, moderate 2D6, 3A4
 3. Mexiletine – 1A2 & 2D6 substrate. Strong inhibitor of 1A2

Class IC Antiarrhythmics – Blocks Na channels; ↓ conduction velocity, These agents are not commonly used

BBW: pro-arrhythmic effects ; Both are 2D6 substrates

- ❖ Flecainide (Tambacor)
 1. S/E : dizziness, visual disturbances, dyspnea, worsening HF
- ❖ Propafenone (Rythmol, Rythmol SR)
 1. S/E: taste disturbances, bradycardia, AV block, dyspnea, dizziness, bronchospasms

Class II Antiarrhythmics – blocks Beta receptors & Ca channels

- ❖ Esmolol (Brevibloc) – B1 selective
- ❖ Propranolol (Inderal LA, InnoPran XL) – non selective, lipophilic

Class III Antiarrhythmics – blocks mainly K⁺, no Δ on conduction velocity

- ❖ **Amiodarone (Cordarone, Pacerone, Nexterone)**
 1. Infusions >2 hrs must be admin in a non-polyvinyl chloride (PVC) container (polyolefin/glass)
 2. BBW: lung damage, liver toxicity
 3. S/E: hypotn (IV), bradycardia, hypothy/hyperthyroid, ↑ LFTs, corneal microdeposits, optic neuritis, pulm fibrosis, ataxia, dizziness, tremor, photosensitivity, slate blue skin discoloration, insomnia
 4. Preg Cat D ; T ½ = 60 days!
 5. DI: amiodarone is a moderate 3A4, 2D6, 2C9 inhibitor; Substrate of 3A4.
 6. **Must ↓ doses of:** digoxin, warfarin, quinidine, procainamide (use lower doses of simva, atorva, lovastatin)
 7. Avoid coadmin of drugs that prolong QT interval (TCA, erythromycin, other antiarrh), do not use grapefruit, ephedra, St John's
 8. Caution with use with other neg. chronotropes (BB, verapamil) due to risk of bradycardia
- ❖ Dronedarone (Multaq)
 1. S/E: new cases of hepatic failure (esp in 1st 6 mths) renal failure, n/d, hypoK⁺, hypoMg
 2. Preg Cat X
 3. Mod inhibitor of 3A4, 2D6. Reduce dose of digoxin
- ❖ Sotalol (Betapace, Betaace AF, Sorine)
 1. Betapace should not be substituted for Betaace AF
 2. S/E: bradycardia, hypotn, torsades, HF, dizziness, bronchospasms
- ❖ Ibutilide (Corvert)
- ❖ Dofetilide (Tikosyn)
 1. **REMS program** avail to prescribers and hospitals – provides info of importance in hospt txt initiation & dosing
 2. **TIPS (tikosyn in pharmacy system)** –designed for retail pharmacies to stock Tikosyn, RPh must verify Dr. is a participant.

Class IV Antiarrhythmics – blocks Ca channels

- ❖ Diltiazem (Cardizem, Dilacor, Cartia, Taztia)
- ❖ Verapamil (Calan, Isoptin, Verelan, Covera)
 1. May be preferred over BB if coexisting asthma/COPD
 2. S/E: hypotn, bradycardia, edema, exacerbation of HF, constipation (more with verapamil), gingival hyperplasia

Agents Not in Vaughan Williams Classification

- ❖ Adenosine (Adenocard)
 1. Dec conduction thru AV node restoring NSR
 2. Used in paroxysmal supraventricular tachycardia (6 mg IV push)
 3. S/E: transient new arrhythmia, facial flushing, HA, CP
- ❖ **Digoxin (Lanoxin, Digitek)**
 1. ↑ refractory period, ↓ conduction velocity
 2. Therapeutic range for A.fib = 0.8-2.0
 3. S/E: dizziness, HA, d/n/v, rash, mental changes
 4. **Toxicity:** first signs are n/v, loss of appetite & bradycardia. Others include blurred vision, yellow skin, vent tachy, confusion, delirium
 5. Renally cleared. HYPO K, HyperCa ↑ risk of dig toxicity

Amiodarone Counseling

1. Dispense Med Guide
2. Used to treat certain types of irregular heart beats, used to restore normal heart beat and regular rhythm
3. Use +/- food, but imp to choose one and take the same way with each dose
4. Like other meds to treat irreg heartbeat, it can cause them to become worse
5. Can cause serious vision changes, thyroid changes, photosensitivity
6. Do not drink grapefruit

Digoxin Counseling

1. This med helps make your heart beat stronger with more regular rhythm. Keep taking it even if you feel well
2. Do not stop taking it w.o talking to Dr., stopping suddenly can make condit worse
3. Symptoms of OD

[35] PULMONARY ARTERIAL HYPERTENSION (PAH)

- Characterized as continuous high BP in the pulmonary artery. It is due to an imbalance in VD/VC substances (↑ in VC such as endothelin-1 & thromboxane A₂, ↓ PGs)
 - VC → leads to dec BF and high BP within the pulm vasculature → this causes the pulm arteries to thicken as the amt of muscle inc and scar tissue form → this leads to the arteries becoming more narrow → it now is harder for the R. ventricle to pump blood thru the pulm artery into the lungs → the heart has to work harder and the R. ventricle becomes enlarged & right HF can occur.
 - ↑ Tx A₂ ↓ PGs lead to a pro-thrombotic state and pts will req anticoag (warfarin target INR 1.5-2.5 is recom.)
1. **Meds that can cause it:** dexfenfluramine (Redux) & Fen/Phen, cocaine, methamphetamine, recently – **dasatinib (Sprycel)**
 2. Symptoms: dyspnea, CP, syncope, tachycardia, Raynaud's phenomenon (reduced BF causes discoloration & coldness in fingers & toes)

Pharmacologic TXT

1. Some pts are candidates for CCB (long acting nifedipine, diltiazem, amlodipine – verapamil is not recom due to its neg. inotropic effects (dec HR))
2. Digoxin – used in pts with R. HF and low CO and in pts with atrial arrhythmias
3. Prostacyclin analogues- cause VD (IV infu, inf under the skin, inhaled)
4. Endothelin receptor antagonists – block endothelin (a VC)
5. PDE-5i – same drugs used for ED but diff name and doses, these relax the BV in the lungs

PROSTACYCLIN ANALOGS – act as potent VDs and inhibitors of platelet aggregation

- ❖ Epoprostenol (Flolan, Veletri) IV
 - ❖ Treprostinil (Remodulin is IV, Tyvaso is inhaled)
 - ❖ Iloprost (Ventavis)
 1. S/E: drug dose titration, d/n/v (dose limiting), flushing, HA, hypotn, anxiety, CP, tachycardia, edema
 2. With chronic use – anxiety, flu like symptoms, jaw pain
3. Avoid interruptions in therapy, avoid large sudden reductions in dose
 4. Flolan – needs to be on ice packs for proper cooling
 5. IV agents are considered the most potent of all PAH meds
 6. These may inc effects of antihypertensives & antiplatelet agents

ENDOTHELIN RECEPTOR ANTAGONIST (ERAs) – block endothelin receptors on vascular endothelium & SM (endothelin is a VC)

- ❖ Bosentan (Tracleer)
 1. REMS drug – T.A.P. program; due to risk of hepatic impairment & teratogenic effects (Preg Cat X)
 2. S/E: HA, ↓ Hgb, anemia ↑ LFTs, URI, edema, spermatogenesis inhibition
 3. CI: with use of CSA & glyburide; should not be used with St. John's or grapefruit
- ❖ Ambrisentan (Letairis)
 1. REMS drug – LEAP program; due to teratogenic effects (Cat X)
 2. S/E: periph edema, HA, ↓ Hgb, flushing, palpitations, nasal congestion;
 3. should not be used with St. John's or grapefruit

PHOSPHODIESTERASE 5 INHIBITORS – normally, PDE5 degrades cGMP (cGMP causes pulm vascular relaxation and VD)

∴ this is an inhibitor

- ❖ sildenafil (Revatio) IV: 10 mg TID PO: 20 mg TID
- ❖ Tadalafil (Adcirca) PO: 40 mg QD
 1. S.E: dizziness, sudden drop in BP, ha, flushing, dyspepsia, back pain (tadalafil), epistaxis
 2. Priapism – seek medical atten
 3. Sudden vision loss in one or both eyes- seek help, may be permanent
 - a. Other visual probs: blurred vision, inc sensitivity to light, bluish haze, difficulty btw blue/green
- 4. Sudden dec in loss of hearing has been reported
- 5. CI: concurrent use with nitrates, avoid in severe hepatic impairment (tadalafil when CrCl <30)
 - a. DI: do not give with nitrates, ketoconazole, itraconazole
 - b. If used PDE5i and develops ED, do not use nitrate until it has been 24 hrs for sildenafil, 48 hrs for tadalafil. Other antianginal/antiischemic therapies may be used (CCB, BB, ASA, morphine, statins)

[36] ASTHMA

1. Chronic inflammation of the lungs in which the airways are reversibly narrowed
2. S/S: wheezing, breathlessness, chest tightness, coughing
3. Common triggers:
 - a. Allergens - airborne pollens, host dust mites, animal dander, cockroaches, fungal spores
 - b. Drugs – ASA, NSAIDs, sulfites, BB
 - c. Environmental – cold air, fog, ozone, sulfur dioxide, nitrogen dioxide, tobacco, wood smoke
 - d. Exercise – cold air or humid, hot air
 - e. Occupational – bakers (flour dust), farmers (hay mold), spice, enzyme workers; painters, chemical workers, plastics rubber, wood workers
 - f. Resp infxn – RSV, rhinovirus, influenza, parainfluenza, mycoplasma pneumonia

Oral Steroid Dose Equivalents

Betamethasone	0.6 mg
Dexamethasone	0.75 mg
Methylpred/Triamcinolone	4 mg
Prednisone/Prednisolone	5 mg
Hydrocortisone	20 mg
Cortisone	25 mg

Exercise Induced Bronchospasms (EIB)

1. Pretreat before exercise with short acting B2 agonist, LTA, mast cell stabilizers
2. SABA – DOC ; taken right before exercise, lasts 2-3 hrs
3. LABA – longer duration, take 15 mins before (formoterol), 30 mins before (salmeterol) – LABAs should not be used as monotherapy in pts with asthma
4. Montelukast – take 2 hrs before, lasts up to 24 hrs; but only works in 50% of pts
5. Cromolyn (Intal) – give 10-15 mins before; not as effective as SABAs

Pregnancy

1. Albuterol is the preferred SABA
2. Budesonide is the preferred ICS

Drugs used for asthma exacerbations

1. SABA
2. IV steroids
3. Anticholinergics

Asthma maintenance therapy

1. Inhaled steroids
2. LT antagonists
3. Theophylline
4. LABA
5. Cromolyn
6. Omalizumab (Xolair)

BETA 2 AGONISTS

Epinephrine (Primatene Mist) Metaproterenol (Alupent)	Agents should not be used due to non-beta 2 selective	S/E: tremor, shakiness, lightheadedness, cough, palpitations, HYPOK, Hyperglycemia, tachycardia Shake well before use. Prime prior to use and again if >2 wks – breathe in deeply & slowly HFA inhalers have softer, less forceful sprays (CFC inhalers have been d/c due to environmental concerns) If using SABA >2days/wk, need to inc maintenance therapy
Albuterol (Ventolin HFA, Proventil HFA, ProAir HFA, AccuNeb)	1-2 inhalations Q4-6 (MDI)	
Levalbuterol (Xopenex, Xopenex HFA) <i>R isomer of albuterol</i>	1-2 inhalations Q4-6 (MDI)	
Pirbuterol (Maxair Autohaler)		

LABA		
Salmeterol (Serevent Diskus) Salmeterol + fluticasone (Advair Diskus)	1 inh BID, except HFA is 2 inh BID	BBW: ↑ asthma related deaths. Do not use LABA as monotherapy
Formoterol (Foradil) Formoterol + budesonide (Symbicort)	Foradil-1 cap via aerolizer BID ; do not swallow capsule. Symbicort - 2 inh BID	

MAST CELL STABILIZERS – prevents mast cell release of histamine & LT by inhibiting degranulation after contact with allergens/antigens

Cromolyn sodium (Intal)	S/E: unpleasant taste, cough, nausea OTC cromolyn nasal spray- for nasal allergies (NasalCrom)
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CORTICOSTEROIDS

Beclomethasone HFA (QVAR HFA) – solution, do not shake	S/E: dysphonia, oral candidiasis, cough, hoarseness, URI, hyperglycemia, inc risk of fx and pneumonia (with high dose long term)
Budesonide (Pulmicort Flexhaler, Pulmicort Respules) Budesonide + formoterol (Symbicort HFA) – 2 inh BID	
Ciclesonide (Alvesco) do not have to shake before use	ICS are 1 st line for long term control of all ages with asthma Systemic steroids have rapid onset of action and are used as ‘pulse’ therapy – for up to 15 days after asthma attack
Flunisolide HFA (Aerospan HFA)	
Fluticasone (Flovent HFA, Flovent Diskus) Fluticasone + salmeterol (Advair Diskus, Advair HFA) Advair Diskus – 1 inh BID Advair HFA – 2 inh BID	Advair diskus – breathe in quickly & deeply Pulmicort Respules – for ages 1 to 8
Mometasone (Asmanex Twisthaler) Mometasone + formoterol (Dulera) – 2 inh BID	Advair Diskus – for ages ≥ 4 Advair HFA, Symbicort HFA, Dulera – for ages ≥ 12
Triamcinolone (Azmacort)	

LEUKOTRIENE MODIFYING AGENTS - ↓ edema, constriction & inflammation

Zafirlukast (Accolate) LTE4 antagonist	20 mg BID (empty stomach) For ≥ 5 yo	Caution: neuropsychiatric events have been rpt S/E: HA, dizziness, abd pain, ↑ LFTs, URI, pharyngitis, sinusitis, churg strauss syndrome (rare) <i>The granules can be mixed with 1 teaspoonful (5 mL) of baby formula / breast milk/applesauce/mashed carrots, rice, or ice cream (cold or room temperature)</i>
Montelukast (Singulair) LTD4 + E4 antagonist	10 mg QD in evening 6mths-5 yrs = 4 mg, 5-14 yo=5mg	
Zileuton (Zyflo CR) 5-LOX inhibitor that inh LT formation	1200 mg BID Not recom for children	

THEOPHYLLINE – blocks PDE causing ↑cAMP which releases Epi.

Theophylline (IR-Elixophyllin, ER-TheoCap, Theo 24, Theochron)	Therapeutic range = 5-15 mcg/mL Signs of tox: persistent vomiting, vent tachy, seizures	S/E: nausea, HA, tachy, insomnia, tremor, nervousness Avoid excessive amts of caffeine
Has 1 st order kinetics followed by MM	↑ theophylline levels: (3A4 inhibitors)	Theophylline will ↓ Lithium
Drugs that ↑ theophylline levels (1A2 inhibition) – OC, zafirlukast, acyclovir, cimetidine, ciproflox, fluvoxamine, ison	↓ theophylline levels : 3A4 inducers, levothyroxinem charbroiled foods	

Omalizumab (Xolair) – used in moderate to severe asthma (step 5-6 of guideline) for pts with allergies

1. Drug should always be given in the Dr. office. (BBW: anaphylaxis)
2. S/E: HA, inj site rxns, URI, sinusitis

[37] COPD

1. Encompasses chronic bronchitis (chronic inflam, in larger airways) & emphysema (inflamm in alveoli)
2. Caused by noxious particles/gas, most commonly from tobacco smoking.
3. Diagnosis should be considered in pts with: dyspnea, chronic cough/sputum production. Dx should be confirmed by spirometry.
4. Smoking cessation has been proven to slow progression of disease. Vaccinations & drug therapy are also used to manage symptoms.

Pharmacological TXT – used to dec symptoms

1. Bronchodilators (B2 agonists, anticholinergics) – used as needed or on regular basis
 - a. Regular basis : long acting bronchodilators are more effective
 - b. Combo SABA + antichol have greater improvements in lung fxn than either drug alone. + inhaled CS (is approp. for symptomatic severe COPD pts)
2. Vaccines – influenza & pneumococcal are recom to prevent infxn to dec risk of acute exacerbations
3. **Txt algorithm**
 Mild (FEV1 >80% predicted) – SABA
 Moderate (50 < FEV1 < 80%) – add LABA
 Severe (30 < FEV1 < 50%) – Add inhaled glucocorticosteroid if repeated exacerbations
 Very Severe (FEV1 < 30% predicted) – add long term O2 if chronic resp failure; consider surgical txt

ANTICHOLINERGICS

<u>Short acting AC</u> Ipratropium bromide (Atrovent HFA) Ipratropium + albuterol (Combivent, combivent respomat, DuoNeb)	Combivent contains soya lecithin, caution in pts with soybean/peanut allergy	Precaution: use caution in pts with myasthenia gravis, narrow angle glaucoma, BPH, bladder neck obstruction
<u>Long acting AC</u> Tiotropium (Spiriva Handihaler)	1 capsule inhaled QD (req 2 puffs)	S/E: dry mouth (more common w. tiotropium), URI, sinusitis, bitter taste Avoid spraying in eyes Do NOT swallow capsules of tiotropium

LABA

Salmeterol (Serevent Diskus) Salmeterol + fluticasone (Advair Diskus, HFA)	1 inh BID, except HFA is 2 inh BID	S/E: tremor, shakiness, lightheadedness, cough, palpitations, hypokalemia, tachycardia
Formoterol (Foradil) Formoterol + budesonide (Symbicort) Formoterol + mometasone (Dulera)	Foradil-1 cap via aerolizer BID ; do not swallow capsule. Symbicort - 2 inh BID	Bronchodilators are used on a PRN or scheduled basis to reduce symptoms
Arformoterol (Brovana) Indacaterol (Arcapta)		Combo therapy w/ inhaled steroids can ↑ risk of pneumonia, but showed ↓ in exacerbations & improvement in lung fxn

PDE4 inhibitor – ↑cAMP to reduce lung inflammation

Roflumilast (Daliresp) Only used in severe COPD	S/E: wt loss, dec appetite, diarrhea, insomnia, depression, psychiatric events
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Counseling

Albuterol MDI (Proair HFA)

1. Shake inhaler well before each spray
2. Prime inhaler 1st time and if >14 days (spray in air 3x)
3. Push top of canister down while you breathe in deeply and slowly.
4. If must repeat, wait 1 minute and shake inhaler again
5. Throw inhaler away after 200 sprays. You may not be receiving the correct amt of medicine

Advair Diskus

1. Dose indicator on the top tells you how many doses are left
2. Breathe out away from the diskus and put the mouthpiece to your lips. Breathe in quickly and deeply.
3. Rinse your mouth with water and spit. Do not swallow
4. Never wash the mouthpiece, keep it dry

Flovent HFA

1. Prime the inhaler – shake for 5 sec, spray the inhaler into the air. Shake and spray 3 more times. The counter should now say “120”
 - a. Must prime upon 1st use and if not used >7 days
2. Breathe deeply and slowly. Hold for 10 sec. rinse mouth with water and spit
3. Clean the inhaler Qweek

Symbicort HFA

1. Take 2 puffs QAM, 2 every evening (Rinse mouth with water)
2. Prime before using first time and if >7 days (shake for 5 sec, release a test spray, repeat 1 more time)
3. Clean inhaler Q 7 days

Singulair

1. Take QD in the evening +/- food
2. Singulair oral granules to a child: can be given directly in mouth, dissolved in 1 tsp of baby formula or breast milk, or mixed with spoonful of applesauce, mashed carrots, rice, ice cream – do not put in any other liquids

COPD - Atrovent Counseling

1. Keep eyes closed so that no medicine sprays in the eyes – can cause blurry vision, eye pain, dilated pupils, narrow angle glaucoma
2. Breathe in slowly and at the same time spray the Atrovent

COPD - Combivent counseling

1. Can cause the narrowing of the airways to get worse (paradoxical bronchospasm)
2. Shake and test spray when using it for the 1st time and when has not been used for >24 hrs (vigorously shake the container and test spray in the air 3x – avoid eyes)
3. Keep eyes closed so that no medicine sprays in the eyes – can cause blurry vision, eye pain, dilated pupils, narrow angle glaucoma
4. Breathe in slowly and at the same time spray. Wait approx. 2 mins and repeat.

COPD - Spiriva counseling

1. Always store Spiriva capsules in sealed blister packs. Remove only 1 spiriva capsule right before use.
2. Insert capsule in center chamber and close the mouthpiece. Press the green button until it is flat against the base and release
3. Breathe in slowly and deeply so that you hear/feel the capsule vibrate. Breathe in until lungs are full
4. To make sure you get the full dose, you must breathe out and inhale again
5. Clean the Handihaler Qmonth (rinse with warm water and let air dry for 24 hrs)

[38] SMOKING CESSATION

1. Counseling + medication are more effective when used together than either alone
2. There is a strong correlation btw counseling intensity & quitting success (sessions should be >10 mins & number of sessions should be ≥ 4)
3. 1st line = nicotine replacement
 - a. Use combination products when a single agent is not enough (patch + gum, NS, inhaler OR bupropion + patch)
4. Smoking induces P450 isoforms, therefore when quitting, smokers can exp. s/e form supratherapeutic levels of caffeine, theophylline, fluvoxamine, olanzapine, clozapine
5. Smoking in pregnancy: can cause spon abortion, low birth weight, sudden infant death.
 - a. women who smoke < 5 cigs/day → encourage quitting with behavioral support
 - b. > 5 cigs/day → ACOG recom bupropion, other sources recom nicotine replacement
 - c. All nicotine replacement products are Cat D (gum Cat C), bupropion Cat C.

Nicotine Replacement Therapy

Nicotine gum (Nicorette) – OTC	If <25 cigs/day – 2 mg gum >25 cigs/day – 4 mg gum Max 24 pieces/day Dyspepsia, mouth soreness, hiccups, jaw ache	<ul style="list-style-type: none"> • All are Preg Cat D (gum Cat C) • Must be 18 yo to purchase • Gum has been shown to dec or delay wt gain • Inhaler has hand to mouth use, mimics smoking action • Inhaler has fastest delivery, highest dependence potential • Patch is worn for 24 hrs, 16 to avoid insomnia
Nicotine inhaler (Nicotrol inhaler) - RX		
Nicotine NS (Nicotrol NS) - RX		
Nicotine patch (NicoDerm CQ, Habitrol) –OTC or RX Highest adherence rate	Apply upon waking on quit date >10 cigs/d use 21 mg/24 hrs.. <10 cigs/d use 14 mg/24 hrs -insomnia, vivid dreams, local skin rxn	
Nicotine lozenge (Commit) - OTC	1 st cig smoked >30 mins after waking up – use 2 mg 1 st cig smoked <30 mins after waking up – use 4 mg	

Bupropion SR (Zyban)

1. Blocks neural reuptake of DA and/or NE and blocks nicotinic Ach receptors
2. Can be used in combo with NRT
3. Start 1-2 wks before quit date
4. BBW: not approved for bipolar, inc risk of suicidal thoughts in young adults w/ depression/other psychiatric d/o
5. S/E: dry mouth, insomnia, HA/migraine, n/v/c, **seizures** * wt loss (no effects on 5HT ∴ **no sexual dysfxn**)
6. CI: hx of seizures, eating disorder, MAOi use in 14 days, taking another form (Wellbutrin)
7. **DNE 450 mg QD due to seizure risk**
8. **MedGuide** required bc its an antidepressant

Varenicline (Chantix)

1. A partial neuronal alpha4-beta 2 agonist, also stimulates DA to a small degree.
2. Combo NRT NOT recommended (bc of nicotine antagonist properties)
3. Start 1 wk before quit date
4. Take with food & water to dec nausea; take 2nd pill at dinner not HS due to insomnia
5. BBW: serious neuropsychiatric events incl depression, suicidal ideations and attempts
6. S/E: **nausea (>30%)**, abnormal dreams, constipation, vomiting, **serious skin rxn**
7. **Use with caution in pts with underlying psych d/o & while driving (avoid use in pilots, air traffic controllers, truckers)**
8. **MedGuide** req.

Nicotine Replacement Counseling

1. GUM –
 - a. Gum should be chewed until a peppery/flavored taste emerges, then “parked” for 30 mins.
 - b. Acidic beverages (coffee, juices, sodas) dec buccal abs. so avoid anything except water for 15 mins before/during chewing
 - c. Use at least 1 piece Q 1-2 hrs
2. Inhaler
 - a. Freq, continuous puffing for 20 mins is advised with each cartridge. Once a cartridge is opened, its only good for 1 day
 - b. Acidic beverages dec buccal absorption
3. Lozenge
 - a. Allow it to dissolve in the mouth, do not chew/swallow it
 - b. Acidic bev dec absorption
 - c. Use 1 lozenge Q 1-2 hrs (minimum 9/day)
4. Patch
 - a. Apply in hairless location, typically between the neck and waist
 - b. Should be applied as soon as pt wakes up on quit day. For those who experience sleep disruption, remove the 24 hr patch before bedtime or use 16 hr patch
 - c. Can experience local skin rxns (50%), can treat with hydrocortisone cream 1% or triamcinolone cream 0.5% & rotation site can help

Bupropion counseling

1. It takes about 1 wk for med to start working. Do not stop smoking until after 1 week
2. Most common s/e = dry mouth, trouble sleeping (generally mild and disappear after a few wks)
3. Some pts experience allergic rxns (rash, itching, hives, fever, sores in mouth, etc) – notify Dr.
4. Do not take if hae seizure d/o, taking Wellbutrin, MAO within last 14 days
5. Do not exceed 450 mg /day due to risk of seizures
6. If you notice agitation, change in mood, etc – notify Dr.

Varenicline counseling

1. Choose quit date and start taking medication 1 wk before quit date. This allows medication to build up in body
2. Take med after eating with food glass of water
3. Most ppl take it for up to 12 wks. Another 12 wks may help if pts stopped smoking after 1st 12 wks
4. Tell Dr. if you’ve had depression/ other mental d/o before
 - a. If you notice agitation, change in mood, etc – notify Dr.
5. Some pts experience allergic rxns to this med (swelling of face, mouth, throat) – seek help
6. Some ppl can have serious skin rxns – rash, redness, peeling of the skin. If rash with peeling of skin/blisters in mouth. Stop taking medication and seek help
7. Caution with driving, can cause sleepiness, dizziness, trouble concentration – until you know how the med affects you

[39] ALLERGIC RHINITIS

- Symptoms of Rhinitis (inflam of membrane linings in nose) = sneezing, nasal itch, rhinorrhea, nasal congestion, postnasal drip
- 1st line for mild-moderate disease = oral antihistamines
- 1st line for moderate-severe disease = intranasal corticosteroids

INTRANASAL CORTICOSTEROIDS – most effective medication class in controlling symptoms of allergic rhinitis.

1. S/E: local irritation, burning/stinging, nasal bleeding, nasal septal perforation (rare)
 - ❖ Beclomethasone (Beconase, Beconase AQ, Vancenase)
 - ❖ Budesonide (Rhinocort Aqua)
 - ❖ Ciclesonide (Omnaris)
 - ❖ Flunisolide (Nasarel, Nasalide)
 - ❖ **Fluticasone furoate (Veramyst)**
 - ❖ **Fluticasone propionate (Flonase)**
 - ❖ **Mometasone (Nasonex)**
 - ❖ **Triamcinolone (Nasacort AQ)**

ORAL ANTIHISTAMINES – H1 antagonist; 1st line for mild-moderate disease

- Effective in reduction symp of itching, sneezing, rhinorrhea. Little effect on congestion. Also help with allergic conjunctivitis
- 2nd generation has less side effects (less sedation)

1st Generation → S/E: sedation, anticholinergic (dry mouth, blurry vision, urinary retention, constipation); caution with BPH-more difficult to urinate

- ❖ Chlorpheniramine (Chlor-Trimeton)
- ❖ Clemastine (Tavist) do not use in pregnancy
- ❖ **Diphenhydramine (Benadryl)**

2nd Generation → sedation can be seen occasionally (more with cetirizine & levocetirizine – these also have a faster onset of ~1 hr)

- ❖ **Cetirizine (Zyrtec)**
- ❖ **Desloratidine (Clarinox)**
- ❖ **Fexofenadine (Allegra) → orange, grapefruit, apple juice ↓ GI abs. separate by 4 hrs.**
- ❖ **Levocetirizine (Xyzal)**
- ❖ **Loratadine (Claritin, Alavert)**

Intranasal antihistamines → S/E : bitter taste, helps with congestion as well.

- ❖ **Azelastine** (Astelin, Astepro)
- ❖ Olopatadine (Patanase)

DECONGESTANTS

1. MOA: **α Agonists** that causes nasal VC to urinate). Antihistamines & decongestants will make it more diff. to urinate
2. S/E: (moreso with pseudoephedrine) nervousness, restlessness, excitability, dizziness, HA, fear, anxiety, tremors, possibly seizures.
3. Use caution with HTN, tachycardia, CV conts, hyperthyroidism (worsens), glaucoma (can worsen IOP), DM (can raise BG), prostate enlargement (more difficult
4. **DO NOT use with MAOIs (both are Preg C)**
5. If a product contains “D” after it (mucinex D or robitussin D), it usually contains a decongestant (pseudoephedrine, phenylephrine)

- ❖ **Pseudoephedrine (Sudafed)** 30 mg 1-2 tabs Q12 hrs
- ❖ **Phenylephrine (Sudafed PE)** – much less effective than pseudoephedrine, 5 mg 1-2 tabs Q4-6 (max 8/day)

Topical Agents – also effective, also are α Agonists & have similar s/e if used excessively.

- ❖ Naphazoline (Privine)
- ❖ Phenylephrine (Neo-Synephrine 4 hr)
- ❖ Oxymetazoline (Afrin, Neosynephrine 12 hr)
→ *generally causes less s/e than phenylephrine & lasts 12 hrs; it's a popular product RPhs recommend*
- ❖ Tetrahydrozoline (Tyzine)
- ❖ Xylometazoline (Otrivin)

ADDITIONAL ALLERGY AGENTS

- ❖ Intranasal cromolyn (Nasal crom)
 - Takes 4-7 days to see symptom relief. Not as effective as other agents
 - Due to safety profile, consider for young children & pregnancy
- ❖ Intranasal ipratropium bromide (Atrovent NS)
 - Effective for rhinorrhea, but no effect on other symptoms (can cause nasal dryness)
 - Usually used in combo if rhinorrhea is the major problem
- ❖ Oral antileukotrienes (Singulair)
 - Not any more effective than antihistamines and pseudoephedrine
- ❖ Neti Pot
 - Looks like a genie lamp/teapot. Its used to hold salt water (saline solu) that is poured into one nostril and allowed to drain out of the other. Can clear out nasal passage and dec swelling.
 - Safe for children & pregnancy. Can cause burning/stinging in nose

ADDITIONAL COUGH & COLD AGENTS

<u>Influenza</u>	<u>Cold</u>
<ul style="list-style-type: none"> • Causes body aches • Causes a fever • Coughs are worse 	<ul style="list-style-type: none"> • No body aches • Generally no fever • Cough is more like an annoying drip in the back of the throat • Causes more nasal symptoms (dripping/clogged nose)

Natural products used for colds:

1. Zinc – used for cold prevention & txt. Little efficacy data but zinc lozenges may slightly dec cold duration if used correctly (Q2 hrs while awake starting within 48 hrs of symptom onset)
 - a. Do not recom zinc nasal swabs/sprays due to risk of loss of smell
2. Vitamin C suppl – little efficacy for cold prevention. They may dec duration of the cold by 1-1.5 days
3. Echinacea – imp to use correct dose in a reputable formulation
4. Airborne – contains a variety of ingred (Vit C,E, Zn, Echinacea) – costly and has no known benefit in the combos provided

Dextromethorphan (most common brand = **Delsym**)

1. *Most commonly used cough suppressant.*
2. *If a product contains “DM” (robatussin DM) it contains dextromethorphan*
3. MOA: acts as a 5HT reuptake inhibitor, there is a risk of SS if taken in high doses with other 5HT meds.
 - a. *When used as abuse in large quantities, it can act as an NMDA receptor blocker – euphoric, hallucinogenic.*

Guaifenesin (common brand is **Mucinex**)

1. *An expectorant used to dec viscosity of phlegm in the lower resp tract & may inc secretions in the upper resp tract (to move phlegm upwards)*
2. *It is unclear if guaifenesin provides a useful benefit, but some pts feel it is useful.*

COUGH & COLD PRODUCTS FOR CHILDREN

1. OTC cough and cold products should NOT be used in children <4 yo
2. FDA has a warning not to use antihistamines (benedryl) to make children sleepy.
3. Promethazine is used by rx only – do not use promethazine in any form in children. FDA advises against the use of promethazine with codeine cough syrups in children <6 yo (due to risk of resp depression, cardiac arrest)
4. It is safe to recom nasal bulb – for gentle suctioning, saline drops/sprays (Ocean) →tell parents that the medicines have not been shown to work in young children, and symptoms usually resolve in a few days – 2 wks
5. Do not use ASA in children due to risk of Reye's syndrome (ibuprofen & APAP are safe)
6. Menthol & camphor used topically (Vicks' vaporub) do not work well and should not be used in children <2yo. Risk is due to ingestion, Menthol can result in aspiration and cardiac and CNS toxicity if ingested. Camphor is rarely unsafe (debated)
 - a. Vick's babyrub contains petrolatum, it is not thought to be harmful but there is no evidence of efficacy
7. Humidifiers and vaporizers are useful. Hot water types can cause burns in children if spilled.

APAP & Ibuprofen in children (let pediatrician recom if <4 yo) – some Dr. recom alternating so there is no risk for APAP toxicity & due to feared stomach upset from ibuprofen

- | | |
|---|--|
| 1. APAP infant drops = 80 mg/0.8 mL (15 mg/kg) Q4-6 hrs | 3. Ibuprofen infant drops = 50 mg/1.25 mL (10-15 mg/kg) Q6-8 h |
| 2. APAP childrens liquid susp = 160 mg/5 mL (Q4-6 hrs) | 4. Ibuprofen childrens liquid susp = 100 mg/5 mL (Q6-8h) |

Veramyst Counseling

1. Priming : before using it for the 1st time and if has not been used for 30 days, cap left off for ≥5 days
 - a. Shake the device, press the button 6 times or until a fine mist is sprayed
2. Gently blow your nose, tilt your head forward a little bit, and spray
3. Do not spray into eyes – rinse your eyes well if you do

Drug	Allergic Rhinitis	Asthma
Beclomethasone	Beconase, Beconase AQ, Vancenase	QVAR HFA
Budesonide	Rhinocort Aqua	Pulmicort flexhaler/Respules
Ciclesonide	Omnaris	Alvesco
Flunisolide	Nasarel, Nasalide	Aerospan HFA
Fluticasone furoate	Veramyst	-
Fluticasone propionate	Flonase	Flovent HFA/Diskus
Mometasone	Nasonex	Asmanex twisthaler
Triamcinolone	Nasacort AQ	Azmacort

Tussionex : hydrocodone/chlorpheniramine; antitussive (5 ml/12 hrs, do not exceed 10 ml/24 hrs)

[40] CYSTIC FIBROSIS

- An inherited disease that causes thick, sticky mucus to form in the lungs, pancreas, and other organs
 - a. In the lungs, this mucus blocks the airways, causing lung damage, and making it hard to breathe.
 - b. In the pancreas, it clogs the pathways leading to the digestive system, interfering with digestion
- Presentation: SOB (due to reduced expiratory volume), cough and sputum production, digital clubbing due to chronic hypoxia
- TXT for intestinal & nutritional problems:
 - a. Pancreatic enzymes to replace those that are missing
 - b. Vitamin supplements, esp fat soluble vitamins ("F" AKED)
- TXT for lung problems:
 - a. Inhaled bronchodilators (**Albuterol**, dose is 2 puffs prior to therapy 2-4x/day)
 - b. **Hypertonic saline (HyperSal)** – for hydrating the airway mucus secretion and facilitating mucociliary fxn
 - c. DNase enzyme replacement therapy – to thin mucus and make it easier to cough up
 - i. **Acetylcysteine (Mycomyst)** – a mycolytic that is also used for APAP tox. It has questionable benefit in CF as it may damage lung tissue.
 - ii. **Dornase alfa (Pulmozyme)** – the preferred mucolytic agent. It is a DNA enzyme produced from hamster ovaries, it cleaves DNA therefore reduces the viscosity.
S/E: CP, voice alterations, throat irritation
2.5 mg neb QD x 6 mths
 - d. Inhaled abx – to prevent and treat lung and sinus infxn
 - e. Lung txp

Controlling Infxn in Lungs

1. Staphylococcus aureus (early on), H. influenza, pseudomonas aeruginosa (later on) – most common orgs that cause lung infxns in CF pts
 2. Productive cough & change in sputum color (green) are the 1st resp symptoms of an infxn. Extended course of abx (2-4wks) is generally given
 3. Pseudomonas aeruginosa – 2 drugs given IV are given to prevent resistance (aminoglycosides, beta lactams, quinolones, etc)
 - a. Doses tend to be larger than normal due to large VD and the need to obtain therapeutic levels in lung tiss.
 4. Inhaled abx are used to prevent infxn- if these are given, make sure to give them last (bronchodilator → chest percussion to clear mucus → inhaled abx)
- ❖ Tobramycin Inhaled Solution (TOBI) 300 mg via neb Q12 x28 days, followed by 28 day off cycle
 - S/E: **ototox, tinnitus, dizziness, bronchospasm**. Little systemic absorption
 - Do not use TOBI if it is cloudy, do not expose to intense light
 - Take doses close to 12 hrs apart, and not less than 6 hrs apart
 - ❖ Aztreonam Lysine Inhalation Solu (Cayston) 75 mg TID x 28 days, followed by 28 day off cycle
 - S/E: **allergic rxns, bronchospasm, fever**

Pancreatic enzyme products : **Creon, Pancreaze, Zenpep** (these are FDA approved)

1. Thick mucus obstructs pancreatic enzyme flow. Freq greasy, foul smelling stools are manifestations of this pancreatic insuff.
2. Pancrelipase – a natural product harvested from porcine pancreatic glands. They are formulated to dissolve in more basic pH of the duodenum (acts locally to break down fats, proteins, starch)
 - a. do not use doses >6000 units/kg/meal due to colonic stricture risk
3. enzymes are given before meals and snacks : full doses are given before meals, ½ dose are given with snacks
4. if a pt cannot swallow them whole, the microsphere contents can be sprinkled on low pH foods (applesauce, gelatin, baby food) . Do not mix with milk based foods (yogurt/pudding) since they have higher pHs
5. **take entire dose at the beginning of each meal/snack. Take with generous water.**

[41] ONCOLOGY

- Characterized by uncontrolled growth and spread of abnormal cells
- Can be caused by external factors (chemicals, radiation, infxn organisms, viruses) or internal factors (hereditary, hormones, immune d/o, genetic mutations)
- Malignancies are based on tissue type: epithelial, connective, lymphoid or nerve
- Pregnancy & breastfeeding: chemotherapy should be avoided
- Dosing: normally based on $\text{Body Surface Area} = 0.007184 \times [\text{wt}(\text{kg})^{0.425} \times \text{ht}(\text{cm})^{0.725}]$
 - Actual wt is usually used, unless pt is overweight (>130% IBW), then use adjusted body wt

Screening Recommendations

Breast cancer

- Mammograms Q year starting Age 40.
- Clinical breast exam (CBE) 20-30 yo → Q 3 years
40+ → Q year
- Breast self exam (BSE) optional for women 20+
- Am cancer society recom those with FH or genetic tendency or other factors to be screened w. an MRI + mammogram earlier than age 40.

Colorectal cancer

- Men + women follow a schedule (combo sigmoidoscopy, colonoscopy, barium enema, CT scan) + Q year fecal occult blood test (FOBT) or fecal immunochem test (FIT)

Cervical cancer

- All women 3 yrs after begin having intercourse (no later than 21 yo) screen Q year with Pap test or Q 2 years with liquid based Pap test

Prostate cancer

- Not yet proven if benefits outweigh risks
- Provide info for Men 50+ . If FH or Af Am, then screening should be started at 45yo
- PSA blood test +/- digital rectal exam (DRE) is standard

Only listed the bolded/underlined items

Alkylators – cross links DNA, preventing cell replication

- ❖ Cyclophosphamide (Cytosan) IV/PO
- ❖ Ifosfamide (Ifex) IV
- ❖ Temozolomide (Temodar)
- ❖ busulfan (Myleran), carmustine (BiCNU, Gliadel), lomustine (CeeNU)
 1. S/E: myelosupp, n/v, alopecia
 2. Pulm toxicity with busulfan, carmustine, lomustine. Neurological tox with ifosfamide, chlorambucil, temozolomide
 3. Bladder toxicity with HD cyclophosphamide & ALL doses of ifosfamide – Give MESNA (Mesnex) to protect against hemorrhagic cystitis and also ensure adequate hydration

Antiandrogens – used for prostate cancer – blocks androgens at the receptor site. Given PO QD

- ❖ Bicalutamide (Casodex)
- ❖ Flutamide (Eulexin)
 1. S/E: d/n/v, gynecomastia, hot flashes, dec libido, impotence

Antiandrogen – antiestrogen – LHRH Agonist

Used for prostate CA in males and endometriosis, fibroids, and breast CA in females. Initially ↑ production of androgens and estrogens, followed by down regulation thru a neg feedback loop resulting in suppressed gonadotropin release, LH, FSH.

- ❖ Goserelin (Zoladex) Inj
- ❖ Leuprolide (Lupron) Inj
 1. S/E: hot flashes, bone pain, impotence, inj site pain, dyslipidemia, QT prolongation, gynecomastia, periph edema
 2. Dec bone density and inc risk of osteoporosis, consider Vit D and Ca.

Antiandrogen-antiestrogen – Aromatase inhibitor : ALL PO
Prevents conversion of active estrogen, androgen, CS,
mineralocorticoid to reduce cell growth in breast, prostate,
and or adrenal CA ; DOC for estrogen receptor breast
tumors

- ❖ Anastrozole (Arimidex)
- ❖ Exemestane (Aromasin)
- ❖ Letrozole (Femara)
 1. S/E: lethargy/fatigue, rash, menopause symp, hot flashes, n/v
 2. Dec bone density, risk for osteop
 3. Inc CV disease compared to SERMS
 4. Counseling: treats breast CA in pts who have finished menopause, does not work in those who have not.

Antiestrogen/SERMS – most PO, fulvestrant is IM
Selectively blocks estrogen at receptor site. For breast CA
in hormone receptor + tumors

Counseling: used for prevention/txt of breast CA

- ❖ Fulvestrant (Faslodex) *only one in this class that increases the risk of ↓bone density.*
- ❖ Raloxifene (Evista) – Antag at breast, Agonist at bone (used for osteoporosis in women at risk of breast CA)
- ❖ Tamoxifen (Nolvadex)
 1. S/E: menopausal symp, hot flashes, flushing, n/v, edema, wt gain
 2. Tamoxifen inc risk of endometrial cancers, others dec risk
 3. Tamoxifen 2D6 polymorphism *4/*5 results in shorter disease free survival, consider alternative therapy (Aromatase inh)
 4. BBW: inc risk of thromboembolic events with all SERMS

Anthracyclines

- ❖ Daunorubicin (Cerubidine)
- ❖ Doxorubicin (Adriamycin)
- ❖ Epirubicin (Ellence)
- ❖ Mitoxantrone (Novantrone)
 1. Very effective but use limited by cardiac tox and n/v
 2. S/E: myelosupp, alopecia, mucositis, hyperpigmentation, RED urine & bodily secretions
 3. Radiation recall rxns occur

4. Liposomal products are assoc with higher incidence of handfoot syndrome and allergic rxns
5. Cardiotoxic dec by not exceeding max lifetime dose:
 - a. Doxorubicin max lifetime = 400-500 mg/m²
 - b. Daunorubicin max lifetime = 550 mg/m²
 - c. Epirubicin max lifetime = 900 mg/m²
 - d. Idarubicin risk inc >150 mg/m²
6. **Cardioprotective dexrazoxane (Zinecard)** should be considered when doxorubicin doses are >300 mg/m²
7. Mitoxantrone is an anthracendione similar to anthracyclines in toxicity, but has a 3 membered ring instead of 4 and turns bodily fluids **BLUE** not red

Folate Antimetabolites

- ❖ Methotrexate (MTX, Trexall, Mexate, Folex)
 1. Lower doses are used for RA and psoriasis (7.5-22.5 mg Qweek)
 2. S/E: myelosupp, mucositis (irritation in oral cavity, cannot swallow), hepatic and renal tox, pulm toxicity
 3. Red tender palms & feet (hand-foot syndrome)
 4. High dose MTX req. leucovorin (or levoleucovorin) rescue to ↓ MTX toxicity (Leucovorin is the active form of folic acid bypassing the enzyme block of dihydrofolate reductase by MTX → **used with MTX or 5-FU to replace folic acid**)
 5. Active transport elimination is ↓ by: ASA, PCNs, probenecid, NSAIDs (avoid concurrent use)
 6. Maintain hydration & drink fluids

Immunomodulators – dec angiogenesis

- ❖ Lenalidomide (Revlimid) PO – only avail thru special pharmacy
 1. S/E: neutropenia, thrombocytopenia. Constipation, diarrhea, fatigue, fever, cough, itch, rash. DVT & PE – seek medical care if have SOB, BP, arm/leg swelling!
 2. Preg Cat X – severe birth defects. Must be under RevAssist program (pt, prescriber, pharmacist)
- ❖ Thalidomide (Thalomid) PO – take at least 1 hr after a meal
 1. S/E: somnolence, constipation, dizziness, ortho hypotn, rash, neuropathy, neutropenia, thrombocytopenia. DVT/PE. – consider ppx anticoagulation
 2. Preg Cat X – severe birth defects. Must be under STEPS (prescriber, pharmacist)

Interferons

1. All cause: Depression, suicidal ideations, flu like syndrome
- ❖ Interferons-alfa
 - Alfa-2a (Roferon)
 - Alfa-2b (Intron A)
 - ❖ Peginterferon
 - Alfa-2a (Pegasys)
 - Alfa-2b (PEG-Intron, Sylatron)
 - ❖ Interferons-beta
 - Beta-1a (Avonex)
 - Beta-1b (Betaseron)

Monoclonal antibody- Angiogenesis inhibitor

- ❖ Bevacizumab (Avastin)
 1. Only avail for compassionate use. FDA pulled it due to no efficacy data

2 other drugs that need pharmacogenomic testing:

1. Carbamazepine – Asians need bl tst; should also include oxcarba & phenytoin
2. Abacavir – everyone is tested, if (+) then at risk for hypersensitivity syndrome

Monoclonal antibody- Cell Surface Marker Target

- ❖ Alemtuzumab (Campath) – severe prolonged myelosuppr (2-12 mths) req ppx abx for minimum of 2 mths
- ❖ Gemtuzumab (Mylotarg) – very light sensitive, must prepare in the dark
- ❖ Tositumomab (Bexxar) – thyroid protective iodine regimen needed prior to use.
- ❖ Rituximab (Rituxan) – infusion rxn (hypoten, angioedema, bronchospasm, etc) ; infusion must be given in hosp/clinic since they can be fatal. Pretreat before infusion.
 - Rituximab is a RA (refractive agent) never first line, only given if other agents do not work

Monoclonal antibody – over expression targeted

- ❖ Cetuximab (Erbix) – Pharmacogenomics: colorectal CA does NOT respond to cetuximab/panitumumab if pts have K-ras mutation. *must test for K-ras mutation before txt
- ❖ Trastuzumab (Herceptin)
 - Trastuzumab binds and reverses effects of overactive HER2 receptors. Must be >2+ by immunohistochemical (IHC) testing to respond/use
 - Causes cardiomyopathy (CHF, ↓LVEF)

Platinum Based Compounds – x links DNA, leading to apoptosis

- ❖ Carboplatin (Paraplatin-AQ)
- ❖ Cisplatin (Platinol)
 1. Cisplatin S/E: ototox, nephrotox (vigorous hydration and sometimes mannitol used to avoid renal failure. Req K & Mg suppl due to electrolyte wasting. **Amifostine (Ethyol)** may be used ppx against renal damage.
 2. Causes severe n/v *worst nausea drugs
 3. Both drugs: hypersensitivity rxn (pretreat w/ steroids & antihistamine)
- ❖ Oxaliplatin (Eloxatin)
 1. S/E: neuropathy exacerbated by exposure to cold. Infusion of Ca & Mg can reduce neuropathy

Purine Analog Antimetabolites

- ❖ Azathioprine (Imuran) – prodrug of Mercaptopurine; but not used in oncology setting
- ❖ Mercaptopurine (6-MP, Purinethol)
 1. 6-MP undergoes extensive met. in the liver by xanthine oxidase (inhibited allopurinol which can raise levels by 400-500%)
 2. Pharmacogenetic testing for TPMP and ITPA deficiency is req. before starting therapy to properly dose/avoid toxicity

Pyrimidine Analog Antimetabolites

- ❖ Capecitabine (Xeloda) – prodrug of 5-FU, take with meals.
- ❖ Fluorouracil (5-FU, Adrucil) – for chemo its given with leucovorin to inc efficacy of 5-FU
 1. Both require- Pharmacogenomic testing for dihydropyrimidine dehydrogenase (DPD) deficiency (inc risk of severe toxicity)
- ❖ Floxuridine (FUDR)
 - Analog of 5-FU given via intrahepatic artery/portal vein infusion for isolated hepatic metastases, less than 10% reaches systemic circ so less toxicity
- ❖ Gemcitabine (Gemzar) – flu like syndrome (pretreat APAP)

Retinoids (Vit A analogs)

- ❖ Tretinoin (All Trans Retinoic Acid) – Preg Cat X ; lots of SE

Taxanes

- ❖ Docetaxel (taxotere)
 - Hypersensitivity rxn (50%); Cardio-pulmonary : fluid retention – [use CS to prev](#)
- ❖ Paclitaxel (Taxol), albumin bound formulation (Abraxane)
 - Hypersensitivity rxn (78%), pretreat with dexamethasone, diphenhydramine, H2 blocker (not needed with Abraxane bc less hypersen rxn)

Topoisomerase I inhibitors

- ❖ Irinotecan (Camptosar) – acute diarrhea is a cholinergic symp
 - Pharmacogen testing: homozygous for UGT1A1*28 allele are at inc risk of neutropenia

Topo II inhibitor

- ❖ Etoposide (Vepesid, VP-16) – Vepesid capsules req refrigeration
 - Myelo, neurotox, neuropathy, hepatotox, alopecia; hypoten infu if too fast

Tyrosine Kinase Inhibitor (TKI) “-nib”

Targeting BCR-ABL

- ❖ Imatinib (Gleevec) PO with water & full meals

Targeting EGFR

- ❖ Erlotinib (Tarceva) PO 1 hr before, 2 hrs after meal

Vinca Alkaloids

- ❖ Vinblastine (Velban)
- ❖ Vincristine (Vincasar)
- ❖ Vinorelbine (Navelbine)
 1. Cumulative (dose dep) nerve damage (paresthesias, gastroparesis, paralytic ileus, risk falls)
 2. Vesication occurs when extravasated*, treat with hyaluronidase and moderate heat
 3. IV only, do not admin intrathecally (fatal)

Misc

- ❖ Arsenic trioxide (Trisenox)
 - QT prolongation
- ❖ Bleomycin (Blenoxane)
 - Pulm rxns, most common pneumonitis, hypersen rxn
 - Bleomycin max lifetime dose = 400 units

Management of Side Effects

ANEMIA

1. ESAs can shorten survival & inc tumor progression in some cancers
2. Prescribers must be enrolled and certified by the ESA APPPRISE Oncology program. Pts must sign a form stating that they understand the risks and benefits. & MedGuides must be given with each rx and filling
3. Normal levels:
 - a. Female Hgb =12-16 g/dL Hct=36-46%
 - b. Males Hgb = 13-18 g/dL Hct = 37-49%
4. ESAs should only be used if Hgb <10 g/dL and pts should be symptomatic
5. Txt:
 - a. Epoetin alpha (Procrit, Epogen) SC Qweek
 - b. Darbepoetin (Aranesp) SC Q 2-3 weeks
6. ESAs are assoc with: CHF, CP, thrombosis, arrhythmias, CV death
7. Common s/e: HTN, hypotension, arthralgias/myalgias, inj site pain, edema, fatigue, HA

NAUSEA & VOMITING: Prevention is essential

1. Certain agents (cisplatin) have inc risk of emetogenicity, these high risk agents req ppx
2. Pt factors that ↑ risk = female, <50 yo, dehydration, hx of motion sickness, hx of n/v with prior regimens
3. Anthracyclines, carboplatin, oxaliplatin = moderate risk. But if used in high doses = high risk
4. Txt to prevent n/v: (esp if given with a platin)
 - a. Dexamethasone
 - b. Ondansetron or other 5-HT3 blocker
 - c. Aprepitant (NK1 blocker)
5. At any point, an adjunct of lorazepam (Ativan) may be added for anxiety/amnestic response OR an H2 blocker or PPI if upper GI sym (similar to GERD) are present

NEUTROPENIA

1. ANC < 500 = high risk for poor outcome ANC < 100 = severe risk for infection
2. Txt: Colony Stimulating Factors (CSF)
 - a. Sargramostim (GM-CSF, Leukine)
 - b. Filgrastim (G-CSF, Neupogen)
 - c. Pegfilgrastim (pegylated G-CSF, Neulasta)
3. These are expensive and do not improve overall survival outcomes, they do shorten the time a pt is at risk due to neutropenia when given ppx in pts with high risk of febrile neutropenia
4. GM-CSF is limited to use in stem-cell txp, both G-CSF are indicated in febrile neutropenia
5. S/E: bone pain

THROMBOCYTOPENIA

1. Normal range plt = 150,000-450,000
2. Plt transfusions are generally indicated when < 10,000
3. Prevention with Oprelvekin (IL-11, Neumega)
 - a. s/e: significant therefore use is limited in clinical setting. (hypersens rxn, anaphylaxis, edema, tachycardia, a fib, pleural effusions, dyspnea)
6. An agent with low emetogenic risk may req a single agent such as dexamethasone, prochlorperazine, or metoclopramide
 - a. Prochlorperazine (phenothiazine like agents) & Metoclopramide (Reglan) – DA blocking agents and can worsen/cause mvmt disorders. Both are sedating & can cause cognitive dysfxn
 - b. Metoclopramide (Reglan) – req dose reduction in renal dysfxn
 - c. Diphenhydramine- cent acting antihistamine, cause central & periph antichol s/e (may be intolerable in elderly pts)
7. Dronabinol (Marinol) and Nabilone (Cesamet) are used 2nd line
 - a. Synthetic delta-9-tetrahydrocannabinol (THC), a nat. occurring component of cannabis (marijuana)

Antiemetic Agents

5-HT3 Antagonists

- ❖ **Ondansetron (Zofran)**
- ❖ **Granisetron (Kytril, Sancuso transdermal patch)**
- ❖ **Dolasetron (Anzemet)**
- ❖ **Palonosetron (Aloxil)**
 1. S/E: HA, fatigue, dizziness, constipation/diarrhea
 2. Risk of QT prolongation with all agents. Correct Mg, K

Phenothiazines

- ❖ **Prochlorperazine (Compazine)**
- ❖ Chlorpromazine (Thorazine)
- ❖ **Promethazine (Phenergan)** only IM, PO, rectal (no IV due to risk of severe tissue injury (gangrene) or SC)
 1. Do not use in children <2 yo
 2. S/E: sedation, lethargy, hypotn, NMS, QT prolongation, acute EPS (common in children, antidote is diphenhydramine or benztropine)

MUCOSITIS

1. Inflamm. and sores in the mouth, esophagus and lower GI tract.
2. Agents used to try to prevent and treat mucositis : Magic mouthwash, chlorhexidine rinse
3. But the agent FDA approved agent is Palifermin (Kepivance) – restricted to high dose chemo prior to stem cell txp

HYPERCALCEMIA OF MALIGNANCY

1. Bone destruction that results in hypercalcemia causes signif symptoms for the pt (n/v, fatigue, dehydration, mental status changes)
2. To prevent skeletal related events, these agents are used early in metastatic disease : bisphosphonates & denosumab (Xgeva)
 - a. Denosumab does not req renal adjustment, bisphosphonates DO
 - b. Both have risk for osteonecrosis of the jaw (ONJ)
3. **Hypercalcemia is treated with: aggressive hydration, forced diuresis (loops), IV bisphosphonates**

IV bisphosphonates indicated for hyperCa of malignancy: -

bisphos req renal adjustment (cannot be used for severe renal dysfxn CrCl 30)

- ❖ **Zoledronic acid (Zometa)** 4 mg Q month - zoledronic acid as Reclast is indicated for osteoporosis (Inj 5 mg/year)
- ❖ **Pamidronate (Aredia)**

Corticosteroid

- ❖ **Dexamethasone (Decadron)**
 1. S/E: anxiety, insomnia, GI upset, acute psychosis (if high doses + lack of sleep)

Cannabinoids

- ❖ **Dronabinol (Marinol)** C III ; TID-QID, refrigerate capsules
- ❖ Nabilone (Cesamet) C II; BID , no refig needed
 1. S/E: drowsiness, euphoria, inc appe, ortho hypo

Substance P/NK1 Antagonist

- ❖ Aprepitant (Emend)
 1. S/E: dizziness, fatigue, constipation, hiccups

7 Warning Signs of Cancer - C.A.U.T.I.O.N

- Changes in bowel or bladder habits
- A sore that does not heal
- Unusual bleeding or discharge
- Thickening or lump in breast or elsewhere
- Indigestion or difficulty in swallowing
- Obvious changes in warts or moles
- Nagging cough or hoarseness

[42] ANEMIA

1. Anemia can be due to non functional RBC (sickle cell anemia), bone marrow cannot produce RBC (most common), lack of nutrients to provide optimal RBC functioning (Fe, Vit B12, Folate deficiency)
2. s/s: fatigue, malaise, wkness, SOB, dizziness, pale skin.
3. More severe symptoms (usually due to blood loss) = CP, angina, fainting, palpitations, tachycardia, Glossitis (inflamed sore tongue), koilonychias (thin, concave spoon shaped nails), or pica (craving and eating non-foods such as chalk/clay)
4. Lab values:
 - a. Normal - Female Hgb =12-16 g/dL Hct=36-46%
 - b. Normal - Males Hgb = 13-18 g/dL Hct = 37-49%
 - c. MCV < 80 = microcytic anemia (due to small cell size from lack of Fe)
 - d. MCV 80-100 = normocytic anemia (can result from acute bl loss, hemolysis, bone marrow failure, chronic disease)
 - e. MCV >100 = macrocytic anemia (folate or Vit B12 deficiency)
 - f. TIBC 250-400 ; indirectly measure Fe binding capacity of transferrin [↑TIBC = Fe deficiency anemia]
 - g. Serum Ferritin 30-300 (males) 10-200 (females) [↓SFe = Fe deficiency anemia]
5. Majority of pts that need Fe replacement, most can use the PO formulation. IV formulation is mainly for hemodialysis

MICROCYTIC ANEMIA (FE DEFICIENCY ANEMIA)

1. Most common type of anemia. Dx = MCV <80 and low Hgb
2. Dietary iron is avail in 2 forms: Heme iron (meats) , nonheme iron (plant and dairy foods)
3. At risk pts: Preg women, pre term/low birth weight babies, older infants/toddlers, teenage girls, women with heavy menstrual periods, renal failure pts, GI diseases
4. Txt:
 - a. PO Fe therapy – ferrous sulfate is 1st line (except those on hemodialysis)
 - b. An inc of Hgb by 1 should occur Q2-3 wks, however, it may take up to 4 mths to get Fe stores to return to normal
 - c. Sustained release formulations are NOT recom as intial therapy (by delaying time of release, less Fe is present for absorption in duodenum-site of max abs)
 - d. Fe abs is ↑ by acidic gastric environment
5. DI:
 - a. ↓ Fe absorption: agents that inc pH (antacids, H2RA, PPI), ABX (TCN, quinolones due to chelation- take 2hb, 4ha), Food (try to take on empty stomach, if unable to tolerate then take with small meal)
 - b. ↑ Fe absorption: Vit C (need 200 mg of ascorbic acid)
 - c. Fe dec the levels of : levodopa, methyldopa, levothyroxine, mycophenolate (sep doses by 2 hrs)

Ferrous sulfate (Feosol with Ferrous Sulfate, FeroSul) <u>Infant drops:</u> Fer-In-Sol Fe Suppl. Drops Poly-Vi-Sol Vit Drops with Fe (use if they need the Vit D & Fe) <u>Children:</u> Flinstones/Pokemon Children's chewables	Sulfate- 20% elemental Fe Sulfate, exsiccated – 30% elemental Fe Fumarate – 33% elemental Fe Gluconate – 12% elemental Fe BBW: accidental OD of Fe contain products is the leading cause of fatal poinsoning in children <6 yo (antidote is deferoxamine)
Ferrous fumarate (Ferretts, Hemocyte) Ferrous gluconate (Fergon) Ferrous sulfate, dried (exsiccated) Controlled release (Slow Fe)	S/E: stomach upset, nausea, constipation (use docusate), dark & tarry stool
Carbonyl Fe (Feosol with carbonyl Fe, Ferracap, Ferralet 90)	Highest amt of Fe (100% elemental Fe)

IV Fe Supplements Iron Dextran (INFeD, Dexferrum) Sodium Ferric Gluconate (Ferrlecit, Nulecit) Iron Sucrose (Venofer) Ferumoxytol (Feraheme)	BBW (only for Iron Dextran) : risk of anaphylactic rxn. A test dose is req before 1st therapeutic dose. Hx of drug allergy and/or concomitant use of ACEi inc risk S/E: hypoten, risk of anaphylaxis with all agents (highest with Fe Dextran)
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MACROCYTIC ANEMIA

1. Either due to Vit B12 or folate deficiency, or both. Alcoholism, Crohn's disease & celiac disease are also causes
 2. Pernicious anemia is a type of macrocytic anemia that results in low B12 levels due to lack of intrinsic factor, which is req for adequate B12 absorption in the SI.
 - a. Pern. Anemia req life long vit B12 replacement therapy
 3. If macrocytic anemia cont longterm, the pt is at risk for serious neurological consequences – inc cogn dysfxn (dementia), and periph nerve damage
 4. Dx: low Hgb, MCV >100. Low B12 and folate levels
 - a. Schilling test can dx Vit B12 deficiency due to lack of IF
 5. Txt:
 - a. Vit B 12 injections and follow with PO suppl.
 - b. Recom inj for: those with severe deficiency, neurological symp, those that cannot take/adhere to PO meds, or absorb PO meds (v/d, IBD)
- ❖ **Cyanocobalamin (Vit B12)** – S/E: itching, diarrhea, edema
 - DI: Dec B 12 absorption = cochlorine, ethanol, long term metformin
 - ❖ **Folic Acid (Folate)** – S/E: bronchospasms, flushing, rash, pruritus
 - DI: Dec folic acid absorption = phenobarb, phenytoin, OC, cholestyramine, 6-MP, MTX, thioguanine, azathioprine

ANEMIA OF CKD

1. Renal disease causes anemia due to lack of erythropoietin (EPO), a hormone produced by healthy kidneys
2. BBW:
 - a. CKD: pts experience greater risk for death, serious CV events and stroke when admin to hgb >11.
 - b. Cancer: ESAs can shorten survival & inc tumor progression in some cancers; Prescribers must be enrolled and certified by the ESA APPPRISE Oncology program.
 - c. Perisurgery: due to inc risk of DVT, ppx is recom.
3. **ESAs should only be used if Hgb <10 g/dL** and reduce/stop therapy when Hgb is near 11.
4. Txt:
 - ❖ **Epoetin alpha (Procrit, Epogen) IV/SC 3x/wk then individualized**
 - ❖ **Darbepoetin (Aranesp) IV/SC Q 1-2 wks**
 - ❖ **IV route is recom for pts on hemodialysis**
5. ESAs are assoc with: CHF, CP, thrombosis, **arrhythmias**, CV death
6. Common s/e: **HTN**, hypotension, **arthralgias**/myalgias, inj site pain, URI, thrombosis
7. Inject in: outer area of upper arms, abdomen (2 inches out of the naval), front of middle thighs, upper outer area of buttocks

[43] TRANSPLANT/IMMUNOSUPPRESSION

1. Chronic immunodeficiency can lead to serious infxns and lymphoproliferative disease. Pts are started on:
 - a. Bactrim (or atovaquone if they have sulfa allergy) to prevent Pneumocystis carinii pneumonia (PCP) & UTIs
 - b. Valganciclovir (or acyclovir if both donor & recipient are CMV neg) to prevent cytomegalovirus (CMV)
 - c. Nystatin to prevent oral thrush

2. Induction agents (antibodies, IL-2 receptor antagonists) – are used to induce immunity and prevent hyperacute, accelerated and acute rejection

Induction Agents

1. Antibodies
 - a. Antithymocyte Globulin (ATG, Atgam)
 - b. Muromonab-CD3 (Orthoclone)
2. IL-2 Antagonists – Chimeric (murine/humab)
 - a. Daclizumab (Zenapax)
 - b. Basiliximab (Simulect)

Maintenance Medications

Corticosteroids

- ❖ Prednisone

Antiproliferative agents

- ❖ **Mycophenolate mofetil (CellCept)**
- ❖ **Mycophenolic acid (Myfortic)**
 - BBW: infxn, dev of lymphoma and skin malignancies; inc risk of congenital malformations and spont abortions when used during preg
 - S/E: diarrhea, GI upset, vomiting
 - CellCept & Myfortic are NOT interchangeable (diff in absorption). Myfortic is enteric coated to help with diarrhea
 - Should be taken on empty stomach to avoid variability in abs
 - Mycophenolate can ↓: OC
 - ↓ mycophenolate levels : antacids, MVI, CSA, metronidazole, PPI, FQ, bile acid resins, rifamycin derivs
- ❖ Azathioprine (Azasan, Imuran)
 - S/E: myelosupp, hepatotox, n/v/d
 - ↑ AZA levels: allopurinol, ASA, ACEi, Bactrim
 - no monitoring of levels needed (as opposed to Tacrolimus, sirolimus & cyclosporine)

Calcineurin Antagonists – inh T-lymphocyte activation

- ❖ **Tacrolimus (Prograf)**
 - S/E: tremor, HA, hyperglycemia, Hyper K, Hypo Mg, HypoPhosphatemia, hair loss, nephrotox
 - Should be taken on empty stomach
 - 3A4 substrate ; IV:PO = 1:3-4
- ❖ **Cyclosporine (Neoral, Gengraf, Sandimmune)**
 - BBW: renal impairment (with HD)
 - Cyclosporine modified (Gengraf, Neoral) have HIGHER BA than cyclosporine non-modified (Sandimmune) and cannot be interchanged
 - S/E: HTN, hirsutism, gingival hyperplasia, hyperTG, nephropathy
 - 3A4 substrate. Moderate 3A4 inhibitor

mTOR inhibitor

- ❖ Sirolimus (Rapamune)
 - BBW: inc dev of lymphoma (not recom in lung/liver txp)
 - S/E: delayed wound healing, pneumonitis, HLD
 - 3A4 substrate
 - IV:PO = 1:3
- ❖ Everolimus (Zortress)
 - BBW: inc risk of lymphoma & skin cancer ; reduce dose of CSA if used together
 - S/E: periph edema, constipation, HTN, HLD, delayed wound healing, pneumonitis
 - 3A4 substrate

Counseling for all IS:

1. If you stop taking your IS meds, your body will reject the txp organ
2. Do NOT take NSAIDS (advil, naproxen, aleve) – these can cause harm to kidneys
3. Do NOT take OTC, herbal, alt meds w.o consent from Dr
4. Protect skin from the sun. Use sunscreen at least SPF 30
5. Live vaccines should be avoided
6. Pts are more vulnerable to infxn, avoid contact with ppl with the flu & other contagious diseases
7. Chronic IS puts pts at risk for cancer, esp lymphoma and skin cancer
8. If getting blood tests, take medications after blood is drawn

Counseling for Mycophenolate

1. Take exactly as prescribed, 12 hrs apart (8 am, 8 pm) on EMPTY stomach (1 hr before or 2 hr after meal)
2. Do not open/crush tablets.
3. Missed dose: if <4 hrs after scheduled dose, take dose. If >4 hrs after scheduled dose, skip that dose
4. Can cause diarrhea *
5. Do not take with antacids/MVI – separate doses by 2 hrs. Avoid with bile acid resins
6. Limit amt exposure to sunlight. SPF >30
7. Do not switch between mycophenolic acid (Myfortic) and mycophenolate mofetil (Cellcept). They are absorbed differently

Counseling for cyclosporine (Neoral)

1. Usually taken BID. Take at same time each day. Do not crush/chew
2. Diff brands deliver diff amts of medication, do not switch brands of CSA w/o Drs. Permission
3. Avoid Grapefruit juice
4. Missed dose: if <4 hrs after scheduled dose, take dose. If >4 hrs after scheduled dose, skip that dose
5. Neoral oral solution USP modified – should be diluted with orange/apple juice at RT. Milk can be unpalatable
 - a. Do not admin oral liquid from plastic/Styrofoam cup ; use syringe provided to measure dose, mix in glass container & rinse with diluent to ensure all dose was taken
6. Sandimmune can be diluted with milk, chocolate milk, orange juice
7. Inc risk for dev of skin cancer. SPF >30
8. Medication can cause swelling/growth of gums (ging hyperplasia)- brush and floss daily

Counseling Tacrolimus

1. Usually taken BID, 12 hrs apart. Take at same time each day for constant level.
2. Take on empty stomach for best absorption
3. Avoid Grapefruit juice
4. Missed dose: if <4 hrs after scheduled dose, take dose. If >4 hrs after scheduled dose, skip that dose
5. Can cause HTN, tremors/shaking, HA, diarrhea, n/v, diabetes (tell Dr if inc thirst/hunger, freq urination)
6. Can cause a condit that affects the heart rhythm (QT prolongation) ; high or low Mg and K can cause inc risk of QT prolongation (inc if taking drugs that inc K – diuretics)

[44] INTRAVENOUS DRUGS, FLUIDS & ANTIDOTES

2 types of intravenous lines: Peripheral line & Central line

1. **Peripheral IV line** = consists of a short catheter (few cm long) inserted thru the skin into a peripheral vein (usually a hand/arm)
2. **Central IV line** = flows thru a catheter with its tip placed in a large vein (subclavian, internal jugular, inf vena cava) located in the chest/abdomen area
 - a. Peripherally inserted central catheter (PICC) – a type of central catheter that is used when access to a vein is req for prolonged periods of time. It is inserted into a periph vein and advanced until the tip is in a large vein in the chest near the heart
3. Advantages of Central line:
 - a. Can deliver fluids/meds that are overly irritating to peripheral vein (some chemo drugs, TPN, higher concn K)
 - b. Can contain multiple parallel compartments within the catheter so multiple drugs can be given at once (that we otherwise incompatible)
 - c. Some can measure central venous pressure
4. Disadv of central lines:
 - a. High risk of bleeding, infxn, thromboembolism, and they are more difficult to insert

IV:PO ratio

1:1 = metronidazole, phenytoin, Bactrim

1:2 = Furosemide, levothyroxine,

Types of Fluids (used for fluid resuscitation)

❖ Crystalloids

- Based on a solution of sterile water with added electrolytes to approx. content of human plasma
- Used for maintaining fluid status & keeping lines open
- Consist of salt solutions – NS, ½ NS, ¼ NS with or w/o KCl – and lactated rings & dextrose 5% solu

❖ Colloids

- Do not freely diffuse across a semipermeable membrane. It keeps the fluids within the intravascular space.
- Used to increase osmotic press in pts
- More expensive than crystalloids.
- Albumin 5%, 25%, hetastarch 6%, pentastarch 10%, dextran, etc

Septic Shock & Shock Syndrome

1. Shocks results from lack of oxygen due to hypoperfusion and low BP (SBP <90).
2. 1st line = fluid resuscitation with crystalloids/colloids
3. 2nd line = vasopressors/inotropic therapy if pts do not respond to fluids
4. Inotropes inc contractility thru B adrenergic Agonism or PDE inhibition → inc CO
5. Vasopressors work via VC (“pressing down on vasculature”) → inc BP, CO

❖ **Dobutamine (Dobutrex)** - β1 Agonst (inc contractility, CO, HR)

- Used in cardogenic shock
- ↑ BP, HR, tachyarrhythmias, vent arrhythmias, tachyphylaxis

❖ Milrinone (Primacore) – PDEi

- ↑ BP, HR, tachyarrhythmias, vent arrhythmias, tachyphylaxis

❖ **Dopamine** - endogenous precursor of NE

- Low dose = D1 stimulation
- Med dose = β1 stimulation
- High dose = α1 stimulation

❖ **Epinephrine (Adrenalin)** – low dose β1 stimulation, high dose more α1 stimulation

- IV route is 0.1 mg/mL or 1:10,000 . IM route is 1:1,000

❖ **Norepinephrine (Levophed)**

- β + α stimulation (inc contractility, HR, VC) α effects greater
- Used in septic shock

❖ Phenylephrine (Neo-Synephrine) – pure α1 Agonist

- These all cause: arrhythmias, bradycardia, tachyphylaxis, tissue necrosis (gangrene)
- Txt of extravasation (leakage of IV flu into surr tissue) → for NE, use **phentolamine (Regitine)** an α Antagonist that blocks effects of NE

ICU Sedation & Analgesia

1. Agents used for ICU sedation & analgesia include:

- Combo opioids (morphine, fentanyl)
- Benzos (midazolam, lorazepam)
- Antipsychotics (haloperidol, quetiapine, risperidone)
- Hypnotics (propofol, dexmedetomidine)

❖ **Lorazepam (Ativan)**

- s/e: resp depression, oversedation, hypotn, propylene glycol poisoning at high doses and prolonged infusion

❖ **Midazolam (Versed)**

- s/e: resp depression, oversedation, hypotn
- CI: use small doses in elderly (1 mg, not to exceed 2.5 mg)
- Has shorter acting than lorazepam; Has an active metabolite that accumulates in renal dysfxn

❖ **Propofol (Diprivan) CIV**

- s/e: hypotn, apnea, hyperTG, green urine
- 10% lipid emulsion (1.1 kcal/mL)

❖ **Forpropofol (Lusedra) CIV**

- s/e: paresthesias, pruritus, hypotn
- prodrug of propofol

❖ **Dexmedetomidine (Precedex) α2 Agonist**

- s/e: transient HTN during LD, hypotn, bradycardia, dry mouth
- duration of infusion NOT to exceed 24 hrs; pts are arousable, does not cause resp depression

❖ **Morphine**

- s/e: resp depression, hypotn, oversedation, bradycardia, xerostomia
- has an active metabolite (morphine-6-glucuronide) which can accum in renal dysfxn
- causes histamine release

❖ **Fentanyl**

- s/e: resp dep, bradycardia, oversedation
- less hypotn than morphine (no histamine release)

❖ **Hydromorphone (Dilaudid)**

- s/e: resp dep, oversed, high potential for abuse
- no active metabolites

❖ **Remifentanyl (Ultiva)**

- n/v, bradycardia, hypotn, resp dep
- metabolized by tissue esterases, no accum

❖ **Haloperidol (Haldol)**

- Hypotn, QT Prolongation, tachycardia, EPS, antichol, NMS
- Not to be given via cont infusion

Anesthetics

- Used for: numbing of area (local anesthesia), to block pain (regional anesthesia), to cause a reversible loss of consciousness & sleepiness during surgery (general anesthesia)
- They work by blocking the initial and conduction of nerve impulses by dec neuronal permeability of Na ions
- s/e: hypotn, bradycardia, n/v, drop in temp (shivering)
 - ❖ Topical: Lidocaine (Xylocaine), benzocaine
 - ❖ Inhaled: Desflurane (Suprane, sevoflurane (Ultane), isoflurane (Forane), nitrous oxide
 - ❖ Injectable: bupivacaine (Marcaine, Sensorcaine), lidocaine (Xylocaine), ropivacaine (Naropin)

Neuromuscular Blocking Agents (NMBA)

- These agents cause paralysis. They do not provide sedation/analgesia (must give adequate sedation & analgesia before using a NMBA)
- Used in certain scenarios: to facilitate mech intubation, manage inc ICP, treat muscle spasms
- Pts MUST be mechanically ventilated bc these agents paralyze the diaphragm.
- These are high risk meds by ISMP, and must have red aux label stating "Warning, paralyzing agent"

Depolarizing agent

- ❖ Succinylcholine – resembling Ach, binds and activates the Ach receptors

Non Depolarizing agents

- ❖ Atracurium (Tracrium) – short T ½, met by hofmann elim
- ❖ **Cisatracurium (Nimbex)** – short T ½, met by hofmann elim
- ❖ Pancuronium (Pavulon) – long acting agent, can accum in renal/hepatic dysfxn
- ❖ Rocuronium (Zemuron)- intermediate
- ❖ **Vecuronium (Norcuron)** – intermediate, can accum in renal/hepatic dysfxn

VTE PPX

1. Many pts in ICU are at high risk of dev DVT/PE
2. See anticoag chapter

Acid-Base Homeostasis

1. Acid = donates protons (H⁺) Base = accepts protons
2. Normal pH = 7.35-7.45
3. The kidneys help maintain pH by controlling bicarb (HCO₃⁻) resorption & elimination
 - a. Normal bicarb = 24 mEq/L (range 22-26)
 - b. Bicarb is a buffer & a base
4. The lungs help maintain pH by controlling carbon dioxide (PaCO₂)
 - a. Normal PaCO₂ = 40 mmHg (range 35-45 mmHg)
 - b. CO₂ is a buffer & an acid
5. Acidosis = pH < 7.35 Alkalosis = pH > 7.45

Stress Ulcer PPX

1. Can result from metabolic stress exp by ppl in the ICU. Pts with critical illness have red. BF to the gut since blood is diverted to other major organs
2. H₂RAs & PPIs are recommended. H₂RA can cause: thrombocytopenia, mental status changes (elderly, renal/hepatic impairment), tachyphylaxis. PPIs can cause: GI infxn (C.diff), nosocomial pneumonia

Metabolic acidosis has ↓ in plasma HCO₃⁻

- Lactic acidosis, renal tubular acidosis, large doses of propylene glycol (lorazepam IV)
- Txt = sodium bicarbonate to raise pH to ≥ 7.2

Metabolic alkalosis has ↑ in plasma HCO₃⁻

- Loop & thiazides, high dose PCN, vomiting, diarrhea, cystic fibrosis

Respiratory acidosis ↑ PaCO₂

- Opioids, sedatives, anesthetics, stroke, asthma/COPD

Resp alkalosis ↓ PaCO₂

- Pain, fever, brain tumors, salicylates, catecholamines, theophylline

Antidotes for select toxicities

- | | | | |
|---|--|-------------------------------|---|
| 1. Acetaminophen | N-acetylcysteine | 12. Digoxin | Digoxin immune Fab (Digibind, DigiFab) |
| 2. Anticoagulants | phytonadione (AquaMephyton, Mephyton) | 13. Ethylene glycol, methanol | Ethanol or fomepizole (antizol) |
| 3. Anticholinesterase insecticides/ organophosphates (nerve agents) | Atropine/Pralidoxime (Protopam) | 14. Heavy metals | Dimercaprol/Penicillamine |
| 4. Anticholinergic compounds | Physostigmine (Antilirium) | 15. Heparin | Protamine |
| 5. Arsenic, Lead | Succimer (Chemet) | 16. Iron | Deferoxamine (Desferal) |
| 6. Benzodiazepines | Flumazenil (Romazicon) | 17. Isoniazid | Pyridoxine (Vitamin B6) |
| 7. Beta Blockers | Glucagon (GlucaGen) | 18. Methemoglobinemia | Methylene Blue |
| 8. Botulism | Botulism antitoxin | 19. Opioids | Naloxone (Narcan) |
| 9. Calcium channel blockers | Calcium Chloride 10%,
Glucagon | 20. Salicylate | Sodium Bicarbonate |
| 10. Carbon monoxide | Oxygen | 21. Snake bites | Crotalidae polyvalent (Antivenin) |
| 11. Cyanide | Sodium nitrate, sodium thiosulfate | 22. TCA's | Sodium Bicarbonate |
| | | 23. NE | Phentolamine (alpha antag) |

Flash cards: <http://quizlet.com/5835282/antidotes-for-select-toxicities-flash-cards/>

[45] DEPRESSION

1. Causes of depression: not well understood, but involve some combination of genetic, biologic and environment factors
2. Serotonin (5HT) may be the most imp NT involved with feelings of well being
3. Other imp NTs: ACh, catecholamines (DA, NE, EPI)
4. Lag effect: pts should be told to take their medication daily. It is imp to inform them that physical symptoms (energy) may improve within 2 weeks, but psychological symptoms (low mood) may take 4-6 wks.

Diagnosis – DSM IV

- At least one symptom must be depressed mood or loss of interest/pleasure
- ≥ 5 symptoms in same 2 week period
 - Suicide Concentration
 - Interest Appetite
 - Guilt Psychomotor agitation or retardation
 - Energy Sleep

Concurrent Bipolar or Anxiety Disorders

1. It is necessary to rule out bipolar d/o before starting antidepressant therapy to avoid rapid cycling.
2. BZD are often used adjunctively in depression with concurrent anxiety.
 - a. Can cause/mask depression and put the pt at risk for physiological dependence

Pharmacotherapy:

1. Acute phase txt include: pharmacotherapy, psychotherapy, somatic therapies (ECT, vagal nerve stimulation, light therapy)
2. For most pts, SSRI, SNRI, mirtazapine or bupropion is preferred
3. MAOIs (phenelzine, tranylcypromine, isocarboxazid) due to DDI are restricted to pts that do not respond to other txts
 - a. Serotonin syndrome is more severe when an MAOI is admin with another serotonergic medication
4. Withdrawal symptoms = anxiety, agitation, insomnia, dizziness, flu like symptoms
 - a. Paroxetine and some other agents carry a high risk of symptoms & must be tapered upon d/c
5. Pts should try at least 6 wks on a medication at a therapeutic dose before concluding that it does not work
 - a. Can try dosage inc
 - b. Combo of antidepressants
 - c. Augmentation with buspirone (BuSpar) or low dose atypical AP
 - d. Agents approved for augmentation therapy with an antidepressant : ariprazole (Abilify), olanzapine + fluoxetine (Symbyax), quetiapine ER (Seroquel XR)
6. Suicide risk in Adolescents and young adults: req MedGuide
 - a. AD inc the risk of suicidal thinking & behavior in children, adolescents & young adults in short term studies.
7. **Natural products:**
 - a. St John's Wort or SAME (s-adenosyl-L-methionine) may be helpful.
 - b. Both agents CANNOT be used with other serotonergic agents

For TXT Resistance Depression Only - Rule out bipolar d/o and check if AD dose is optimal.

All can cause metabolic issues (dyslipidemia, wt gain, DB, risk of NMS, TD, leukopenia, neutropenia, agranulocytosis, orthostasis)

1. **Aripiprazole (Abilify)**
 - Akathisia/restlessness, insomnia, constipation, blurred vision
2. Olanzapine/fluoxetine (Symbyax)
 - Cogn dysfxn, dry mouth, fatigue, wt gain, edema, tremors
3. **Quetiapine ER (Seroquel ER)**
 - Sedation, dry mouth, constipation, wt gain, nausea

SSRI

[All below are approved for depression and other anxiety d/o except for fluvoxamine]

- ❖ **Fluoxetine (Prozac, Sarafem, Prozac weekly)**
 - Sarafem is for premenstrual dysphoric d/o (PMDD)
 - ❖ Fluoxetine + olanzapine (Symbyax)
 - ❖ **Paroxetine (Paxil, Pexeva, Paxil CR)**
 - ❖ Fluvoxamine (Luvox, Luvox CR) → IR form is for OCD, CR is for OCD & SAD (social anx d/o) – [has more DI](#)
 - ❖ **Sertraline (Zoloft)**
 - ❖ **Citalopram (Celexa)**
 - FDA warning [not to use >40 mg due to QT risk](#)
 - ❖ **Escitalopram (Lexapro) – isomer of citalopram**
 - ❖ Vilazodone (Viibryd) – starter kit, [take all with food](#)
1. Fluoxetine – causes activation, so take QAM . others are QAM (usually) or PM if sedating
 2. S/E: akathisia (restlessness), sexual s.e (dec libido, ejaculation diff, anorgasmia), n/v/d, HA, inc wt gain (more with paroxetine), restless leg syndrome, inc bleeding risk (if concurrent with warfarin, dabigatran, etc), inc fall risk (use caution in elderly)
 3. C/I : [potentially lethal DI with SSRI + MAOIs](#)
 - a. Washout period : 2 weeks (if going from MAOI → SSRI) except fluoxetine, req 5 weeks if going from fluoxetine → MAOI (fluox T $\frac{1}{2}$ = 7 days)
 4. DI:
 - a. 2D6 inhibitors = fluoxetine, fluvoxamine, paroxetine .
 - b. 2C19 inhibitors = fluoxetine, fluvoxamine.
 - c. 3A4, 1A2, 2C9 inhibitor = fluvoxamine
 - d. ↓effectiveness of tamoxifen with : fluoxetine, paroxetine, sertraline, duloxetine, bupropion
 5. Do not stop suddenly, will get anxiety, insomnia, flu like symptoms. Fluoxetine can be stopped with less of a taper due to long T $\frac{1}{2}$

SNRI

- ❖ **Venlafaxine (Effexor, Effexor XR)** – Dep, GAD
 - ❖ **Desvenlafaxine ER (Pristiq)** – Depression
 - ❖ **Duloxetine (Cymbalta)** – Dep, GAD, Periph neuropathy, fibromyalgia, Chronic lower back pain, osteoarthritis pain
1. S/E: similar to SSRI: n/v, sexual dysfxn + NE s/e (↑ pulse, dilated pupils, dry mouth, excessive sweating, constipation)
 2. All have warning of ↑ BP (greatest risk due to venlafaxine)
 3. CI : potentially lethal DI w. SNRI + MAOI
 - a. 2 wk wash out period
 4. DI: duloxetine is a 2D6 inhibitor
 5. Desvenlafaxine – may see [empty capsule](#) in stool

Tricyclic Antidepressants

Tertiary amines – may be more effective, but more s/e

- ❖ **Amitriptyline (Limbitrol, Elavil)**
- ❖ **Doxepin (Sinequan)**
- ❖ Clomipramine (Anafranil)
- ❖ Imipramine (Tofranil)
- ❖ Trimipramine (Surmontil)

Secondary amines

- ❖ Amoxapine (Asendin)
- ❖ Desipramine (Norpramine)
- ❖ Maprotiline (Ludiomil)
- ❖ Nortriptyline (Pamelor)
- ❖ Protriptyline (Vivactil)

1. S/E: **cardiotoxicity** (QT prolongation with OD) – *can be used for suicide*, orthostasis, tachycardia, **Anticholinergic** (dry mouth, blurred vision, urinary retention, constipation), wt gain, vivid dreams, myoclonus, inc fall risk
Counseling: may cause constipation (may need stool softener), dry/blurry vision (may need to use lubricating eye drops), dry mouth (can contribute to dental decay, can use sugar free lozenges), anxiety/insomnia with vivid dreams (usually go away, contact dr if doesn't)
2. 2 wk washout period
3. Metabolized by 2D6

MAOI – these inhibit monoamine oxidase that breaks down catecholamines incl 5HT, NE, Epi, DA

- ❖ Isocarboxazid (Marplan)
- ❖ Phenelzine (Nardil)
- ❖ Tranylcypromine (Parnate)
- ❖ Selegiline transdermal (Emsam) MAO iB selective inh

1. S/E: anticholinergic, orthostasis, sedation (except tranylcypromine – stimulation), sexual dysfxn, wt gain, HA, insomnia
2. CI: DDI and Drug food (tyramine)
3. Selegiline patch – avoid tyramine rich foods/drinks while 9 mg, 12 mg patches. No dietary issues with 6 mg patch
 - a. Apply QD, to upper chest/back, upper thigh, outer arm

4. Cannot be used with: bupropion, ephedrine and analogs (pseudoephedrine), levodopa, linezolid, Lithium, meperidine, tramadol, mirtazapine, dextromethorphan, cyclobenzaprine & other muscle relaxants, St John's
5. Tyramine rich foods = aged, fermented, pickled or smoked. Aged cheese, yeast extract, air dried meats, sauerkraut, soy sauce, fava beans, some red wines, tap beer (canned/bottle are ok)

Other Agents

- ❖ **Bupropion (Wellbutrin, Budeprion XL, Aplenzin)**
Zyban is for smoking – don't use together
 - DA & NE reuptake inhibitor
 - S/E: **dry mouth, insomnia, tremors/seizures, wt LOSS**
 - No effect on 5HT ∴ **no sexual dysfxn**
 - CI: **do not use in seizure d/o. Do not exceed 450 mg/day due to seizure risk (or 150/dose for IR)**

- ❖ **Mirtazapine (Remeron, Remeron soltab)**
 - Commonly used in oncology & skilled nursing facilities since it helps with sleep and inc appetite
 - NE and 5HT reuptake inhibitor
 - S/E: **sedation, inc appetite, wt gain**, dry mouth
- ❖ **Trazodone (Desyrel)**
 - Rarely used as an AD due to sedation
 - Inh 5HT reuptake, $\alpha 1$ blocker, histamine blocker
 - S/E: **sedation**, orthostasis (risk in elderly), **sexual dysfxn, priapism**
- ❖ Nefazodone (Serzone)
 - Similar to trazodone but less sedating. Rarely used due to hepatotoxicity

[46] SCHIZOPHRENIA/PSYCHOSIS

1. A debilitating brain disorder. Pts suffer from hallucinations, delusions, disordered thinking and behavior.
2. Onset of symptoms usually begins in young adult. DX is based on pts behavior (negative & positive symptoms)
3. Causes: there is an increase in DA in the mesolimbic pathway. Antipsychotics are primarily DA blockers.

Negative S/S (normal behaviors that are missing)	Positive S/S
<ul style="list-style-type: none">○ Loss of interest in everyday activities○ Lack of emotion○ Inability to plan○ Poor hygiene○ Social withdrawal○ Loss of motivation (avolition)○ Poverty of speech (alogia)	<ul style="list-style-type: none">○ Hallucinations: hearing voices○ Delusions : beliefs the pt has○ Thought disorders, or difficulty speaking○ Difficulty paying attention

Natural Products:

1. Fish oils are used for psychosis as well as ADHD and depression
2. Do NOT recommend cod liver oil (due to risk of Vit A toxicity)

Pharmacotherapy

1. In general, SGAs are used 1st line due to lower risk of EPS (however, some pts respond better to FGA)
2. Adequate trial is at least 4-6 wks
3. **MOA:** FGA & SGA **primarily are D2 receptor blockers**. (excess DA is the primary contributing factor to psychosis)
 - a. All SGA block D2 and 5HT_{2A} receptors (except aripiprazole, it's a D2 and 5HT_{1A} partial agonist and 5HT_{2A} antagonist)
4. Formulations:
 - a. Long acting injections: Haloperidol (Haldol deconate) 4 weeks, Risperdal Consta (2 wks), Invega Sustenna (4 wks)
 - b. Oral disintegrating tablets (ODT) : used to help solve the problem of cheeking. Clozapine, olanzapine, risperidone, asenapine
 - c. Acute IM injections: work stat to help calm the pt down. Often used along with other drugs such as BZDs.
5. **AP BBW:** **AP inc risk of mortality in elderly pts with dementia related psychosis, due to inc risk of stroke.**
6. **Neuroleptic Malignant Syndrome (NMS)** – rare but highly lethal. Occurs most commonly in FGA and less in SGA and other DA blocking agents (metoclopramide)
 - a. Signs: **hyperthermia**, **muscle rigidity**, mental status changes, tachycardia, BP changes
 - b. Txt: supportive care (O₂), cooling them down (cooling bed, antipyretic, cooled IV fluids), Dantrolene (muscle relaxant)

Choosing a SGA based on side effect profile *

- If a pt has CV risk → do not choose an agent with risk of QT prolongation/arrhythmia (ziprasidone, risperidone, paliperidone, iloperidone, asenapine, lurasidone)
 - All AP can cause QT prolongation; some are higher risk than others. The higher risk SGA are noted. Thioridazine (Mellaril) is a high risk FGA QT drug
- If a pt is overweight, has little physical activity/metabolic issues → most notably in olanzapine, quetiapine, clozapine has high metabolic risk but is used in refractive cases)
- Inc prolactin levels (causes galactorrhea – milk production w/o pregnancy, sexual dysfxn, gynecomastia – painful swollen breast tissue, irregular/missed periods) → risperidone, paliperidone
- Hx of TD or any type of movement d/o → risperidone, paliperidone (Quetiapine =low risk, clozapine has very low risk)
- Cost → the only available generic SGA is risperidone

First Generation Antipsychotics

- ❖ Haloperidol (Haldol)
- ❖ Chlorpromazine
- ❖ Thioridazine - **BBW QT prolongation**
- ❖ Fluphenazine

1. All are sedating & all cause EPS
2. Mvt disorders include: **TD** (facial mvmts – stop drug if this occurs, can be irrev.) , **Dystonias** (prolong contraction of muscles- higher risk in young males) , **Akathisia** (restlessness and anxiety), **Dyskinesias** (abnormal mvmts – more with Parkinson drugs), **CV effects**, **Orthostasis**, **QT Prolongation**

Second Generation Antipsychotics “Atypicals”

- ❖ **Clozapine (Clozaril, FlazaClo ODT)**
 - Only use if failed to respond to 2 standard AP txts or had signif ADR
 - Most effective atypical, but use is limited due to **agranulocytosis** and **seizures**
 - **REMS**: pt & pharmacy must register
 - To start: **WBC \geq 3,500, ANC \geq 2,000**
ANC = WBC x % Neutrophils [Segs + bands]
- ❖ **Olanzapine (Zyprexa, Zydys ODT)**
 - Relprevv inj lasts 2-4 weeks, restricted use
 - **REMS** drug – can cause sedation (coma) & delirium
 - **sedation (take QHS)**, **wt gain**, **↑ lipids**, **↑ glucose**
- ❖ **Risperidone (Risperdal, Risperdal M tabs ODT)**
 - s/e: **EPS**, **↑ prolactin**- sexual dysfxn, **galactorrhea**, **irreg periods**, **QT prolongation**
 - **sedation**, **wt gain**, **↑ lipids**, **↑ glucose**
 - oral solu- can be taken directly or mixed with water, coffee, juice, milk, no cola
- ❖ **Quetiapine (Seroquel, Seroquel XR)**
 - s/e: **sedation**, **orthostasis**, **an eye exam for cataracts** s recom at beginning of therapy, **wt gain**, **↑ lipids**, **↑ glucose**
 - **little EPS risk** ; take XR w/o food (food ↑absorption)

- ❖ **Ziprasidone (Geodon)**
 - C/I: **QT prolongation**, contraindicated with QT risk
- ❖ **Aripiprazole (Abilify, Abilify Discmelt ODT)**
 - Not sedating, but activating
 - **Anxiety**, **insomnia**. **No/less wt gain**
- ❖ **Paliperidone (Invega)**
 - Invega sustenna is long acting Qmonth inj
 - This is the active metabolite of risperidone; OROS delievery so dosed QD
 - **↑ prolactin** – sexual dysfxn, **galactorrhea**, **irreg periods**, **EPS**, **QT prolongation**, **wt gain**, **↑ lipids**, **↑ glucose**
- ❖ **Iloperidone (Fanapt)**
 - Prolongs QT
- ❖ **Asenapine (Saphris) SL tab under tongue**
 - **Tongue/mouth numbess (do not eat/drink for 10 mins)**
 - Prolongs QT
- ❖ **Lurasidone (Latuda)**
 - Prolongs QT

[47] BIPOLAR DISORDER

Dx: Bipolar Disorder

Manic episode:

- Expansive or irritable mood lasting ≥ 1 week**
- ≥ 3 symptoms or 4 symptoms if mood is irritable
 - Distractibility
 - Inflated self-esteem or grandiosity
 - \uparrow Goal-directed activities
 - Flight of ideas or racing thoughts
 - \uparrow Activities with painful consequences
 - \downarrow Sleep
 - Talkativeness or pressured speech

Pharmacotherapy

1. 'Atypical' or SGA have proved to be effective in txt of Bipolar mania. Mood stabilizers may also be used as 1st line. Combo txt may also be used.
2. All SGA are approved for mania. Two SGAs have indications for both mania & depression – can be used to treat both stages of BD : aripiprazole (Abilify) & quetiapine (Seroquel XR)
3. Lamotrigine can be used for txt of the depressive stage but does not have benefit in mania. Lithium is beneficial for both.
4. All antidepressants, anticonvulsants, and antipsychotics req MedGuides.
5. **Meds in Pregnancy**
 - a. Valproate, carbamazepine, and Lithium = Cat D (known fetal risk)
 - b. Lamotrigine = Cat C (often considered the safer option)
 - c. Li exposure can cause congenital cardiac malformations
 - d. Valproate inc risk of fetal anomalies, neural tube defects, longterm cognitive effects
 - e. Carbamazepine assoc with fetal carbamazepine syndrome
 - f. BZD used shortly before delivery is assoc with floppy infant syndrome
 - g. If an antidepressant is used, avoid paroxetine (Cat D)

Primary Bipolar Mania Agents (SGA are also used in Bipolar d/o)

- ❖ **Valproate / valproic acid (Depakene, Stavzor)** sol or liquid filled capsules
- ❖ **Divalproex (Depakote)**
 - Preg D
 - Serum levels keep btw : 50-125 mcg/mL
 - **BBW:** Hepatic failure, teratogenicity, pancreatitis
 - **S/E:** GI upset, alopecia (treat with selenium and Zn), sedation, tremor, wt gain, thrombocytopenia
 - Cannot subs Depakote ER for the delayed release Depakote
 - VA can \uparrow levels of: amitriptyline, carbamazepine, LTG, lorazepam, nortriptyline, paroxetine, phenobarb, warfarin, zidovudine (caution with use with LTG- can inc risk of serious rash)
 - Salicylates can displace VA from binding site & INC levels
 - VA can displace phenytoin from albumin, resulting in phenytoin toxicity

❖ **Lamotrigine (Lamictal, Lamictal ODT, Lamictal CD-chewable, Lamictal XR)**

- Preg C
- **BBW:** serious skin rxns (SJS, TEN) – follow titration schedule to dec risk of rash
- **S/E:** diplopia, sedation, ataxia, HA
- **DI:** valproate, divalproate and strong inhibitors INC LTG levels → inc rash risk

❖ **Lithium (Eskalith, Lithobid)**

- Preg D
- Titrate slow to dec nausea
- If tremor/thirst/confusion, may try QHS dosing
- Therapeutic range = 0.8-1.2 mEq/L for acute mania, may need 1.5 mEq
- Cannot use in renal impairment, 100% renally cleared
- **s/e:** GI upset (take with food), cognitive effects, fine hand tremor, cogwheel rigidity, wt gain, polyuria/dipsia, hypothyroidism
- **toxicity:** >1.5 (coarse hand tremor, vomiting, persistent diarrhea, confusion, ataxia) >3 (CNS dep, arrhythmia, seizures, irr brain damage, coma)
- inc serotonin syndrome if given with Li : SSRI, SNRI, triptans, linezolid

↑ Lithium Levels	↓ Lithium Levels
Thiazides	Acetazolamide
ACE Inhibitors/ARBs	Mannitol
Furosemide	Aminophylline
NSAIDs	Theophylline
Low Sodium Diet	High Dietary Sodium Intake
Dehydration	Mania
Elderly	Pregnancy
Renal disease	Caffeine

[48] PARKINSON DISEASE

1. A brain disorder that occurs when part of the brain called the substantia nigra die or is impaired. Normally, these cells produce DA (allows smooth coordinated fxn of muscles and mvmt). When 80% of DA producing cells are damaged, symptoms appear.
2. Initially, tremors will appear on one side and eventually spreads bilaterally. Eventually, even with high doses of the 2 most effective classes of drugs (levodopa/carbidopa and DA agonists), the “off” periods will increase
 - a. Off periods = period of time with muscle stiffness, slow mvmts, and difficulties starting mvmts
3. Apomorphine is a drug that treats end stage disease, but is hard to take and only produces mvmt for ~1 hr
4. **s/s:** TRAP Tremor (during resting), Rigidity (arms, legs, face), Akinesia/Bradykinesia (lack/slow of mvmt), Postural instability (poor balance, freq falls)

Drug Induced Parkinson Disease (due to their DA

Antagonism)

1. **Phenothiazines** (prochlorperazine, etc)
2. FGA (**haloperidol**)
3. SGA (to a less degree – **Risperidone at higher doses is high risk**)
4. DA blocking agent **Metoclopramide** (Reglan) – **most likely when its overdosed, which is common in the elderly due to dec renal fxn**
5. Cholinesterase inhibitors (donepezil (Aricept), rivastigmine (Exelon))

Initial Therapy selection

- Levodopa is a commonly used agent. Levodopa/carbidopa is the most effective agent – better tolerated in elderly than DA agonists
- Anticholinergics – initial txt of tremors for younger pts (due to anticholinergic s/e, use is prohibited in elderly)
- Amantadine is sometimes used for initial txt of tremors in younger pts
- MAOI- may be used for mild benefit as initial txt

DA Replacement & Agonists

Levodopa/Carbidopa

MOA: Levodopa is a precursor of DA. Carbidopa inhibits dopa decarboxylase, preventing peripheral metabolism of levodopa

❖ **Carbidopa/Levodopa (Sinemet, Sinemet CR)**

- Usual starting dose = 25/100 (**need 70-100 mg carbidopa to be effective and ↓ nausea**)
- **SR tab can be cut into half**. Do not crush/chew
- S/E: **nausea, dizziness, orthostasis, Dyskinesia (abnormal mvmt), can cause brown/black/dark urine, possibility of unusual sexual urges, priapism**
- **Separate from Fe, possible separate from protein** (these can ↓ absorption)

- Do not use with DA blockers – these will worsen disease; do not take with MAOI- need 2 wk washout

COMT Inhibitor – **used only with levodopa to ↑ levodopa duration of action**

Inhibits COMT to prevent peripheral conversion of levodopa

❖ **Entacapone (Comtan)**

- ❖ Levodopa/carbidopa + entacapone (Stalevo)
- ❖ Tolcapone (Tasmar) – not used much due to hepatotoxicity
 - 200 mg with each dose of levo/carbidopa
 - S/E: similar to levodopa: nausea, dyskinesia, dizziness, orthostasis, hypotn, urine discoloration

DA Agonists

- ❖ **Pramipexole (Mirapex, Mirapex ER)** 0.125 mg TID
- ❖ **Ropinirole (Requip, Requip XL)** 0.25 mg TID
 - A slow dose titration (weekly) is req due to orthostasis, dizziness, sleepiness
 - S/E: *drowsiness, sudden daytime sleep attacks, nausea, dizziness, orthostasis, hallucinations, dyskinesias*,
 - *renal* - ↓ Pramipexole (CrCl <60)
- ❖ Apomorphine (Apokyn) – SC injection for advanced disease, rescue mvmt drug
 - Lasts 45-90 mins
 - S/E: *SEVERE NAUSEA & vomiting, hypotn.* Yawning, dizziness, swelling of hands, feet, QT prolongation
 - Trimethobenzamide (Tigan) or similar antiemetic should be started 3 days before initial dose of apomorphine.
 - *Contraindicated with 5HT receptor antagonists* (ondansetron, granisetron, dolasetron, palosetron & alosetron) due to severe hypotn and loss of consciousness

Additional Parkinson's Medications

Centrally Acting Anticholinergics: used primarily for tremors in younger pts

- ❖ Benztropine (Cogentin)
- ❖ Trihexyphenidyl
 - s/e: dry mouth, urinary reten, blurred vision, drowsiness, confusion, tachycardia

DA reuptake inhibitor: Use for mild disease or for dyskinesia in advanced disease

- ❖ Amantadine (Symmetrel)
 - S/E: nausea, dizziness, toxic delirium (with renal impairment), cutaneous skin rxn called livedo reticularis (reddish skin mottling- req d/c)

MAO-B inhibitors: used with levodopa or as initial therapy
DI: meperidine (can be fatal), tramadol, methadone, dextromethorphan, st johns, mirtazapine, cyclobenz, tyramine foods

- ❖ Selegiline (Eldepryl, Zelapar ODT) Emsam-selegiline patch is for depression
 - Only has benefit when used WITH levodopa
 - S/E: DA excess s/e
- ❖ Rasagiline (Azilect)
 - Can be used as initial monotherapy or combo with levodopa
 - S/E: ha, joint pain, indigestion. If taken with levodopa – any s/e from DA excess

[49] ALZHEIMER'S DISEASE

1. AD is the most common type of dementia → **due to DEC ACH**
2. **TXT:** Acetylcholinesterase inhibitors are the mainstay of therapy. These are used alone, or with memantine for more advanced disease
 - Antidepressants (sertraline, citalopram, escitalopram) can be used to treat depression & anxiety
 - Antipsychotics can be used to treat delusion/anger (but they inc the risk of death in elderly pts due to inc risk of stroke)
 - **Vit E** – provides little benefit, doses >150 IU carry risk
 - Ginkgo biloba is commonly used for memory. An 8 yr study found NO benefit in prevention of dementia, but older studies have seen modest benefit.
Ginkgo inc bleeding risk
3. **Symptoms:** memory loss, difficulty communicating, inability to learn new info, poor coordination, personality changes, inapprop behavior

Drugs That Can Worsen Dementia

1. Peripheral anticholinergics (incontinence & IBS drugs)
2. Central anticholinergics (benztropine)
3. Antihistamines & antiemetics
4. Antipsychotics
5. Barbiturates
6. Benzodiazepines
7. Skeletal muscle relaxants

ACETYLCHOLINESTERASE INHIBITORS (ACHEi)




- S/E: bradycardia, **GI s.e (n/v/loose stools), dizziness, falls**
- DI: caution with drugs that dec HR (BB, CCB, digoxin) & those that cause dizziness (AP, antiHTN, alpha blockers, muscle relaxants, opioids)
- ❖ **Donepezil (Aricept, Aricept ODT)**
 - Used alone (mild-moderate disease) or with memantine in more severe disease
 - Aricept 23 mg QHS is used for advanced disease
 - **Donepezil started at 5 mg QHS to help with nausea**
- ❖ **Rivastigmine (Exelon, Exelon patch)**
 - Patch – 4.6, 9.5 mg/24 hr (*patch or ODT dec GI s/e*)
 - **Take with food** (start at 1.5 mg BID)
 - Apply patch to lower back, upper arm, or chest
- ❖ **Galantamine (Razadyne, Razadyne ER)**
 - IR : start at 4 mg BID, ER: start at 8 mg QD, **then inc to 16-24 mg**
- ❖ Tacrine (Cognex) – not used much due to **hepatotox**

Memantine – Blocks NMDA which inhibits glutamate from binding to NMDA receptors & ↓ abnormal activation

- ❖ **Memantine (Namenda, Namenda XR)** - for moderate to severe disease
 - Take XR with food/drink, IR +/- food
 - XR cap can be opened and sprinkled on applesauce
 - S/E: dizziness, diarrhea, ha. Rare=flu like symp, arthralgia, UTIs, small seizure risk






[50] ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) & STIMULANT AGENTS

1. Primary txt for ADHD are stimulant medications, 1° methylphenidate formulations
2. **Stimulants are used to ↑ DA levels** [In those with ADHD, it is thought that there is a lack of DA, lack of functioning DA receptors, or defect in DA pathway]
3. **DSM-IV Dx:**
At least 6 of 9 symptoms of inattention (trouble keeping atten, not listening, etc) OR at least 6 of 9 symptoms of hyperactivity (fidgeting, talking excessively, etc)
 - a. Symptoms must be present for ≥ 6 mths
 - b. Some symptoms were present before age 7
 - c. Some impairment from symptoms is present in ≥ 2 settings (home, school)
 - d. Clinically signif impairment in social, adademic, occupational fxning
4. **TXT:**
 - a. 1st line = stimulants (methylphenidate or lisdexamfetamine (Vyvanse – prodrug of dextroamphetamine)
 - b. After trials of 2-3 agents, can try atomoxetine (Strattera) – non stimulant
 - c. Guanfacine ER (Intuniv), clonidine ER (Kapvay) are antidepressants sometimes used as adjunctive txts
5. **BBW for Stimulants for ADHD – CII**
 - a. Heart related problems - sudden death in pts who have heart problems, stroke and heart attack in adults, inc BP and HR
 - b. Mental (Psychiatric) problems – all pts: new or worse behavior and thought probs, bipolar illness, aggressive behavior
 - c. Children and teenagers – new psychotic symptoms (hearing voices, delusions) new manic symptoms
6. **Natural products:** fish oils +/- evening primrose oil (provides omega-6-fatty acids) may be helpful in some pts
 - a. Combo product used in the study that showed benefit used 6 capsules QD

 Focalin XR, Ritalin LA, Metadata CD, Adderall XR – can be taken whole or the capsules sprinkled on applesauce
 Vyvanse can be sprinkled in water, not applesauce
 Concerta, Metadata CD, Ritalin LA - QAM

S/E for ALL agents: nausea, loss of appetite, insomnia, ↑ BP (2-4mmHg), ↑ HR (3-8 bpm), exacerbation of mixed/mania episodes if bipolar d/o, withdrawal rxns – do not stop suddenly


METHYLPHENIDATE

- ❖ Methylphenidate IR (Ritalin, Methylin)
- ❖ long acting (Ritalin LA) ½ IR, ½ SR in one capsule
 
- ❖ sustained release (Ritalin SR)
- ❖ ext-release (Methylin ER, Metadata ER)
- ❖ **Methylphenidate IR-ex rel (Concerta)**  – OROS system, harder to crush & abuse
 - Capsules outer coat dissolves fast to give immediate action, rest is released slowly
- ❖ IR-ex rel (Metadata CD)   – beads that dissolve at diff rates
- ❖ **transdermal patch (Daytrana)**
 - Daytrana – QAM, alternate hip **2 hrs before** desired effect


DESMETHYLPHENIDATE

- ❖ **Dexmethylphenidate IR (Focalin)**
- ❖ **Dexmethylphenidate ER (Focalin XR)** 

DEXTROAMPHETAMINE & AMPHETAMINE

- ❖ **Dextroamph + amphe IR (Adderall)**
- ❖ **Dextroamph + amphe ER (Adderall XR)** 
- ❖ **Dextroamphetamine IR (Dexedrine, Dextrostat)**
- ❖ IR & IR dextroamphetamine (Dexedrine Spansules)

LISDEXAMPHETAMINE (Prodrug of dextroamphetamine)

- ❖ **Lisdexamphetamine (Vyvanse)**  – prodrug, may have dec risk abuse (cannot be injected/snorted)
 - Can mix capsule contents with water (NOT applesauce) QAM +/- food

NON STIMULANTS FOR ADHD- 2ND LINE AGENTS, not controlled

❖ **Atomoxetine (Strattera)**

- s/e: upset stomach, nausea, constipation, fatigue, loss of appetite, dry mouth, mood changes, ↓ libido
- do not open capsule – irritant
- **BBW**: suicidal ideations, possible liver injury
- CI: glaucoma, MAOI use in 14 days

❖ Guanfacine ext rel (Intuniv)

- For pts using stimulants for addt benefit, or alone
- Do not crush, or eat with high fat meal (↑absorption)
- s/e: somnolence, hypotn, bradycardia ; 3A4 substrate

❖ Clonidine ext rel (Kapvay)

- For pts using stimulants for addt benefit, or alone
- Do not crush
- Take QHS due to : dry mouth, bradycardia, drowsiness
- Rebound HTN if stopped abruptly (anxiety, sweating, tremors)

STIMULANTS used to improve wakefulness in adults with Excessive Sleepiness assoc with: Narcolepsy, Obstructive Sleep Apnea, Hyponea syndrome, Shift Work Sleep Disorder

❖ **Modafinil (Provigil) C IV**

❖ Armodafanil (Nuvigil) C IV – R isomer of modafinil

- Both: common s/e – ha, dizziness, anxiety, agitation, n/d, insomnia, dry mouth, risk of severe rash
- Both agents req MedGuide due to risk of rash

[51] ANXIETY

1. Common types of anxiety disorders include: generalized anxiety d/o (GAD), panic d/o (PD), social anxiety d/o (SAD), obsessive compulsive d/o (OCD), post traumatic stress d/o (PTSD), and specific phobias
2. **Text: generally with SSRIs, SNRIs, TCAs**
 - a. Hydroxyzine (Vistaril) – sedating antihistamine occasionally used for short term anxiety, works by sedating pt.
 - b. Pregabalin (Lyrica) – C V bc it is slightly euphoric, calming effect. Useful for pts with neuropathic pain
 - c. Quetiapine (Seroquel) – sometimes used for anxiety
 - d. Propranolol (Inderal) – used to reduce symp of stage fright/performance anxiety. Dosed 10-40 mg 1 hr before event; can cause CNS effects (confusion, dizziness)
 - e. Buspirone (Buspar) – an option for pts who do not respond to AD or for pts at risk of abuse with BZDs
3. **Natural Products:**
 - a. Valerian, lemon balm, glutamine, passion flower (in tea), hops (in tea), chamomile tea, theanine, skull caps
 - b. Kava is used as a relaxant- but causes liver damage, do NOT recom
 - c. Valerian may rarely be hepatotox.
 - d. Passion flower- rated as ‘possibly effective’
4. **Benzodiazepines:**
 - a. Often used for anxiety; provides fast relief for acute symptoms.
 - b. Appropriate use in short term situations where anxiety cause extreme stress, loss of sleep, disrupt life (should be used for 1-2 wks in these cases)

BENZODIAZEPINES – potentiate GABA an inhibitory NT, causing CNS depression

- ❖ **Lorazepam (Ativan)**
- ❖ **Alprazolam (Xanax)**
- ❖ Chlordiazepoxide (Librium)
- ❖ **Clonazepam (Klonopin)**
- ❖ Clorazepate (Tranxene)
- ❖ **Diazepam (Valium)**
- ❖ Oxazepam (Serax)
- C IV ; potential for abuse, physiological dependence & tolerance with chronic use
- **s/e: Drowsiness, dizziness, ataxia, lightheadedness**
- Withdrawal symptoms when d/c: seizures, insomnia, mental/mood changes, n/v/d, loss of appetite, hallucinations, muscle pain, tachycardia, etc
- **LOT – lorazepam, oxazepam, temazepam- are considered less harmful in elderly or with liver dysfxn (since they are met to inactive glucuronide metabolites)**
- Librium, valium, serax- used for alcohol withdrawal.
- Klonopin, tranzene is used for seizures
- DI: additive effects with sedating drugs (pain meds, muscle relaxants, antihistamines, AD-mirtazapine, trazodone, alcohol)

BUSPIRONE 5HT₁ partial agonist; NO abuse/physiological dependence

- ❖ **Buspirone (Buspar)** start 7.5 mg BID
 - 2-4 wks for optimal effect
 - No abuse/tolerance/physiological dependence.
 - s/e: nausea, dizziness, ha, lightheadedness, excitement
 - avoid use in severe kidney/liver impairment
 - DI: do not use with MAOI, 3A4 inhibitors

Common medication that can worsen anxiety

1. Albuterol (if used incorrectly-swallowed)
2. Caffeine – high doses
3. Stimulants
4. Decongestants (pseudoephedrine)
5. Steroids
6. Bupropion
7. Fluoxetine
8. Illicit drugs- cocaine, LSD, methamphetamines

[52] INSOMNIA

Natural products used for insomnia:

- St Johns wort – if insomnia is due to depression ; but has many interactions
- Chamomile tea taken in the evening helps many ppl feel calmer
- Melatonin is useful for some pts
- Valerian can be useful, but there have been isolated rpts of causing liver tox; still unclear

Drugs that likely to contribute to insomnia

- Bupropion
- Stimulants (methylphenidate)
- OTC appetite suppressants
- Decongestants (pseudoephedrine)
- MAO B inhibitors, if taken late in day
- Fluoxetine, if taken late in the day
- Caffeine
- Steroids
- Alcohol (initially induces sleep, but prevents deeper stages of sleep and causes nocturia)
- Any drug that causes urinary retention or nocturia, including antihistamines & diuretics taken later in day

NON-BENZODIAZEPINES : acts selectively at BZD receptors to inc GABA

❖ **Zolpidem (Ambien, Ambien CR)** C IV

- Zolpimist (spray) Edular (SL tabs) Intermezzo SL (for nighttime awakening)
- Potential for abuse & dependence
- Preferred over BZD for 1st line of insomnia due to ↓ abuse, dependence and tolerance
- Do not take with fatty food, a heavy meal/alcohol within 2 hrs of med (may prevent med from working properly)
- S/E: somnolence, dizziness, ataxia, lightheadedness, 'pins & needles' feeling on skin, may cause parasomnias (unusual actions while sleeping)
- Withdrawal symptoms if used longer than 2 wks (muscle cramps, sweating, skakiness- goes away in 1-2 days)

❖ **Zaleplon (Sonata)** C IV

❖ **Eszopiclone (Lunesta)** C IV

- Not limited to short term use (although all 3 are commonly used long term)
- Eszopiclone (*Lunesta*) has unusual dosing: 1 mg if difficulty falling asleep, 2 mg if difficulty staying asleep or 3 mg if helpful for a longer duration of sleep.

Tricyclic Antidepressants

- ❖ Doxepin ext-rel (Silenor) – not controlled
 - Used for sleep maintenance
- Somnolence, low incidence nausea and URI, possibly antichol SEs

Benzodiazepines : s/e see anxiety section

- ❖ **Lorazepam (Ativan)**
- ❖ **Temazepam (Restoril)**
- ❖ Estazolam (Prosom)
- ❖ Quazepam (Doral)
- ❖ Flurazepam (Dalmane)
- ❖ Triazolam (Halcion)

Anti-histamines – competes and blocks H1 receptor

- ❖ **Diphenhydramine (Benadryl, Sominex)**
- ❖ Doxylamine (Unisom)
 - Due to side effects, "DO NOT USE IN ELDERLY"
 - s/e: signif antichol: sedation, confusion, peripheral antichol s/e (dry mouth, urinary retention, dry/blurry vision, risk inc IOP, constipation)
 - some children exp. excitability instead
 - Best to avoid in BPH/glaucoma

Melatonin Receptor Agonist

- ❖ Ramelteon (Rozerem) – not controlled
 - Do not take with fatty food

[53] EPILEPSY/SEIZURES

1. Epilepsy is a neurological d/o defined by unprovoked seizures, or abnormal 'electrical storms' in the brain.
 - a. Generalized seizure = involves the entire brain and loss of consciousness
 - b. Focal/partial seizure = begin in one part of the brain & may or may not spread
2. **Status epilepticus** – continuous seizure lasting > 5 mins or 2 or more discrete seizures with incomplete recovery of consciousness between the two .
 - a. TXT = diazepam, lorazepam. Chlordiazepoxide used occasionally.
3. When anticonvulsants are used in women of reproductive age, **it is imp to consider teratogenicity**.
 - a. Carbamazepine, clonazepam, phenobarbital, phenytoin, topiramate and valproate = Preg Cat D (known fetal risk, benefits must outweigh risks) –valproate & phenobarbital have the highest fetal risk
 - b. **Lamotrigine is Cat C** and may be a safer option
4. **Weight gain (Valproic acid) 1° reason for non adherence** – 3 drugs produce modest **WT LOSS = topiramate, levetiracetam, zonisamide**
5. CNS s/e (**dizziness, cognitive dysfxn**) are common since these drugs must penetrate CNS to work; many cause ataxia (drunk like uncoordination) and somnolence and blurry vision.
6. Most AEDS req MedGuides with suicidality warning

1ST LINE AND ALTERNATIVE AGENTS

❖ **Phenytoin (Dilantin)** – mix in NS only

❖ **Fosphenytoin (Cerebyx)** –**prodrug of PHT**; can mix fosPHT in NS or D5W

- Max infusion for PHT is 50 mg/min (if faster, can cause severe bradycardia/hypotn)
- Max fosPHT is 150 mg PE/min
- 1 mg PE=1 mg PHT IV:PO = 1:1
- **Usually dosed 100 mg TID, up to 600 mg/d**
- Kinetics: **saturable MM** ; if albumin is low (<3.5) the true phenytoin level is higher than it appears (adjust with formula) PHT correction = $\text{PHT measured} / [(0.2 \times \text{alb}) + 0.1]$
- Therapeutic range = **10-20 mcg/mL**
- Enteral feedings (tube feeds) may ↓ absorption, must separate

- S/E: sedation, cognitive impairment
 - **Toxicity symptoms** = ataxia/slurred speech, nystagmus (wobbly eye balls), blurred vision, diplopia, lethargy, drowsiness
 - **With chronic therapy** = skin thickening of facial features, lupus like syndrome, gingival hyperplasia, hirsutism, periph neuropathies, osteomalacia, osteoporosis, Vit D , Ca, folate deficiency (bone & anemia)
 - **Serious adverse effects**: serious skin rxns (SJS, TEN, behavior changes, hepatotox, blood dyscrasias, purple glove syndrome if IV extravasates

P – potent inducer, purple glove
H – hirsutism
E – enlarged gums (gingival hyperplasia)
N – nystagmus (wobbly eye balls if toxic)
Y – yukky blood dyscrasias, yukky purple skin if drug extravasates
T – teratogenicity
O – osteomalacia, osteoporosis
I – interference with folic acid absp (anemia)
N – neuropathies

- ❖ **Carbamazepine (Tegretol, Tegretol XR, Carbatrol, Epitol)**
 - Potent P450 inducer & autoinducer
 - Therapeutic range = **4-12 mcg/mL**
 - S.E: **nausea, dizziness, drowsiness, ha**
 - **Rare** = **hepatotoxicity**, lupus like syndrome, **SIADH**/Low Na levels
 - **BBW**: **serious skin rxns, aplastic anemia, agranulocytosis**
 - If **Asian**, **MUST** test for **HLA-B 1502 allele**, if positive, cannot be used
- ❖ **Oxcarbazepine (Trileptal) 300-600 mg BID**
 - Potent 3A4 inducer
 - S.E: **sedation, GI effects, diplopia, ataxia, serious skin rxns, hyponatremia**
- ❖ **Valproate or valproic acid (Depakene, Stavzor)**
- ❖ **Divalproex (Depakote, Depakote ER)**
 - P450 inhibitor
 - Therapeutic range = **50-100 mcg/mL**
 - s/e: **GI upset, alopecia (treat with selenium & Zn), sedation, tremor, wt Gain, thrombocytopenia**
 - **BBW**: **hepatic failure, teratogenicity, pancreatitis**
- ❖ **Lamotrigine (Lamictal, ODT, CD-chewable, XR) – titrate***
 - Preg cat C
 - s/e: **nausea, diplopia, sedation, ataxia, ha**
 - **BBW**: **serious skin rash**, esp if rapid inc in dose or coadmin with valproic acid (inc LTG >2 fold)
 - To dec rash- follow titration
 - Fda warning: ↑ risk aseptic meningitis
- ❖ Ethosuximide (Zarontin)
 - s/e: blood dyscrasias, SLE, effects on renal & hepatic fxn
- ❖ **Topiramate (Topamax) *titrate**
 - s/e: **oligohydrosis/hyperthermia** – try to limit sun, hydrate, **nephrolithiasis** (kidney stones-hydrate), **paresthesias, diff with memory, diff with concentration**
 - **wt loss**
 - **Preg D**
- ❖ Clonazepam (Klonopin)
 - See BZDs
- ❖ **Levetiracetam (Keppra, XR)**
 - S/E: somnolence, dizziness, behavior changes, Wt loss, hematologic abnormalities
 - No signif DI
- ❖ Zonisamide (Zonegran)
 - S/E: **ha, confusion, somnolence, wt LOSS, anorexia**
 - **Do not use in pts with sulfa allergy**
 - **Serious skin rxn, oligohydrosis/hyperthermia** – limit sun, **nephrolithiasis-hydrat**, met acidosis, agranulocytosis

ANTICONVULSANTS NOT USED IN MEDICAL LETTER RECOM.

- ❖ **Phenobarbital (Luminal, Barbital) C IV**
- ❖ Primidone (mysoline) – prodrug of phenobarbital
 - MOA: **enhances GABA** and ↑ seizure threshold
 - P450 inducer
 - Therapeutic range = **20-40 (adults), 15-30 (children)**
 - S/E: **Major Somnolence***, **cognitive impairment**
 - **Dependence, tolerance** – do not stop abruptly, seizures can result
 - **Serious skin rxn**
- ❖ **Pregabalin (Lyrica) C V**
 - s/e: **slight euphoria, periph edema, wt gain, dizziness, somnolence, blurred vision**

[54] MULTIPLE SCLEROSIS

1. MS is a chronic, progressive autoimmune disease in which a pts immune system attacks the fatty myelin sheaths that surround the axons in the brain and spinal cord
2. As demyelination occurs, the symptoms worsen and nerves can no longer conduct electrical transmission
3. **s/s**: muscle weakness, tingling, numbness, deterioration of cognitive function, incontinence, depression, sexual dysfunction
4. **TXT**: disease modifying drugs to prevent disease progression. Many chemotherapeutic drugs are used off label (cyclophosphamide, MTX, cladribine, alemtuzumab, rituximab). Steroids are used to help with exacerbations
5. **DMARDS**
 - a. Interferon beta formulations (Betaseron, Avonex, Rebif, Extavia) & glatiramer acetate (Copaxone) have been the mainstay of treatment
 - b. Fingolimod (Gilenya) – the first PO DMARD
 - c. Natalizumab (Tysabri) a humanized mAb that targets $\alpha 4$ integrin is used only in pts who could not tolerate or had poor responses to other agents – bc it has inc risk of progression of PML (progressive multifocal leukoencephalopathy)
 - d. Consider varicella vaccination before starting treatment (since live vaccine cannot be used with DMARDS)

Interferons : reduce antigen presentation & T cell proliferation.

- ❖ **Interferon- β -1a lyophilized (Avonex)** Cat C
- ❖ **Interferon- β -1a liquid form (Rebif)** Cat C
- ❖ Interferon- β -1b (Betaseron) Cat X
- ❖ Interferon- β -1b (Extavia) Cat C
 - All: do not shake
 - If refrigerated, let stand to RT before injection
 - s/e: flu like rxn (some pts take APAP or NSAID before inj), inj site rxn (mild rash to skin necrosis), liver enzyme elevations, seizures, thyroid dysfunction

Copaxone: Immune modulator

- ❖ Glatiramer acetate (Copaxone)
 - Some get chest tightness, CP, palpitations, anxiety, flushing

Tysabri: Recombinant humanized monoclonal antibody

- ❖ Natalizumab (Tysabri) – for refractory pts due to risk of PML

Gilenya : Oral Immune modulator

- ❖ Fingolimod (Gilenya) – blister packs, protect from moisture
 - s/e: bradycardia, monitor ECG

Ampyra: K⁺ channel blocker, may inc nerve conduction

- ❖ dalfampridine (Ampyra) – most do not respond.
 - s/e: UTI, insomnia, dizziness, headache, nausea, possibility of seizures (CI)

[55] STROKE

1. A stroke or cerebrovascular accident (CVA) occurs when BF to an area of the brain is interrupted by ischemia due to a clot (thrombus/emboli) or rupture of BV (hemorrhage)
2. Acute ischemic stroke refers to stroke caused by thrombosis or embolism is more common than hemorrhagic strokes.
3. Clinical presentation:
 - a. Sudden numbness/wkness of face, arm, leg (esp on one side of the body)
 - b. Sudden confusion, trouble speaking or understanding
 - c. Sudden trouble seeing in one of both eyes
 - d. Sudden trouble walking dizziness, loss of balance/coord.
 - e. Sudden severe HA

Primary Prevention : recommended for pts with A. fib

Secondary Prevention : pts with prev cardioembolic stroke should be placed on anticoag therapy for 2° stroke prevention.

Any of the 3 agents below are acceptable options for intial therapy

- ❖ **Aspirin** 50 mg – 325 mg QD
- ❖ **Clopidogrel** 75 mg QD
- ❖ **Dipyridamole/ASA (Aggrenox)** 200/25 mg BID

Management of Acute Ischemic Stroke Goal is to maintain normal intracranial pressure (ICP), control BP, remove the clot (MERC device) or dissolve the clot with t-Pa

Thrombolytic therapy – causes fibrinolysis by binding to fibrin in a thrombus and converts entrapped plasminogen to plasmin

- ❖ **Alteplase (Activase, rt-PA)** – must confirm clot on head CT
 - Infuse 0.9 mg/kg (max 90 mg) over 60 mins
 - Must be initiated within 3 hrs of symptom onset (new data shows benefit up to 4.5 hrs but not yet FDA approved)
 - s/e: major bleeding, angioedema
 - CI: active bleed, recent surgery, PLT ct <100,000, INR >1.7, severe HTN (>185/110), prev MI in 3 mths

Antiplatelet therapy – benefit in reduction of early recurrent stroke

- ❖ **Aspirin** 325 QD
 - Oral admin within 24-48 hrs after stroke onset. NOT recom within 24 hrs of tPA

Antihypertensive therapy- used to dec BP & possibly qualify pts for t-PA therapy

- ❖ Labetalol 10-20 mg over 1-2 mins , may repeat (max 300 mg)
- ❖ Nicardipine (Cardene) 5 mg/hr infusion

Management of Intracerebral Hemorrhage

Osmotic diuretic – inc the osmotic pressure to reduce intracranial pressure assoc with cerebral edema

- ❖ **Mannitol (Osmitol)**
 - s/e: fluid and electrolyte loss, dehydration, hyperosmolar induced hyperkalemia, hypernatremia

Management of Acute Subarachnoid Hemorrhage

- ❖ Nimodipine (Nimotop) – DHP CCB
 - BBW: do not admin IV. Label syringes with “for oral use only”
 - s/e: hypotn, ha, diarrhea

[56] GASTROESOPHAGEAL REFLUX DISEASE (GERD)

1. A condition in which the stomach contents leak backwards into the esophagus.
2. **Typical symptoms of GERD:** heart burn, hypersalivation, regurgitation, acid taste in mouth. Less commonly – recurrent cough, sore throat, hoarseness and CP
3. **Non-pharmacological txt:**
 - a. Avoid foods that can reduce LES pressure or aggravate the condition: **spicy foods, nicotine, coffee/caffeine/tea, alcohol, fatty foods, citrus, chocolate, peppermint**
 - b. Dec portion size
 - c. Wt loss
 - d. Avoid drugs that can dec LES pressure: anticholinergics, barbiturates, DHP CCB, estrogen, nitrates, NSAIDS, theophylline, etc
 - e. Elevate head of the bed by 6-8" (not with pillows but a wedge)
 - f. Avoid tight fitting clothes

ANTACIDS – neutralize the gastric acid in a buffering rxn; good for mild or infreq symptoms

- ❖ **Calcium carbonate (Tums)**
 - *Fast onset = < 5 mins. Lasts = 1-2 hrs*
- ❖ Aluminum (Alternagel)
 - S/E: Al causes constipation, Mg causes diarrhea – the two together can counter balance but still get loose stool
- ❖ **Magnesium (Phillips Milk of Magnesia)**
 - Renal – Al and Mg can accumulate with severe renal dysfxn, not recom with CrCl <30
- ❖ **Mg + Al or Ca (Maalox, Mylanta, Rolaids)**
 - Alka seltzer contains >1g Na per serving, not generally used as an antacid anymore
- ❖ **Mg + Al + simethicone - anti gas (Maalox Max, Mylanta max St)**
 - DI: take 2 hr before or 4 hrs after : quinolone or TCA (dec abs due to chelation), itraconazole, ketoconazole, Ca carbonate, Fe (dec abs due to inc pH)
- ❖ Sodium bicarbonate (Alka Seltzer Heart burn relief)
- ❖ Calcium carbonate, Mg hydroxide, famotidine (Pepcid complete)

H2RAs – reversibly inhibits H2 receptors on the gastric parietal cells inhibiting gastric acid secretion

- ❖ **Famotidine (Pepcid AC, Pepcid AC Max Strength)**
 - Onset = 30-45 min lasts = 4-10 hrs
- ❖ **Famotidine + Ca carbonate + MgOH (Pepcid Complete)**
 - Occasionally may be approp with PPI if H2RA is used at bedtime for night time reflux
- ❖ **Famotidine 26.6 mg + ibuprofen 800 (Duexis)**
 - s/e: agitation/vomiting in children <1, ha, dizziness, diarrhea, constipation
- ❖ **Ranitidine (Zantac)**
 - may ↑ risk of GI infxn, ↑ risk of pneumonia in hosp pts
- ❖ **Nizatidine (Axid)**
 - cimetidine – CNS effects, gynecomastia, impotence, blood dyscrasias, inc LFTs, arthralgia
- ❖ Cimetidine (Tagamet, Tagamet HB 200) – 3A4 inhib

PPI – irreversibly binds to gastric H/K ATPase pump in parietal cells. They block the final step in acid production and are more effective when **taken 30 mins before a meal (breakfast)**

- ❖ **Omeprazole (Prilosec OTC, Prilosec)** ⚡ in applesauce/acidic juice
 - Onset = 2-3 hrs lasts=12-24 hrs
- ❖ **Omeprazole + Na Bicarb (Zegerid, Zegerid OTC)**
 - s/e: ha, dizziness, diarrhea, constipation, Vit B12 def, hypomagnesemia, acid rebound
- ❖ **Pantoprazole (Protonix)**
- ❖ **Lansoprazole (Prevacid, Solutab, 24H OTC)** ⚡
- ❖ Lansoprazole + naproxen (Prevacid NapraPAC)
- ❖ Dexlansoprazole (Dexilant) ⚡
- ❖ **Esomeprazole (Nexium)** ⚡
- ❖ **Esomeprazole + naproxen (Vimovo)**
- ❖ **Rabeprazole (Aciphex)**
 - can ↑ risk of C. diff, ↑ risk osteoporosis/fx with long term use, can ↑ INR using warfarin, ↑ risk pneumonia in hosp pts
 - caution with drugs that req acidic envr PPIs inhibit 2C19

Cytoprotective Agents

- ❖ **Misoprostol (Cytotec)** – QID dosing; PG E1 analog that replaces the gut protective mech removed by NSAIDS
 - BBW: not to be used to reduce NSAID induced ulcers in women of childbearing potential unless has effective contraceptive mechs.
 - Preg Cat X . s/e: diarrhea, abd pain (both signif)
- ❖ Sucralfate (Carafate) – forms a complex by binding to pos charged proteins that protect the stomach lining against pepsin and HCL acid
 - s/e: constipation. Drug is in Al complex, can accumulate
 - DI: avoid taking antacids within 30 mins before or after. Separate from other drugs 2 hr b, 4 hr a

Metoclopramide – DA Antagonist. At higher doses it blocks 5HT receptors in chemoreceptor zone of CNS. It also enhances response to Ach in upper GI tract to inc motility & inc LES tone

- ❖ **Metoclopramide (Reglan)**
 - S/E: CNS (dizziness, restlessness, akathisia, confusion, depression)
 - Serious ADR due to DA blockage : EPS, parkinsonism, acute dystonic rxns, TD, rarely neuroleptic malignant syndrome.
 - Do not use in pts with Parkinsons disease

[57] PEPTIC ULCER DISEASE (PUD)

1. Occurs from mucosal erosion within the GI tract. Unlike gastritis and erosions, the ulcers in PUD extend deeper into the mucosa
2. **3 most common types of PUD:**
 - a. Helicobacter pylori (H. pylori) G- pH sensitive bact. That lives in acidic enviro of stomach
 - b. NSAID induced ulcers
 - c. Stress ulcers (from critical illness)
3. **Mucosal defense & repair mech:** mucus & bicarbonate secretion, mucosal BF, PG synthesis, cellular regeneration, epithelial cell renewal. These protect the gastroduodenal mucosa from NSAIDS, H. pylori, acid, pepsin, etc.
4. **Symptoms:** epigastric pain* (upper region of abdomen), burning sensation, heart burn, belching, bloating, nausea, anorexia
 - a. If an ulcer is duodenal (usually H. pylori) → eating **lessens** the pain
 - b. If an ulcer is gastric (NSAIDS) → eating **worsens** the pain

H. Pylori

1. Diagnostic tools:

- a. Urea Breathe test (UBT) = Identifies gas (CO₂) produced by the bact. False negatives can be due to recent H₂RA, PPI, bismuth or abx – d/c H₂RA, PPI 1-2 wks and abx 4 wks before testing
- b. Fecal antigen test = Detects H. pylori in the stool. D/C drugs above 2-4 wks before testing
- c. Blood (serologic) test = Detects antibodies to the bacteria. Cannot distinguish btw current/previous infxn since pts can remain serologic (+) for 6 mths – 1 yr after eradication

2. Txt:

- a. **Triple therapy** with antisecretory agent (PPI) + 2 abx (clarithromycin + amoxicillin or metronidazole) x 14 days
 - **PPI BID (esomeprazole is 40 mg QD)**
 - **Amoxicillin 1 g BID**
 - **Clarithromycin 500 mg BID**
 - **If PCN or macrolide allergy, replace amox/clarith with metronidazole 500mg BID**

- b. **Quadruple therapy** (for pts that failed triple therapy, have taken a macrolide/metronidazole in the past, high local resistance rate to clarithromycin) → PPI + bismuth + metronidazole + tetracycline x 10-14 days
 - **PPI BID - if cannot tolerate PPI, subs with H₂RA (ranitidine, famotidine, nizatidine)**
 - **Bismuth subsalicylate 525 mg QID – do not use in children <8 yo**
 - **Metronidazole 250 mg QID**
 - **Tetracycline 500 mg QID – no pregnancy, no children <8 yo**
- c. Sequential therapy : PPI + amoxicillin x 5 days, then PPI + clarithromycin + tinidazole x 5 days
- d. (14d) Prevpac (lanso/amox/clarith), (10d) Pylera (bismuth/metron/tetracy) + PPI, (14d) Helidac (bismuth/metron/tetra) + H₂RA

3. Counseling:

- a. Meds may cause upset stomach
- b. Bismuth subsalicylate: pink tablets should be chewed, all others are swallowed. Bismuth can cause temporary and harmless darkening of tongue +/- dark stool
- c. Tetracycline : do not use if preg or <8 yo. Use back up method for BC. Makes skin more sensitive to light, SPF
- d. Metronidazole : do not use alcohol
- e. Clarithromycin: may cause diarrhea, nausea, abnormal taste.

NSAID Induced Ulcers (1° Gastric)

1. Use of high dose NSAIDs or chronic NSAID greatly inc risk for GI ulcers. NSAIDS (inclu ASA) can cause direct irritation to gastric epithelium & inhibition of PG (by inhibiting COX-1)
2. **Risk factors:** Age >65, Prev ulcer, high dose NSAID, concomitant use of steroids, anticoag, antiplatelets (asa, clopidogrel, prasugrel), oral bisphosphonates, SSRIs
3. **TXT**
 - a. Use of concomitant PPI will ↓ risk. High risk pts on chronic NSAIDS should receive PPI regardless of prev hx of ulcers
 - i. COX2 inhibitors can be used if pts DO not have CV risk factors
 - ii. **For those with CV risk, naproxen + PPI is recom.**
 - b. If ulcer develops- best to d/c the NSAID & trewt with PPI x 8 wks.
 - c. If NSAID cannot be stopped, dec dose or switch to APAP or use COX2 inhibitor

[58] CONSTIPATION & DIARRHEA

CONSTIPATION

1. Infrequent or hard stools, or difficulty passing stools. It can involve pain during passage of bowel mvmt, inability to pass a bowel mvmt after straining/pushing for >10 mins, no bowel mvmt after > 3 days.
2. Looking for offending drugs, correct fluid intake (64 oz), limit caffeine & alcohol, inc fruits & veg, inc physical activity, don't delay going to the bathroom.
3. **Opioids & constipation:**
 - a. Regular use of senna (stimulant) + stool softener (docusate), alone or in combo
4. **TXT** : lactulose, sorbitol, MOM, Mg citrate or Miralax
5. **Fecal impaction:** Enema, may req digital evacuation

Bulk Laxatives – usually 1st line

- ❖ Wheat bran
- ❖ **Calcium polycarbophil (FiberCon)**
- ❖ **Psyllium (Metamucil)**
- ❖ **Methylcellulose (Citrucel)**
 - Onset 12-24 hrs
 - s/e: inc gas, bloating, bowel obstruction if strictures present
 - choking of powder forms are not taken with enough liquid, adequate fluid intake, take 2 hrs before/after drugs

Emollient, lubricant (stool softeners)

- ❖ **Docusate sodium (Colace)**
- ❖ Docusate Ca
- ❖ Mineral Oil
 - Onset = 24-48 hrs
 - Do not use docusate with mineral oil

Stimulants & Irritants

- ❖ **Bisacodyl (Dulcolax)**
- ❖ **Senna (Ex-Lax)**
 - Onset rectal = 10 mins Oral = 8-12 hrs
 - s/e: stomach upset, cramping, electrolyte imbalance

Gut Opioid R Blocker

- ❖ **Methylnaltrexone (Relistor)**
 - Blocks opioid receptors in the gut- only for use with opioids (for pts that have failed DSS + laxative (senna, bisacodyl))
 - Given SC QOD

Meds that are Constipating

1. Opioids
2. Anticholinergics
3. Antihistamines, phenothiazines, TCAs, antispasmodics, urge incontinence (esp darifenacin (Enablex))
4. NDP CCB (esp verapamil)
5. Clonidine
6. Metals
7. Bismuth
8. Fe
9. Al antacids & complexes
10. Antineoplastics
11. Alkaloids, oxaliplatin, taxanes

Osmotics

- ❖ Lactulose
- ❖ **Mg salts (MOM)**
- ❖ Sorbitol
 - Onset = 2-48 hrs
 - Salts lead to retained fluid in the bowel lumen, with a net inc of fluid secretions in the SI
 - S/E: electrolyte imbalance, excessive gas, hyperMg, HyperPhos, HypoCa

Fleets

- ❖ Phospho-Soda
 - Onset = within 30 mins
 - s/e: dehydration; do not use phospho-soda in CHF, renal disease (dec Ca, inc PO4)

Nonabsorbable solutions

- ❖ **Polyethylene glycol (Golytely, MiraLax, Carbowax)**
- ❖ Nulytely, Trilyte - are sulfate free
- ❖ HalfLyte, MoviPrep- are less volume (2L)
 - MiraLax is OTC, full capful with powder and mix into glass of water
 - GoLyteLyte onset = within 4 hrs
 - s/e: nausea, abd fullness, bloating

Glycerin sup

- ❖ bablylax is a liquid in rectal applicator
 - avail in 2 sizes, adult and pediatric
 - onset = within 20 mins

Lubiprostone (Amitizia)

- activates Cl channels in the gut leading to fluid in gut and mvmt
- s/e: Nausea (30%), take with food

DIARRHEA

1. abdominal cramps, nausea, vomiting or a fever may occur along with the diarrhea

2. **TXT:**

- a. Most cases are viral. Can also be caused by bacterial or parasitic infections. E.coli is the most common bacterial cause.
- b. If the infxn is parasitical, most are caused by Giardia lamblia – diarrhea can develop 1-4 wks after exposure
 - i. Txt includes: metronidazole, tinidazole (Tindamax) , nitazoxanide (Alinia)

3. **Traveler's diarrhea ppx/avoidance**

- a. Ppx with abx is NOT recommended (except for those that high risk traveler's – immunocompromised)
- b. If txt is used for an active infxn : quinolones, azithromycin or rifaximin is commonly used
- c. Pts may choose to ppx with bismuth subsalicylate (BSS, Pepto-Bismol)
 - i. BSS should be avoided in pts with ASA allergy, renal insuff, gout, those taking anticoagulants, probenecid, or MTX
 - ii. Avoid in children with viral infections (varicella, influenza) bc of risk of Reye's Syndrome

- ❖ Psyllium – soaks up liquid, see constipation section

❖ **Bismuth subsalicylate (BSS or Pepto-Bismol)**

- Antisecretory and antimicrobial properties
- s/e: black tongue/stool, caution in travelers on ASA therapy or anticoagulants
- avoid in children with viral infxn – reyes syndrome
- salicylate tox can be present as tinnitus

4. **Counseling for all diarrhea causes**

- a. High fever / blood in stool → do not self treat , see Dr. if no improvement after 2 days
- b. Diarrhea txt should include fluid and electrolytes
- c. Moderate-severe fl loss → replacement is best accompanied by oral rehydration solutions (Pedialyte, Infalyte, Gatorade)
- d. Caution with Imodium and Lomotil, if infxn is from Shigella, Salmonella, and toxigenic strains of E.coli, a dec in intestinal motility may cause toxic megacolon. These products are NOT recom for C.diff infxns, since the body might be trying to get rid of the toxin
- e. Fever/cold symptoms → parent may try APAP or ibuprofen instead of ASA for children
- f. Rule out lactulose intolerance

Meds that can cause Diarrhea

1. Colchicine
2. Metoclopramide
3. Misoprostol
4. Antacids containing Mg
5. ABX (any and incl erythromycin – rule out C.diff)
6. Quinidine
7. Li
8. Theophylline (if toxic)

❖ **Loperamide (Imodium)**

- Inhibits peristalsis on intestinal muscles to slow motility
- 4 mg PO after 1st loose stool, then 2 mg after each subsequent (max 16 mg/d)
- Do not self treat for >2 days
- Not for use in children < 2yo
- Avoid use if infxn is due to c. diff, shigella, salmonella, toxigenic strains of E.coli

❖ **Diphenoxylate with atropine (Lomotil)**

- Diphenoxylate is constipating meperidine congener and atropine is to discourage abuse
- May cause sedation, constipation, urinary retention, tachycardia, blurred vision, xerostomia

[59] INFLAMMATORY BOWEL DISEASE (IBD)

1. A group of inflammatory conditions of the colon and SI. The majority of IBD are ulcerative colitis (UC) and Crohn's disease.
 - a. Crohn's can cause malabsorption (vit deficiencies) and anal fistulas
2. Symptoms inc when pt is under stress or eats foods that may trigger disease (beans, alcohol, lactose containing dairy products, cabbage, broccoli)
3. **Ulcerative Colitis**
 - a. Affects only the rectum & colon
 - b. Superficial ulcerations
 - c. Abd pain, bloody diarrhea, wt loss, fever
4. **Crohn's disease**
 - a. Affects any part of the GI tract, mostly (2/3) are in the ileum- last part of the SI
 - b. Ulcers can be deep
 - c. Abd pain, diarrhea and wt loss – NO fever and diarrhea is generally not bloody
5. Risk factors of IBD:
 - a. Smoking cigs (UC = it's protective, relapses occur with cessation ; CD =2x inc in risk for exacerbations, cessation can improve symptoms)
 - b. NSAID use
 - c. Diet
6. **TXT:**
 - a. Simpler cases – only need antidiarrheal meds (1° loperamide (Imodium)) ; antispasmodics for UC may be useful (1° dicyclomine (Bentyl) – an anticholinergic)
 - b. Acute flare ups – short courses of oral steroids (occasionally IV)
 - c. Moderate symptoms – aminosalicylates (sulfasalazine/mesalamine) are used to control inflammation
 - d. Moderate – severe cases of Crohn's may req stronger IS agents (azathioprine, 6-mercaptopurine, MTX)
 - e. Severe – UC (fistula dev. or severe symptoms) TNF blockers (1° infliximab) may be needed
 - f. Some pts find rifaximin (Xifaxan) indicated for GI infxn to be helpful, but not FDA indication
7. **Natural products:**
 - a. Cascara & senna are natural laxatives for constipation
 - b. Psyllium (Metamucil) and bulk forming fiber products for diarrhea
 - c. Peppermint oil or tea can be useful as an antispasmodic. Some use chamomile tea
 - d. Probiotic lactobacillus or bifidobacterium infantis may help reduce abdominal pain, bloating, urgency, constipation/diarrhea. DO NOT use abx and probiotics together. Separate by 2 hrs

Clinical Pearls

- » 5-ASA is LESS effective for Crohn's disease
 - Budesonide would be a better choice to treat terminal ileum or Right sided (ileal) disease
 - » Mesalamine topical products effective if disease is isolated to rectum or left-side of colon and avoid having to take oral meds
 - » AZA and 6-MP are not used as induction b/c of slow onset
 - Induce with CSS and begin immunomodulator during steroid taper so that full action will occur when steroids are discontinued.
 - » Methotrexate is NOT effective in Ulcerative colitis, ONLY used in Crohn's disease
8. **Avoidable problems:**
 - a. sorbitol – a sweetener that is in some diet foods and drugs. It causes GI distress in some pts with IBS and has laxative properties
 - b. Lactose intolerant pts – lactose is in dairy products but also in oral drugs as excipients
 - c. Sorbitol and lactose are excipients (binders) to hold tablets together.

Steroids to dec Severity of Acute Attacks

- ❖ Prednisone 5-60 mg/d
- ❖ Budesonide (Entocort ED- do not crush) – 3A4 substrate
 - Budesonide is preferred if disease is in the ileum or ascending colon
 - May use ADT (alt day therapy) to dec adrenal suppression
 - Steroids are not supposed to be used long term, but some pts use chronically due to severity. If use longterm, assess bone density and consider bisphosphonates, optimize Ca and Vit D

Maintenance Therapy

- ❖ **Mesalamine** (Priso, **Asacol**, **Asacol HD**, **Pentasa**, **Lialda** – long acting PO ; **Canasa**-supp, **Rowasa**-enema)
- ❖ Sulfasalazine (Azulfidine, Sulfazine, Azulfidine EN, Sulfazine EC)
 - Can cause **yellow-orange coloration** of skin/urine
 - **Impairs folate absorption**, may give 1 mg/d folate supplement
 - Take food and 8 oz of water to prevent crystalluria
 - **Enema or rectal mesalamine suppositories are 1st line for UC mild-mod distal disease**
 - **Crohn's req oral therapy w/ mesalamine or sulfasalazine for mild-mod cases**
 - Oral sulfasalazine is 1st line in UC mild-mod **extensive disease**
 - Mesalamine or sulfasalazine can be used for Crohn's
 - Mesalamine : pancreatitis, **CI if hypersensitivity to salicylates** ; avoid concomitant use with antacids, H2RA, PPI
 - Sulfasalazine : **CI in pts with sulfa allergy or salicylate allergy**

If failed above therapy or in combo with above

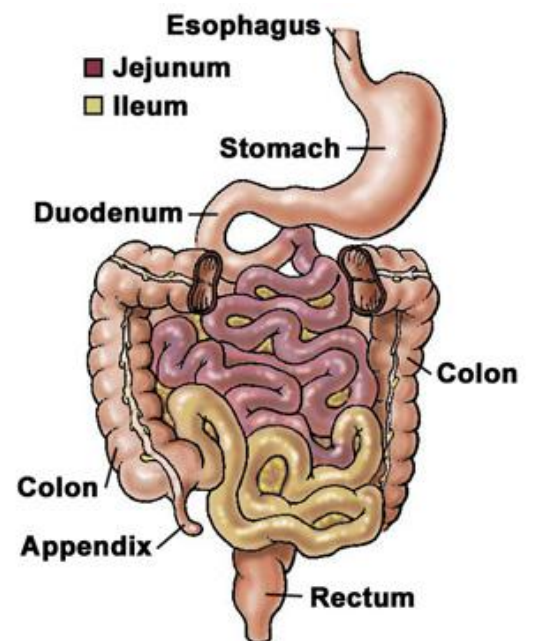
- ❖ Azathioprine (AZA, Imuran)
- ❖ 6-Mercaptopurine (6-MP)
- ❖ MTX (Rheumatrex)

If failed above therapy : Monoclonal antibodies to TNF

- ❖ Remicade : chimeric mab
- ❖ Humira : humanized mab
- ❖ Cimzia : PEG-linked humanized mab
- ❖ Tsyabri: humanized mab that inh $\alpha 4$ integrin

Infliximab (Remicade) – alternative 1st line in moderate-severe UC or Crohn's

- ❖ Used alone or with AZA
- ❖ Chimeric mab against THF
- ❖ IV only
- ❖ CI: NYHA III/IV



[60] ERECTILE DYSFUNCTION

1. The common direct cause of ED is reduced BF to the penis, commonly caused by DM, HTN, heart disease, nerve damage. Hormone imbalances (low testosterone), stress, and neurological illness can also cause ED

Common drugs that cause sexual dysfunction

- 1) BP meds (BB, clonidine, methyldopa)
- 2) Antipsychotics (haloperidol, chlorpromazine, fluphenazine, thioridazine)
- 3) Antidepressants – SSRI, SNRI
- 4) BPH meds – finasteride, dutasteride, silodosin
- 5) CT agents that dec sex hormone levels – leuprolide (Lupron)
- 6) Cimetidine – blocks androgenic hormones
- 7) Opioids- esp methadone
- 8) Nicotine- smoking

PHOSPHODIESTERASE 5 INHIBITORS

Following sexual stimulation (required), PDE5i inc BF to the penis, causing an erection

- ❖ **Sildenafil (Viagra)** 25, 50, 100 mg (start at 50 mg, >65 – 25 mg)
- ❖ **Vardenafil (Levitra, Staxyn ODT)** 5, 10, 20 mg (start at 10 mg, >65- 5 mg)
- ❖ **Tadalafil (Cialis)** 2.5, 5, 10, 20 mg start at 10 mg. if using >2 tabs/wk, use 2.5-5 mg QD
 - Take 1 hr before intercourse
 - Sildenafil & vardenafil are **best on an empty stomach (avoid fatty foods)** ; tadalafil is +/- food
 - May cause **dizziness, sudden drop in BP**, ha, dyspepsia, flushing, stomach pain, back pain (Cialis)
 - **Priapism** that is painful >4 hrs – get medical help
 - **Sudden vision loss in one or both eyes** – get medical help. May cause permanent vision loss
 - **Blurred vision, inc sensitivity to light, bluish haze**
 - **Sudden dec / loss of hearing** have been reported, usually in 1 hear
 - **CI: with nitrates!** Caution for use with **alpha blockers (tamsuloxin-Flomax, doxazosin- Cardura)** →has additive BP lowering effects
 - All are 3A4 substrates – use lower doses with inhibitors

ALTERNATIVE AGENTS – if pt cannot use PDE5i

- ❖ Intracavernosal alprostadil (Caverject) – injected via syringe into penis ; lasts 1 hr
- ❖ Transurethral alprostadil (MUSE) – inserted into urethra
- ❖ Tri-Mix gel (papverine, phentolamine & alprostadil) – inserted into urethra

[61] BENIGN PROSTATIC HYPERPLASIA (BPH)

- The prostate is a walnut sized gland that forms part of the male reproductive system. It surrounds the urethra and squeezes fluid into the urethra as sperm moves thru during sexual climax, energizing sperm and forming semen
- Both testosterone and estrogen contribute to prostate growth. As the prostate enlarges, the tissue surrounding it stops it from expanding, causing the gland to press against the urethra like a clamp on a garden hose.
- The bladder wall becomes thicker and irritated. The bladder begins to contract even when it contains small amts of urine, causing more freq urination. Eventually, the bladder weakens and loses the ability to empty itself, and some urine remains in the bladder.
- PSA – a protein produced by prostate cells. It freq is \uparrow in prostate cancer, but can also inc from other cond such as BPH
- There are 3 types of alpha receptors: 1A (prostate mainly has these), 1B, 1D

1. Symptoms:

- a. Hesitant, interrupted weak stream of urine
- b. Urgency and leaking or dribbling
- c. More freq urination, esp nocturia (if the blockage is severe, urine could back up into the kidneys and result in acute renal failure)

2. Drugs that worsen BPH symptoms:

- a. Combo cold medicines
- b. Decongestants
- c. Antihistamines
- d. Anticholinergics

3. Txt: depends on the pts perception of how bothered they are by the symptoms

- a. Initially **α -blockers are used +/- 5 α reductase inhibitors**
- b. **Cialis** was *approved for mild symptom improvement in BPH* (1 $^\circ$ dec urinary freq) – the benefit is mild but it can help men with concurrent ED and might provide a way to obtain ins. coverage for the ED drug

4. Natural products

- a. Saw palmetto – rated as possibly ineffective.
- b. Pygeum – may be useful but do not recom a pygeum product unless it has been harvested ethically.
- c. Beta sitosterol- comes as supplements, in margarine substitutes, Af. wild potato extract products, pumpkin seed, soy & red clover
- d. Rye grass pollen – has also been used

ALPHA BLOCKERS – relax the SM of the prostate & bladder neck to improve urine flow ; should see improvement in 1-2 wks

Non-selective α blockers

- ❖ **Terazosin (Hytrin)** QHS (to help with dizziness/orthostasis)
- ❖ **Doxazosin (Cardura)** QHS
 - Non selective therefore have more **orthostasis, dizziness, fatigue, ha** than the selectives
 - Does not shrink the prostate & will not change PSA levels

Selective α blockers (1A)

- ❖ **Tamsulosin (Flomax)** 0.4 mg (usually) can inc to 0.8 mg
- ❖ Tamsulosin + dutasteride (Jalyn)
- ❖ Alfuzosin (uroxatral)
- ❖ Silodosin (Rapaflo)
 - Less orthostasis and dizziness but still can get dizziness/fatigue/hypotn/HA
 - Do not use alfuzosin with pts at risk for QT prolongation ; silodosin can cause retrograde ejaculation
 - Renal: caution if CrCL < 30, silodosin is CI if < 30

5 α Reductase Inhibitors – inhibits the 5 α reductase enzyme. This blocks the conversion of testosterone to DHT

- ❖ **Finasteride (Proscar)** – 5 mg QD [**also used for hair loss, propecia 1 mg QD**]
- ❖ **Dutasteride (Avodart)**
- ❖ Dutasteride + tamsulosin (Jalyn)
 - Preg Cat X – women should not handle/take these meds
 - s/e: \downarrow libido, \downarrow ejaculation, impotence (sexual s/e dec over time)
 - 6 mths of txt may be req for max efficacy
 - These SHRINK the prostate & \downarrow PSA levels

[62] OVERACTIVE BLADDER

1. OAB is not a normal sign of ageing. The detrusor muscles contract freq and before the bladder is full, leading to the classic symptoms of:
 - a. Urinary urgency with or without urge incontinence
 - b. Urinary freq (voiding ≥ 8 x/day)
 - c. Nocturia (≥ 2 awakenings to void per night)
2. Forms of urinary incontinence:
 - a. Functional incontinence: no abnormality in the bladder, but the pt may be cognitively, socially or physically impaired (pt in wheelchair)
 - b. Overflow incontinence: leakage that occurs when the quantity of urine stored in the bladder exceeds its capacity, BPH is the most common cause
 - c. Stress incontinence: urine leaks out during any form of exertion (exercise, coughing, sneezing, laughing) as a result of pressure on the bladder
 - d. Urge incontinence: pt cannot hold in urine long enough to reach toilet. Assoc with parkinson's or MS. Can be a warning sign of bladder cancer
 - e. Mixed incontinence: combo of urge and stress incontinence
3. Non-Pharmacological therapy:
 - a. **Kegel exercises** = done to strengthen the pelvic floor muscles, can improve/dimish s/s of urinary incon. Imagining that you are trying to stop yourself from passing gas, squeeze the muscles you would use and count to 3, then relax for a count of 3. Do 3 sets of 10 TID.

ANTICHOLINERGICS – muscarinic receptor antagonists that compete with Ach ∴ blocking contractions of the detrusor muscle

- ❖ **Oxybutynin (Ditropan, XL)**, patch 2x/wk (Oxytrol), 10% topical (Gelnique)
- ❖ **Tolterodine (Detrol), ER (Detrol LA)**
- ❖ Trospium (Sanctura, Sanctura XR) – take on empty stomach
- ❖ **Solifenacin (Vesicare)**
- ❖ **Darifenacin (Enablex)** – causes more constipation
- ❖ Fesoterodine (Toviaz)
 - s/e: dry mouth, dry eyes, constipation, urinary retention, dizziness, cognitive impairment
 - ER formulations have less incidence of dry mouth
 - Oxybutynin patch and gel has less dry mouth & constipation

[63] GLAUCOMA, ALLERGIC CONJUNCTIVITIS, OTHER OPHTHALMICS & OTICS

Eye drops & ear drops are either solutions / suspensions. **Suspensions** must be **shaken** before use.

Eye drops- must wait 10 mins in between each one.

GLAUCOMA

1. An eye disease caused by an increase in intraocular pressure (IOP). If left untreated, glaucoma can result in damage to the optic nerve and gradual loss of vision.
2. There may be no symptoms but some may experience eye pain, HA or dec vision
3. **Two types:** closed-angle glaucoma (medical emergency and treated in hosp) & open-angle glaucoma (commonly treated with eye drops)
4. **Drugs that may ↑ IOP or should be avoided if possible in pts with glaucoma**
 - a. Cough/cold/motion sickness meds (antihistamines)
 - b. Anticholinergics (oxybutynin, tolterodine, benztropine, trihexyphenidyl, tricyclics)
 - c. Chronic CS (esp eye drops like prednisone)
 - d. Beta agonists (albuterol)
 - e. Topiramate (Topamax)
5. **TXT:**
 - a. 1st line = prostaglandin analogs (PA) – latanoprost (Xalatan) → lowers the IOP more than BB
 - b. Beta blockers (non-selectives, timolol) = often used after PAs if needed

BETA BLOCKERS, Non-selective : ↓ aqueous humor production

- ❖ **Timolol 0.25%, 0.5% (Timoptic-QD-BID, Timoptic XE – gel QD)**
- ❖ Levobunolol (Betagan)
- ❖ Carteolol (Ocupress)
- ❖ Metipranolol (OptiPranolol)
- ❖ Betaxolol (Betoptic, S)
 - s/e: burning, stinging, itching of the eyes or eyelids. Changes in vision, inc sensitivity to light
 - although most medicine stays local, it is best to try to avoid in asthma, COPD, chronic bronchitis, etc

PROSTAGLANDIN ANALOGS : ↑ aqueous outflow

- ❖ **Travoprost (Travatan Z)**
- ❖ **Bimatoprost (Lumigan)** – also Latisse (do not use concurrently with same class for glaucoma w.o MD approval)
- ❖ **Latanoprost (Xalatan)** – store unopened bottles in fridge
- ❖ Unoprostone (Rescula)
 - All once QHS except Rescula, BID
 - Cannot be admin with contact lenses, remove and wait 15 mins before inserting.
 - s/e: inc brown pigment in iris & eye color may appear, eyelash growth & pigmentation may inc, skin on eyelids and around eyes may darken
 - eyelash changes: ↑ length, thickness, number (goes away when drug d/c)

- Travatan Z does not contain benzalkonium Cl (BAK), instead has a diff preservative. This may be helpful to some with rxn to BAK or dry eye

MIOTICS : ↑ aqueous outflow

- ❖ Carbachol (Carbastat, Isopto Carbachol, Miostat)
- ❖ Pilocarpine (Pilocar, Piloptic, Pilostat)
 - Use with caution of hx of retinal detachment or corneal abrasion

CARBONIC ANHYDRASE INHIBITORS: ↓ aqueous humor production

- ❖ Acetazolamide (Diamox)
- ❖ Brinzolamide (Azopt) TID
- ❖ **Dorzolamide (Trusopt) TID**
- ❖ **Dorzolamide + timolol (Cosopt)**
 - s/e: bitter or unusual taste 5-10%

ADRENERGICS: ↑ aqueous outflow, ↓ production

- ❖ apraclonidine (Iopidine)
- ❖ **Brimonidine (Alphagan)** + timolol (Combigan)
- ❖ Dipivefrin (Propine)
 - Can cause macular edema (swelling of macula, the center part of the retina) and eye irritation

ALLERGIC CONJUNCTIVITIS

1. A clear, thin membrane called the conjunctiva covers the eyeball and inside of the eyelids. Irritants to this covering can cause the eye to become red, swollen and may itch = conjunctivitis or “pink eye”
2. **TXT:** OTC
 - a. Naphazoline/pheniramine (Visine)
 - b. Antihistamine ketotifen (Zaditor, Alaway)
 - c. Counsel pts to remove contact lens and keep off for 15 mins

DRY EYES

1. Can be caused by medications (anticholinergics/antihistamines), environmental triggers (pollution, smoke) or an imbalance in tear production
2. **TXT**
 - a. 1st line - Artificial teardrops (Systane, Refresh, Clear Eyes, Liquifilm)
 - b. If a preservative is irritating, benzoyl peroxide, most drops come in individual use containers that are preservative free.
 - c. Cyclosporine eye drops (Restasis) is also approved for those who did not get satis. relief from other drugs
 - i. S.E (unusual) burning, stinging, redness, pain, itching eyes

BACTERIAL CONJUNCTIVITIS (PINK EYE) & OTHER INFXNS

- ❖ **Azithromycin (Azasite)** – store in fridge, 14 d at RT
- ❖ **Moxifloxacin (Vigamox)**
- ❖ **Besifloxacin (Besivance)**
- ❖ **Tobramycin/Dexamethasone (Abx/steroid)**
- ❖ Ciprofloxacin (Ciloxan), ofloxacin (Ocuflox), gentamicin (Garamycin), tobramycin (Tobrex), erythromycin, sulfacetamide (Bleph-10, Sulamyd), TMP/SMX (Polytrim), neomycin/bacitracin/polymyxin (Neosporin)

For Blepharitis (eyelid inflammation)

- ❖ 1st line = warm compresses with washcloth to outer lids
- ❖ Bacitracin or erythromycin ointment (BID-QID)

OTIC

- If cold hold the bottle for 1-2 mins to warm the solution. Cold ear drops will be uncomfortable and may cause dizziness
 - Pull ear → UP and back (adults) , DOWN and back (children)
 - Keep ear facing up for 5 mins
1. **Swimmers ear/Otitis media pain**
 - a. Antipyrine and benzocaine (A/B Otic, Auralgan)
 - b. Benzocaine (Americaine Otic)
 2. **For outer ear infxn – abx**
 - a. Cipro + hydrocortisone (Cipro HC)
 - b. Cipro + dexameth (Ciprodex)
 - c. Cipro (Floxin Otic, Floxin Otic singles)
 - d. Neomycin + hydrocortisone (Cortisporin TC)
 3. **Ear wax (cerumen) removal** --flush ear with warm water after 2-3 days
 - a. Carbamide peroxide (Debrox)
 - b. Trethanolamine (Cerumenex)
 - c. Antipyrine and benzocaine (Auralgan)

[64] MOTION SICKNESS

1. **Non pharmacological txt:** **Seaband** – a wrist band that presses on an acupuncture point located on the inside of the wrist (about 2 fingernails from the wrist crease)
2. **Natural products:** **ginger** in teas/supplements & **peppermint** may be helpful
3. **Pharmacological txt:**
 - a. Anticholinergics (may cause drowsiness and impair judgement)
 - i. **Scopolamine (Transderm Scop)** – not more effective than OTC agent
 1. Applied behind the ear **Q3 days**
 2. applied **4-6 hrs before needed** ; **alternate ears**
 3. do not cut patch
 - b. Antihistamines
 - i. Cyclizine (Marezine)
 - ii. **Diphenhydramine (Benedryl)**
 - iii. Dimenhydrinate (Dramamine)
 - iv. **Meclizine (Bonine)**

Take 30-60 mins before needed; These are **highly sedating** and causes anticholinergic s/e (dry mouth, urinary reten, blurry vision, constipation)
 - c. Promethazine – rx only (do not use in children <2, caution in those >2)
 - i. FDA advises against use of prometh + codeine In cough syrups in children <6 due to resp depression, cardiac arrest

[65] COMMON SKIN CONDITIONS

Tea tree oil : Used for a variety of skin condit (acne, onychomycosis)

1. May be useful in athlete's foot symptoms if 10% oil is used (not cream). Higher concentrations 25%, 50% can cure the infxn in up to 50% of pts, but not as effective as antifungal agents

ACNE

1. Retinoids 1st line agent
 - ❖ Tretinoin cream (Retin-A) also comes in micronized Gel (Retin-A Micro), polymerized cream/gel (Avita)
 - ❖ Tretinoin gel + clindamycin (Ziana)
 - ❖ Adapalene (Differin) cream, solution
 - ❖ Tazarotene (Tazorac)
 - ❖ Dapsone gel (Aczone)
 - Retinoids are not recom for use during pregnancy/breastfeeding . tretinoin and adapalene are Cat C, tazarotene is Cat X
 - Limit sun exposure your skin will burn more easily
 - A pea sized amt is suff for facial application. It should be divided into 4 equal parts and smooed over entire face. Do not use as "spot" txt
 - Takes 4-12 wks to see response
2. Benzoyl peroxide (most effective OTC agent) , salicylic acid is alternative
 - ❖ OTC- benoxyl, Benzac, Clearasil
 - ❖ BPO + 3% erythromycin (Benzamycin)
 - ❖ BPO + 1% clindamycin (BenzaClin)
 - ❖ BPO gel + clindamycin (Duac)
 - Duac gel: apply QHS to affected areas. Limit sun exposure!
 - Benzamycin is kept refrig, BenzaClin is kep at RT
3. Oral Isotretinoin (Amnesteem, Sotret, Claravis is generic)
 - a. Only for the txt of severe recalcitrant nodular acne
 - b. (Preg X) Two forms of BC are req when taking this med. Must have had 2 neg preg etest before starting txt – iPLEDGE program
 - c. Do not use Vit A suppl, TCN, steroids, POP BC, St Johns
 - d. s/e: arthralgia, osteoporosis, psychiatric issues (depression, psychosis), dec night vision, dry eyes, dry skin, chapped lips

DANDRUFF – sometimes due to yeast overgrowth

1. Hypoallergenic shampoo = selenium sulfide (Selsun Blue) or Zinc pyrithione (Head & Shoulders) or coal tar shampoos
2. Ketoconazole (Nizoral) is avail OTC now called Nizoral A-D (apply 2x/wk, up to 8 wks) – not more effective than less expensive options
3. Rub shampoo in well and leave in for 5 mins then rinse out
4. Can cause propecia (hair growth)

FUNGAL INFXNS

Ring worm – recom antifungal such as: Clotrimazole, etc

- ❖ Terbinafine (Lamisil AT cream & solution) – **most effective OTC**
- ❖ Clotrimazole (Lotrimin cr, lotion, solu, Desenex)
- ❖ Miconazole (Monistat Derm, Lotrimin powder & spray)
- ❖ Ketoconazole (cr, foam-Extina)
 - a. Creams work best, solutions for hairy areas. Powders do not work well for txt may be used for ppx
 - b. Fingernails 6 wk txt, Toenails 12 wk txt (it may take a long time for nail bed to look better, up to a year)

ECZEMA

1. 1st line is topical steroids. Other txt include: oral steroids, abx, antihistamines
2. If failed steroids, then try:
 - ❖ Tacrolimus (Protopic)
 - ❖ Pimecrolimus (Elidel)
 - Avoid in children <2 yo
 - Keep in moisturized with: Aquaphor, Eucerin, Keri
 - Must dispense MedGuides with these bc Calcineurin inh carry cancer risk (lymphoma and skin cancer)
 - Limit sun exposure, skin will burn more easily
 - Takes weeks to work

LICE

- ❖ Permetrin (Nix, RID, Triple A) – OTC DOC → treat ASAP & follow up with 2nd txt 7-10 days later
 - ❖ Sinosad (Natroba) – newer agents, works well, expensive
1. If 2nd txt fails, refer for Rx therapy [Malathion (Ovide), Benzyl Alcohol Lotion (Ulesfia)]
 - a. Lindane is no longer recom due to high risk of neurotox/seizures.
 2. In addition to OTC txt, remove live lice and nits by inspecting the hair in 1 in segments & using a lice comb. Nits are “cemented” to the hair shaft and do not fall off after txt.

EXTERNAL GENITAL WARTS

- ❖ Imiquimod cream (Aldara)
 - a. Apply 3x/wk to external genital/perianal warts until there is total clearance or for max time of 16 wks
 - b. Apply to entire txt area QHS and wash off after 8 hrs

TOPICAL INFLAMMATION DUE TO VARIOUS CONDT/RASHES

- ❖ **Hydrocortisone 0.5% (infants)** OTC 1-2x/day
- ❖ **Hydrocortisone 1%** (mild condit, thin skin-groin, elderly, children) Aquanil 1% lotion OTC
- ❖ **HC 2.5%** RX only 1x/day
 - a. Use ointments for thick/dry skin
 - b. Use lotions, gels, foams for hairy skin
 - c. Topical steroid over use can cause: thinning of skin, striae in skin folds, worsen acne
 - d. Do not apply for >2 wks to face
 - e. **Camphor, mentol, local anesthetics** in combo with HC can help relieve itching
- ❖ Hydroxyzine (Atarax) – used for general urticarial (hives) which itch badly

DIAPER RASH

- ❖ Desitin (Zn Oxide & petroleum – Zn Oxide is a dessicant that dec moisture)
- ❖ A&D Ointment, plain petroleum

If due to candida:

- ❖ Can use topical (OTC) antifungals (physician will recom) or miconazole + zn oxide + petrolatum (Vusion)
Recom freq changes and to clean well (do not rub hard), do NOT use baby wipes that contain alcohol or propylene glycol.

MINOR CUTS/ABRASIONS

- ❖ Triple abx- polymyxin/bacitracin/neomycin (Neosporin)
 - Used to prevent infxn from minor scrapes/cuts/burns
 - ❖ Bacitracin/polymixin (Polysporin)
 - ❖ Bacitracin (Bacitracin)
 - ❖ Mupirocin (Bactroban) – an RX abx cream, good for staph, strep
1. The wound may be covered with a bandage if it is in a place that can get dirty.
 2. Leaving a wound uncovered helps it stay dry and heal faster. If wound isn't in an area that can get dirty /rubbed by clothing, don't cover it
 3. Large scrapes → should be kept moist and clean to help reduce scarring and speed healing. Use occlusive or semi-occlusive bandages.

POISON IVY/OAK/SUMAC (wash off uroshiol with soap & water ASAP)

- ❖ Ivy Block (bentoquatam)
- ❖ Zanol (binds urushiol- toxin)
- ❖ Al acetate solu (Burrow's)
- ❖ Colloidal oatmeal (Aveeno)
- ❖ Calamine lotion (Caladryl, IvaRest are calamine + topical analgesic)
- ❖ Topical or oral steroids will help
- ❖ Cold compresses will help

PSORIASIS

- ❖ Coal tar (Neutrogen T, Denorex)
- ❖ Keratolytics (salicylic acid, sulfur) + coal tar (Sebutone)
- ❖ Retinoids (see acne)
- ❖ Anthralin (Anthranol)
- ❖ Calcipotriene (Dovonex, a Vit D analog)
- ❖ Calcipotriene + betamethasone ointment (Taclonex, Taclonex scalp susp)

If topicals are not effective:

- ❖ Oral steroids
- ❖ Psoralens + UV therapy
- ❖ Acitretin (Soriatane) severe cases only
- Taclonex: shake susp well, Do not use > 4 wks, do not use > 100 g ointment weekly

Steroid Potency High (top) - Low(bottom)

Clobetasol propionate, Betamethasone dipropionate
Fluocinonide, Desoximetasone
Fluticasone
Mometasone furoate, Triamcinolone acetonide
Desonide
Hydrocortisone

ALOPECIA (Hair loss)

- ❖ Finasteride (Propecia) 5 α reductase inhibitor ; 1 mg QD
 - Do not dispense to someone on finasteride (Proscar)
 - Preg Cat X. **only for men**
- ❖ Minoxidil topical OTC 2%, 5%
 - 5% is more effective, but more facial hair
 - Rx tablets indicated for HTN only (rarely used)
 - For **men & women**

SUNSCREENS

- UVA (blocks aging – ecamsule, avobenzene, oxybenzone, titanium dioxide, zn dioxide)
- UVB (blocks burning)
- Broad spectrum (blocks UVA + UVB)
- SPF – measures how long it would take to burn vs not wearing sunscreen. **SPF 15 = it takes 15 times longer for skin to redden than without sunscreen**

[66] WEIGHT LOSS

1. Healthy BMI = 18.5 – 24.9.
2. OTC drugs:
 - a. Commonly contain stimulants, such as ephedra alkaloid, bitter orange, or related cmpnds + excessive caffeine
 - b. Caffeine is packed under diff names (yerba mata, guarana, concentrated green tea powder)
 - c. New OTC agent – Fastin is being marketed as “thermogenic intensifier” it contains stimulants, synephrine and caffeine – high risk for CVD pts
 - d. Do not recom OTC wt loss agents unless it is orlistat (Alli) – lower dose of rx Xenical

Short term appetite suppressants

- ❖ Phentermine (Adipex –P) **C III**
 - Take 15-37.5 mg before/after breakfast
 - Dizziness, tremor, agitation, tachycardia, inc BP, dependence
- ❖ Diethylpropion (Tenuate) 25 mg IR TID, 1 hr before meals //75 mg SR in mid morning
 - Dizziness, tremor, agitation, tachycardia, inc BP, dependence

Long-term lipase inhibitor

- ❖ Orlistat (Xenical) 120 mg with each meal containing fat
- ❖ Orlistat (Alli) OTC 60 mg with each meal containing fat
 - GI (Flatulence with discharge, fecal urgency, fatty stool)
 - Take MVI with AKED and beta carotene at bedtime or separate by 2 hrs. separate levothyroxine by 4 hrs
 - Do not use with CSA.
 - Xenical dec 13 lbs/yr . Alli 5 lbs/6 mths

**review topical acne drugs*

Max doses:

APAP : 3000 mg

ASA : 3600 mg (for gout)

Ibuprofen: 3200 mg

Naproxen: 1500 mg

Naproxen sodium: 1375 mg