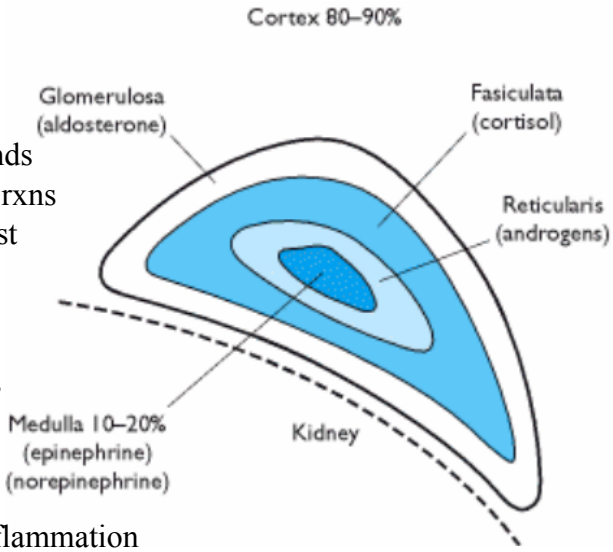
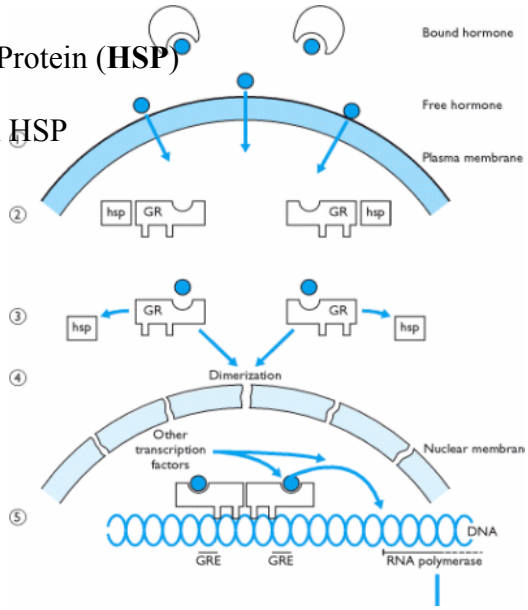
PHA 4107 Final Notes

Corticosteroids as anti-inflammatory agents



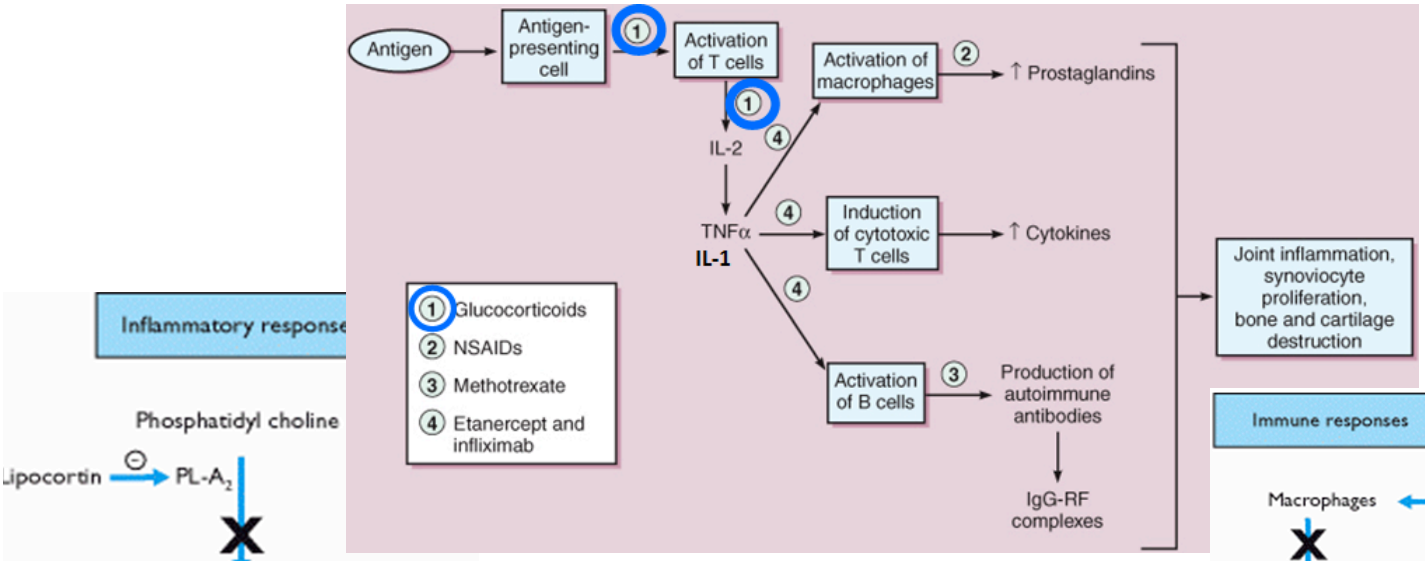
- Intro
  - Immune response (IR) causes
    - Inflammation
    - Acute = quick, to clean cuts, heal wounds
      - Get w/ bact / viral autoimmune rxns
      - Bact = get acute lots = finish fast
    - Chronic
      - Get things like arthritis + gout
  - T lymphocytes
    - **Cytotoxic T**: directly kill IR foreign ¢s
      - Signal other ¢ types
      - Activate macrophages
    - **Macrophages**: engulf bact in vesicle
      - Secrete cytokines = expands inflammation
      - No resolution of process = chronic inflammation
    - **Neutrophils**: engulf + destroy invading orgs
  - Adrenal glands
    - Secrete numerous steroids of which aldosterone + hydrocortisone = major
      - From cortical layer = syn cortisol, aldosterone
    - Struc = 4 rings w/ grp on 5 memb ring
    - **Adrenocorticoids**: steroids secreted by adrenal gland
      - ↓ production of adrenocorticoids
        - ↓ R to trauma + ↑ sensitivity to pain
      - E.g. Aldosterone, Hydrocortisone
      - **Hydrocortisone** = **glucocorticoid** → ↓ inflammation props
    - **Mineralocorticoid**: activity related to retaining salt (NaCl)
      - Maintain electrolyte balance by ↑ Na^+ retention + ↑ K^+ secretion
      - E.g. **Aldosterone** ↑ Na^+ influx → H_2O follows
        - No imflammation

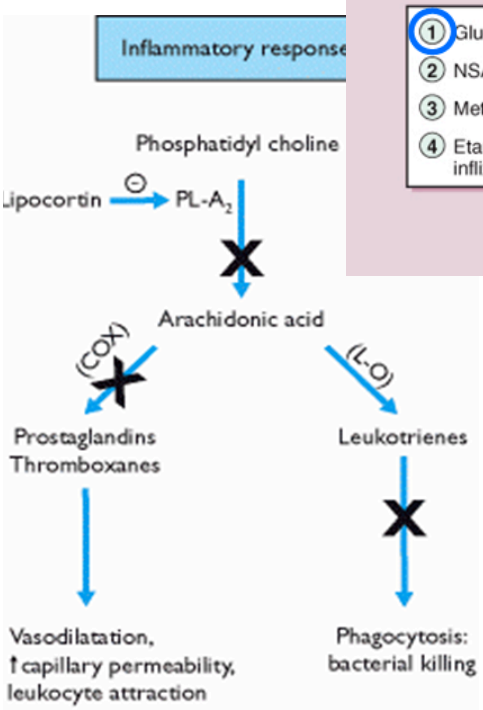
- Process of binding
  - E.g. w/ glucocorticoid
    - No ligand = sit in cyto + bound to Heat Shock Protein (**HSP**)
  1) Free hormone goes into ¢
  2) Binds to glucocorticoid receptor (GR) complexed with HSP
  3) Expose GR's nuclear localization signal
  4) Dimerization to get into ¢ via pore
  5) Binds to GRE on DNA → reg txn

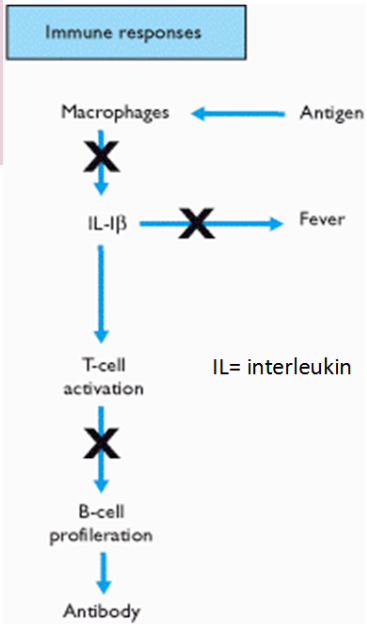


- Physiological fns of corticosteroids
  - **Glucocorticoids** (**GCCs**)
    - 1) Carbs + protein metab

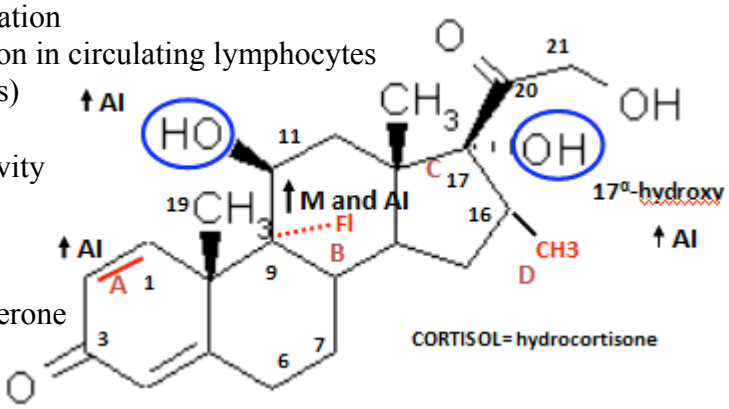
        - ↑ formn glucose = syn
        - ↓ use of glucose (except brain)
        - ↑ metab aas = syn glucose
    - 2) Lipid metab
        - ↑ lipolysis of adipose tissue
        - Unequal in body (↑ in extremities)
            - Arms + legs = thinner
            - Torso/trunk = fatter
        - Fat deposition
            - Get in face + neck w/ long-term steroidal use
    - 3) Ca^{2+} balance
        - ↓ Ca^{2+} abs in GI tract
        - ↑ Ca^{2+} excretion in kidney
        - **Osteoporosis**: very ↓ balance of Ca^{2+}
    - 4) Potent anti-inflammatory fx
        - Most widely therapeutically targeted → hydrocortizone
    - Therapeutic use
        - For replacement in ppl w/o normal adrenal gland fn → **Addison's**
        - E.g. Adrenal gland hypoplasia
        - Hard to maintain lvls in therapy though
- Flow diagrams → CHECK NOTES
    - GCCs influence beginning of pathway
    - **TNFα** = activate IS + inflammatory response







- Anti-inflammatory fx of **cortisol** (GCC)
  - 1) Direct
    - ↓ phospholipid metab by inhibition of **PLA_2** = ↓ AA syn
    - Inhibition of txn factor **NF-kappa B**
      - Important in txn of all cytokines
        - E.g. **Tumour necrosis factor** (**TNF**),
        - E.g. **Interleukin-1** (**IL-1**) = mediate proliferation of immune ¢s to establish inflammation
      - Corticosteroids block fn
  - 2) Indirect
    - ↓ monocytes + ↑ neutrophil release from bone marrow → imbalance
      - **Monocytes** = immature macrophages
        - Reach tissue = differentiate → usu in tissues
      - GCCs inhibit maturation of blood ¢s
        - Overall ↓ in accumulation of leukocytes / macrophages at site of inflammation
    - **Lymphopenia**: severe reduction in circulating lymphocytes
    - Lymphoid tissue **atrophy** (loss)



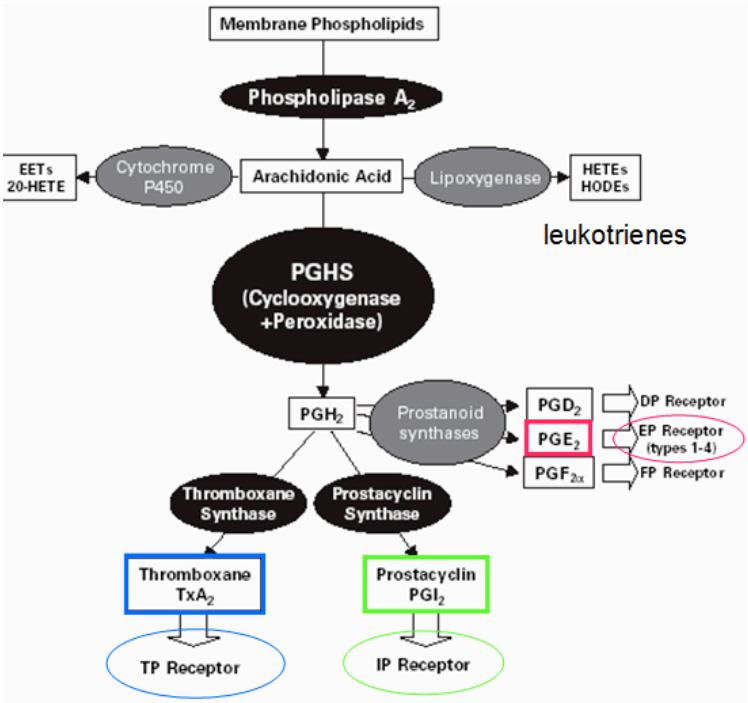
- **Struc** determinants of anti-inflammatory activity
  - AI = α-inflam
  - M = mineralocorticoid (reg Na^+/H_2O)
  - –OHs give α-inflam fx
    - 17 OH = only diff from aldosterone
    - 17 OH = ↑est α-inflam
  - **Bethamethasone** = Red additions
    - Add F = gives both fx → extra alterations remove aldosterone activity
  - Struc reqs for anti-inflam activity
    1) Δ^4-3-keto, 11β-OH, 17β-OH req = on all GCCs
    2) Sub of 9α-, 6α-, 16-α fav α-inflam activity → can ↑ aldosterone…
    3) Planarity of A ring w/o losing 19-CH_3 grp for α-inflam activity
    4) F>Cl>Br>I for α-inflam activity → F = best

- Pharmacology
  - Absorption
    - Gut + Skin (Can be conj to lipophilic ester)
    - I.M. admin → more prolonged fx
      - H_2O soluble when formulated as **Na Succinate / +Phos salt** buffer
  - Metabolism
    - 90% protein bound by **CBG** (corticosteroid-binding globulin) + **albumin**
      - Xporter for steroids
    - 10% bioavailable
    - Liver sulfate esters/glucuronides
      - H_2O soluble metabs → excreted by kidney to urine
  - ½ life
    - 60-90 min for cortisol → dep on dose / struc alterations → Δ ½ life

- Anti-inflammatory steroid **therapy**
  - 1) Only during active disease = acute treatment like asthma
    - Only relieve inflam → never 100% treat b/c attenuates / sec
  - 2) Empirical dosage → adjust
  - 3) Local steroid when possible (inhalants) → if not alternate day systemic
  - 4) Careful to prevent withdrawal syndrome → reactivation worse vs. initial inflam
  - 5) Be aware of side fx
    - Long-term osteoporosis
    - Complete symptom relief should not be sought → kills IS
- GCCs treat:
  - Refractive arthritis → all other therapies tried 1st like NSAIDs, COX-2 inhibitors
  - Bronchial asthma
    - During refractive asthmatic episodes
    - Inhaler + oral forms
  - Many inflammatory skin conds → finance minister Jim Flaherty
  - Opthalmopathy associated w/ **Graves Disease**
    - → Autoimmune disorder which ↑ *thyroid* gland activity
  - Following bone marrow/organ transplantation → immunosuppressant

Non-steroidal anti-inflammatory drugs (NSAIDs)

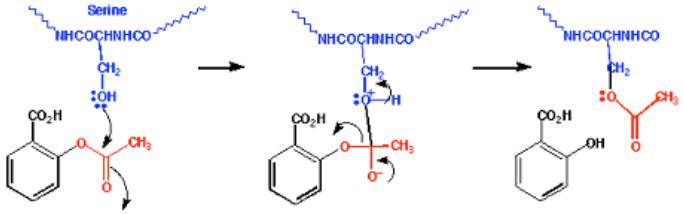
- Intro
  - **Monocytes** attracted to sites of inflammation (e.g. joints in RA)
    - Rheumatoid arthritis (RA) → differentiate into macrophages = activated
  - **Macrophages** play central role in arthritic disease
    - Produce factors involved in inflame
    - Several chemokines attract other immune ¢s → mediators inflam
      - Tumour necrosis factor (TNF)
      - Interleukin-1 (IL-1)
      - Prostaglandins *DRAW AA PATHWAY*



- Biochem pathway leading from arachidonic acid (AA) to formn vasoactive prostanoids
  - Liberation of AA from memb phospholipids → dep on **phospholipase A_2** activity
    - Receptor mediated → bact intn in blood
    - Inhibited by **corticosteroids** like **cortisol**
  - 1st pathway AA does = through cyclooxygenase
    - **PGHS** competes w/ **cytochrome P_{450}** + **5-lipooxygenase** for metab of AA
      - PGHS has **cyclooxygenase** + **peroxidase** moiety = dual activity
        - Cyclizes then oxidizes
      - **NSAIDs** inhibit cyclooxygenase
        - **Aspirin** = irrev inhibitor
        - **Indomethacin**
        - **Phenylbutazone** = rev inhibitor
      - Produces **PGH_2**
    - **PGH_2** further metab by tissue-specific enz (**prostanoid synthase**) to form specific **prostanoids** → PGI_2, TxA_2 → PGD_2, PGE_2, PGF_{2x}
      - All act on specific receptors → also syn everywhere
      - PGI_2 + TxA_2 = vascular fn **synthases**
        - **PGI_2** → IP receptor = ↓ platelet aggregation in epithelial ¢s
          - Syn by **Prostaglandin synthase** in BV endothelium
          - *Vasodilation*
          - ↑ cAMP
        - **TxA_2** → TP receptor = ↑ platelet aggregation
          - Syn by **Thromboxane synthase** in platelets
            - Inhibited by **Dipyridamole**
          - *Vasoconstriction* → mobilize Ca^{2+} for contraction
          - ↓ cAMP
      - G-protein coupled receptors → from **prostanoid synthases**
        - **PGE_2** = renal fx → for normal fn of tissues
          - *Vasodilation* → relax smooth muscles
          - Used to induce *labour*
        - **PGF_{2x}** = stim uterine contractions
          - *Vasoconstriction* → contraction of smooth muscles
      - All Non PG letters = X_2 → e.g. PGD_2 for prostaglandin D_2 receptor

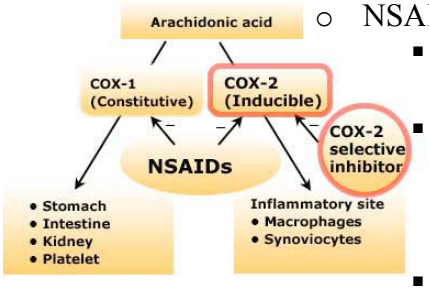
  - 2nd pathway = **5-lipoxygenase**
    - If blocked = shunt AA to COX pathway for fx
    - Syn **5-HPETE**
    - Make LTA_4 (leukotriene A_4)
      - Syn in leukocytes, platelets, mast cells, ♥ + lung vascular tissues
      - Syn LTC_4 → LTD_4 → LTE_4 = constriction
        - Broncho / vasoconstriction → ↑ vascular permeability
        - Components of slow-reacting subs of anaphylaxis (SRS-A)
      - Syn LTB_4 = ↑ inflam
        - ↑ chemotaxis of polymorphonuclear leukocytes
        - Release of lysosomal enz
        - Adhesion of WBCs

- NSAIDs classifications
  - **Carboxylic** acids
    - 1st line of drugs
      - ↓ t½ (1.5-2 h)
    1) **Salicylic acid (ASA)**



      - From salicylate
      - 1st recog med props of willow bark (salicin) ~1750
      - Purified 1829
      - In other plants like spirea, wintergreen
      - Hoffman → chemist employed by Bayer = 1st to syn ASA 1897
        - Named after St. Aspirinia → patron saint of headches
      - Acetylates **serine** in active site = block AA via covalent bond
    2) Acetic acid (**indomethacin**)
      - Not OTC → reg vasoconstriction/dilation in babies post-birth
    3) Propionic acid (naproxen + ibuprofen)
  - **Enolic** acids
    - For chronic inflam issues
    - **Oxicams** (piroxicam, meloxicam)
      - Very ↑ t½ (20h) = 1 / day = ↑ compliance
      - **Meloxicam** = ↑ specificity over COXs
  - **Para-aminophenol** (acetaminophen, paracetamol, phenacetin)
    - Not α-inflam
    - Just pain relief (analgesic)

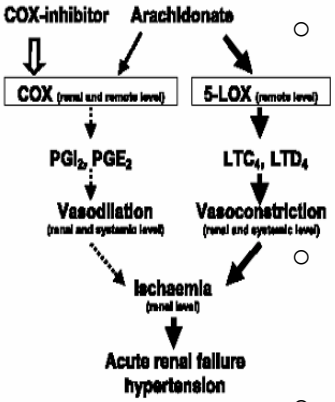
- COXs



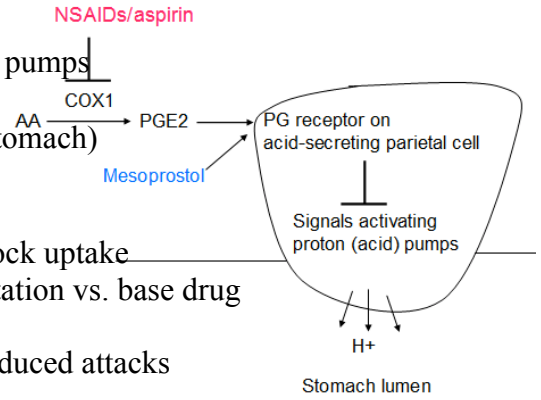
  - NSAIDs inhibit both COX-1 + COX-2
    - **COX-1** = constitutive w/ physiological fns → originally thought to block
      - In stomach, intestine, kidney, platelets
    - **COX-2** = inducible inflammatory sites → actual enz target for α-inflam
      - In macrophages, synoviocytes
      - COX-2 selective inhibitors = intn + block but not bonded
      - No fx on other tissues
    - Interact w/ Arg 120
  - Mech of selectivity
    - COX-1 = has Iso 523 selectivity → large not in b/c no side pocket to bind
      - E.g. **Flubiprofen**
    - COX-2 = has Val 523 → config to let larger drugs w/ bulky side grps in
      - E.g. **DuP697, Meloxicam, Etodolac, Celecoxib, Rofecoxib**
        - 1st ones = -xibs = cause stroke + renal failure at ↑ doses
    - **NSAIDs** block opening of both COX-1 + COX-2 by interacting w/ Arg 120 in both enz *rev*
      - E.g. Aspirin, indomethacin = non-selective
    - **COXibs/hibs** block only COX-2 enz *irrev* (covalent)
      - Longer-lasting → need turnover to produce PGs

- Prostaglandins in **acute/chronic inflam**
  - **Hallmarks** = heat, redness, edema, pain (4)
  - PGE_1, PGE_2, PGI_2 induce / augment 4 hallmarks
  - PGs involved in *late* phase of inflam
    - Local heat, vasodilation in most compartments → more blood ↑ heat
    - ↑ vasopermeability, platelet aggregation at site of injury
      - Blood contents leak out into tissue
      - Accumulate ¢s b/c sticky platelet agg
  - Asipirin, NSAIDs, COXibs, + **stroke**
    - **TxA_2**: platelets contain COX-1 = inhibited by ↓ dose aspirin w/o Δ COX-2
    - **COXib** inhibition of COX-2: ↓ PGI_2 (non-platelets) = prevent α-thrombotic activity
      - **Thrombus** = blood clot → can cause stroke
        - In old men → aspirin prevents thrombosis
      - Prothrombotic = ↑ clotting %
    - **NSAIDs**: inhibit both COX-1 + 2 = pro + α-thrombotic fx balanced

- Side fx of NSAIDs + COXibs



  - **Hypertension** and **acute renal failure** by 2 mechs
    - ↓ renal blood flow by inducing leukotriene production
      - Block syn of PGI_2 + PGE_2 = cause vasoconstriction in kidney/body
      - Shunt all to lipoxygenase (LOX) pathway → leukotrienes
        - Cause vasoconstriction → **ischemia** ($\downarrow O_2$)
      - Eventually cause acute renal failure + hypertension
  - PGs ↓ **Na^+ retention** in kidney + ↑ Na^+ excretion in urine
    - H_2O follows Na^+ out of body = maintain normal BV = normal BP
    - NSAIDs + COXibs ↑Na^+ + BP to result in peripheral edema = retain H_2O
      - i.e. does opp of usu PG fx
  - **Stomach mucosa**
    - PGE_2 = protective for stomach = block proton pumps
      - ↑ protective mucus secretion
    - Add NSAID = block COX-1 (COX-2 not in stomach)
      - Let proton pumps go in parietal ¢s
      - ↑ acidity of stomach
    - Add Mesoprostol = same fx as NSAID but block uptake
    - Relative risk DIAGRAM → ↑ risk = ↑ GI irritation vs. base drug

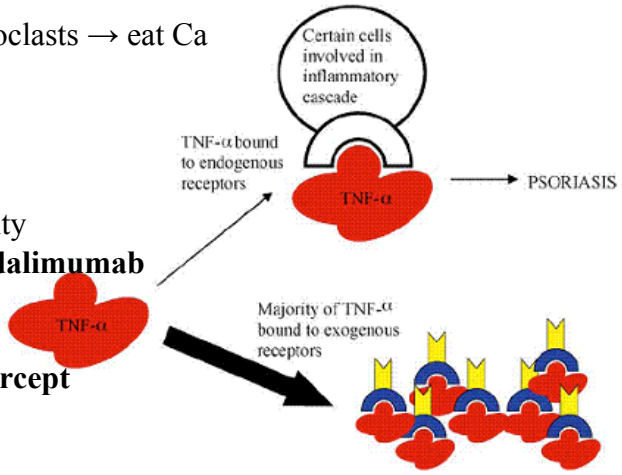


  - Aspirin-induced **asthma** + **urticaria** (hives/rashes)
    - In up to 10% ppl w/ bronchial asthma ASA induced attacks
    - COX-1 + 2 exp in respiratory epithelium
      - COX-1 inhibition most potently induces bronchospasm
      - COX-2 inhibition well tolerated
      - Asthmatic response most likely related to inhibition of PGE_2 syn
        - ↓ bronchodilation → ↑ constriction = asthma attack
    - NSAIDs also result in production + release of Cys-Leukotriene of PGE_2
      - Skin rxn may have similar etiology

- Other side fx
    1) GI upset
    2) Aspirin/NSAIDs-induced asthma
    3) Reyes syndrome → in kids/teens w/ viral infections = never use Aspirin
        - Use ibuprofen → otherwise have liver failure encephalopathy
    4) Dose-dep urate (uric acid) accumulation (↓ dose aspirin) → gout
        - Joints + toes get crystals → more common in men
    5) ↑ BP / renal failure / stroke
    6) Bleeding → never use for surgery

- **Acetaminophen** (para-aminophenol)
    - From coal tar
    - Not α-inflam drug
    - Mech of action = unknown → maybe COX-3 in CNS?
    - Long-term ↑ dose = liver toxicity b/c formn of reactive intermediates

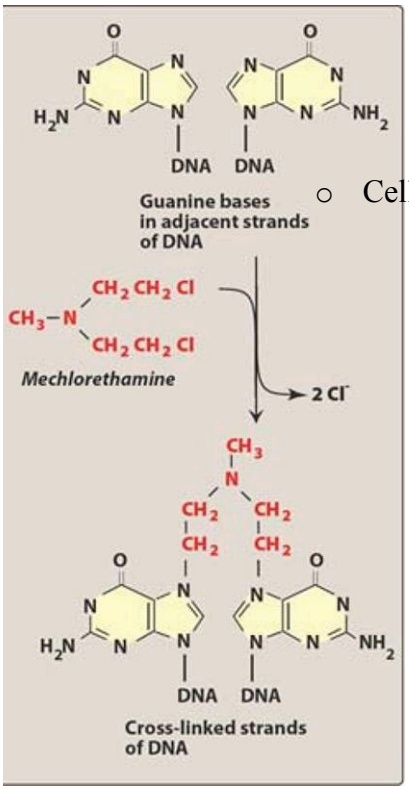
- **DMARDs** (disease modifying **anti-rheumatic** drugs)
    - In arthritis
        - Macrophages make + secrete tumour necrosis factor (**TNFα**) + interleukin-1 (**IL-1**)
        - **Fibroblasts** + bone ¢s in **joint** have TNFα receptors (synovial fibroblasts)
            - Bind TNF = activate ¢s in inflam cascade = **psoriasis** (inflam rxn)
            - Respond to **TNFα** + IL-1 to secrete mediators of tissue destruction
        - Endothelial ¢s respond to TNF + IL-1 by promoting adhesion + retention of WBCs at site
            - Syn cytokines
            - Destroy bone by activating osteoclasts → eat Ca
        - **IL-1** = direct w/ **chondrocytes**
            - Make proteinases to eat bone
    - DMARDs
        - Humanized Abs = not recog as foreign
            - α-TNF done via passive immunity
            - e.g. **Infliximab (Remicade)**, **Adalimumab**
        - Recombinant protein
            - Copy receptor of TNF = decoy
            - e.g. **Etanercept (Enbrel), Lenercept**

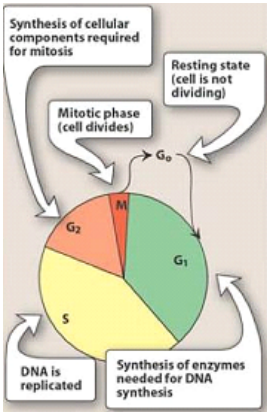


Cancer drugs

- Intro
    - Cancer : proliferative disease
        - Classified on basis of tissue from which it dev
        - Cells div unctrllably
        - All drugs treatments target proliferating ¢s either slowly / rapidly
    - Types of cancer → named from tissues from which they arise
        1) *Carcinomas*: epithelial cancer = 90+% cancer → 80% cancer-related death
            - E.g. breast, colon, melanomas … → also b/c most body ¢s = this

2) *Sarcomas*: cancer of CT, bone, muscle = 1% tumours
    - e.g. osteosarcoma, rhabdomyosarcoma (rare muscle tumours)
3) *Central + peripheral NS ¢s* = 1% cancers (2.5% cancer-related death)
    - e.g. glioblastoma, retinoblastoma
4) *Hematopoetic malignancies* = blood cancers
    - e.g. leukemias, lymphomas, multiple myeloma

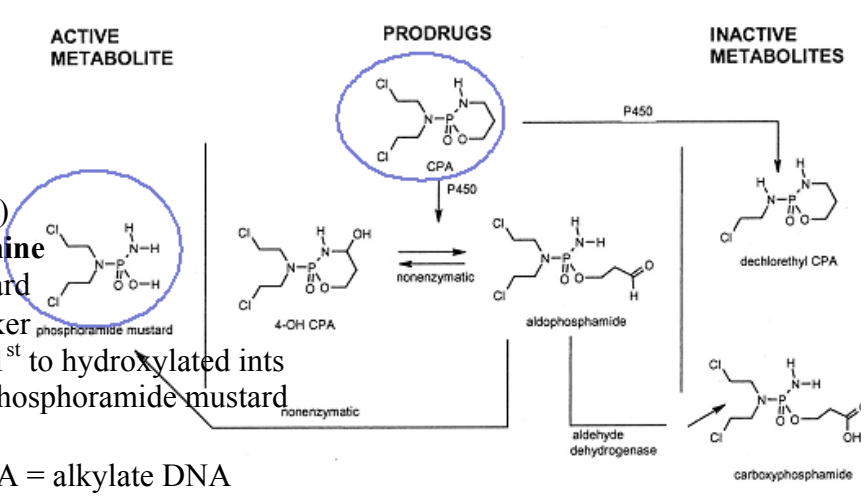




- Cell cycle
    - **Process**
        - G_1 = syn enz needed for DNA syn
        - S = syn phase → DNA replicated
        - G_2 = syn of ¢ components = prep for mitosis
        - M = mitotic phase → ¢ div
        - G_0 = resting state → cell not div = most ¢s in body
    - Cell-cycle specific drugs
        - Good for ↑ growth-fraction malignancies like hematologic cancers
        - E.g. α-metabolites, bleomycin peptide abios, vinca alkaloids, ***Etoposide***
    - Cell-cycle non-specific drugs
        - Effective for both ↓ growth-fraction malignancies like solid tumour
            - i.e. slower growing cancers
        - Good vs. ↑ growth-fraction malignancies too (non-specific)
        - E.g. Alkylating agents, abios, Cisplatin, nitrosoureas

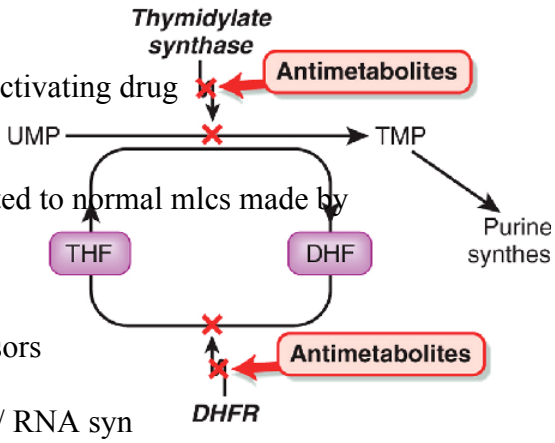
- Classes of anticancer drugs
    - **Antimetabolites** → 5-fluorouracil, Gemcitabine
    - **Antibiotics** → Doxorubicin (Adriamycin), Epirubicin
    - **Alkylating** agents → Cyclophosphamide
    - **Microtubule** inhibitors → Paclitaxel (popular last 15 yrs), Vinca alkaloids
    - **Other** → Camptothecins, Etoposide, Platinum cmpds

- **Alkylating agents**
    - Mech of action
        - Attachment of alkyl grp to guanines / opp strands at **N7** atom of **imidazole**
            - Alkylating agents belong to grp of **Nitrogen mustards**
            - Mustard gas = dev tumours if not killed right away
        - Cross-linked bases result in attempts at repair → result in strand breaks = ¢ death + DNA mismatch repair mut
            - Does Inter strand cross link via G on opp strands
            - G2 checks DNA to see if DNA can be repaired + do mitosis
            - Some α-cancer drugs result in cancer itself yrs later
        - In cell cycle
            - Alkylating agents effective in both resting + cycling (better) ¢s
            - WHY: still make proteins even if not div
                - RNA pol + RNA produced may also be affected

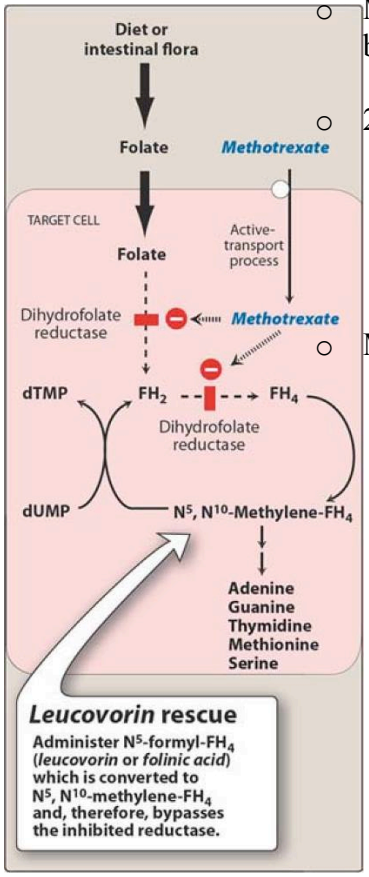


- **Cyclophosaphamide (CPA)**
  - = **Bis(chlorethyl)amine**
  - Phosphoactive mustard
    - Active X-linker
  - Metab by Cyt P450 1st to hydroxylated ints
  - → Metab to active phosphoramide mustard
    - No enz used
    - React w/ DNA = alkylate DNA
  - → or metab by aldehyde dehydrogenase
    - Cyt P450 used
    - ↑ Cyt P450 = ↓ fx b/c inactive metab

- Pharm of cyclophosphamide (CPA)
  - Wide application
    - Hematopoetic, carcinomas, neuroectoderm cancers
  - Side fx
    - Nausea, vomiting, alopecia, bone marrow dep
      - ↑ turnover of GI tract ¢s = ↑ side fx
      - Same w/ bone marrow = ↓ WBC especially
    - 2ndary malignancies may appear yrs later
  - Resistance
    - ↑ repair activity but not perfect
    - ↓ ¢ permeability
    - Glutathione-mediated reduction = inactivating drug

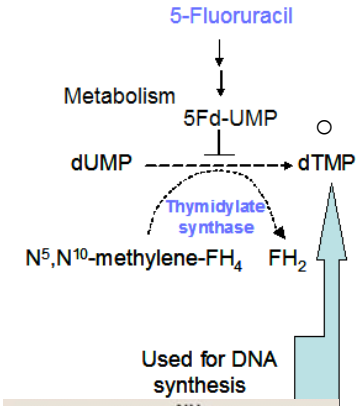


- Antimetabolites
  - Mech of action based on strucs of drugs closely related to normal mlcs made by body + therefore normal processes
    - Mainly w/ DNA + RNA syn
  - 2 classes
    - Inhibiting syn of purine + pyrimidine precursors
      - E.g. **methotrexate** + **5-fluorouracil**
    - Directly competing w/ normal mlcs in DNA / RNA syn
      - E.g. **gemcitabine**

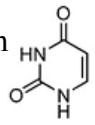


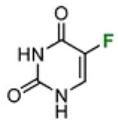
- **Methotrexate (MTX)**
  - Mech
    - Diet / intestinal flora syn folate
    - Folic acid reduced by dihydrofolate reductase (**DHFR**) to syn FH_4
      - Needed to syn DNA + some aas
      - THF + FH_4 use UMP
        - w/o = no syn thymidine → no DNA/RNA syn
    - MTX inhibits DHFR → no FH_4
      - No cofactor for many mlcs
      - Thymidine syn most effected

- N^5,N^{10}-Methylene-FH_4 →→ bases + Met, Ser
  - **Leucovorin rescue** here = reverses MTX
    - MTX only effective vs. ¢s in cell cycle
  - Add **leucovorin** / **folinic acid** to convert to this cmpd
  - No need for DHFR b/c product still there
  - ↑ folinic acid rescues ¢s from methotrexate
- Syn to next cmpd → complete cycle w/ dUMP back to FH_2
- Used in combo w/ other drugs in some leukemias, lymphomas, carcinomas
- Resistance = amplification of DHFR + ↓ influx of drug to cancer

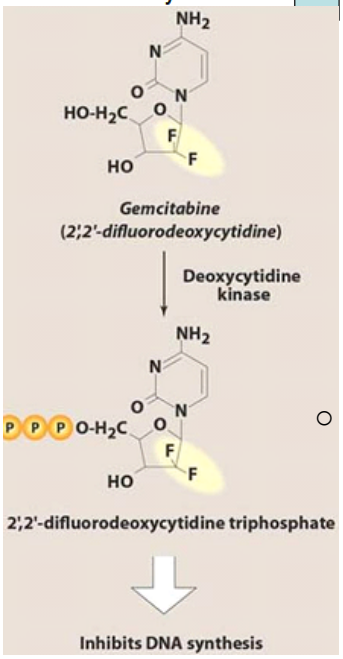


- **5-fluorouracil (5-FU)**
  - Mech
    - F atom in 5-FU interferes w/ conversion to deoxyuridylate by thymidylate synthase enz
    - i.e. no dTMP can be syn = no DNA syn
  - Admin w/ ↓ lvl of Leucovorin N,N-methylene-FH_4 (folinic acid) to ensure formn of **5-FU – Thymidylate synthase – folinic acid** complex
    - Impossible to proceed w/ Me xfer
  - Application: slow growing solid carcinomas
    - Colorectal, breast, ovarian, pancreatic, gastric
  - Blocks S phase
  - Resistance = lose ability to metab 5-FU + ↑ lvls thymidylate synthase
  - Side fx
    - Myelosuppression = bone marrow suppression / ↓ formn blood ¢s
    - GI irritation = oral formulations
    - Stomatitis = inflammation in mouth
    - Hepatotoxicity = liver toxicity
    - R dev in many ppl


Uracil

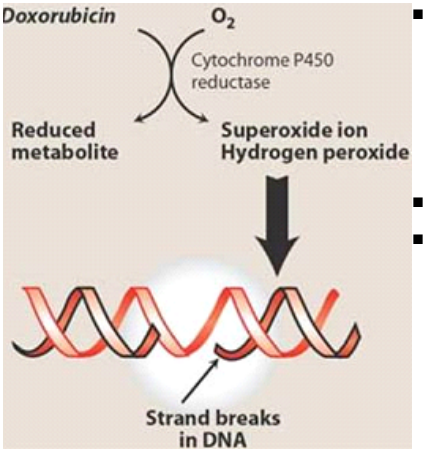

5-Fluorouracil

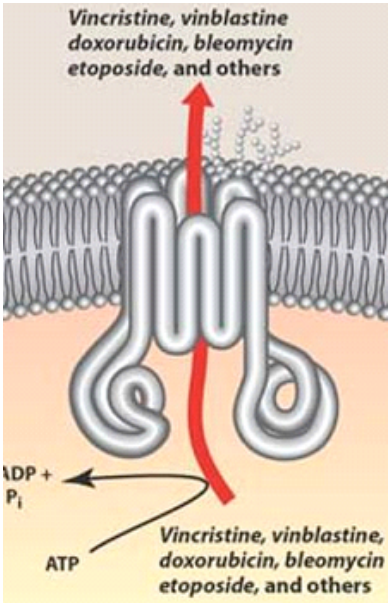
A uracil analogue



- **Gemcitabine**
  - Deoxycytidine pyrimidine analog
  - Competes w/ deoxycytidine for kinase
  - Incorporation into DNA = chain termination b/c F blocks
    - Add = only 1 more base can be added
  - F-F steric hindrance → DNA pol can't add anything else

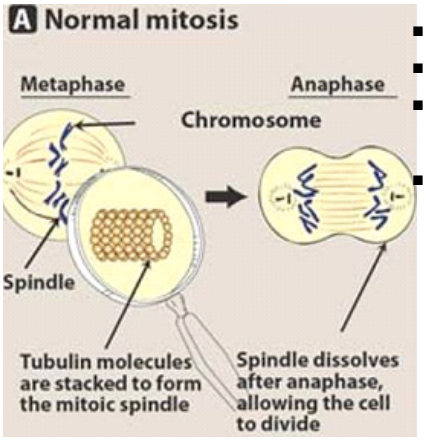
- Antibiotics
  - **Doxorubicin**
    - Abio derived from *Streptomyces peucetius* → oxidized to get product
    - Mech of action:
      - 1) 4-ring struc → 2 **quinones** which reg *reactive oxidative species*
        - Break DNA strands
        - XS strand breaks – can't keep repairing ¢ = must die
      - 2) Intercalation b/w bases = uncoiling
    - Applications: leukemias, lymphomas, sarcomas, adenocarcinomas
    - Metab = hepatic metab → can get hepatotoxicity



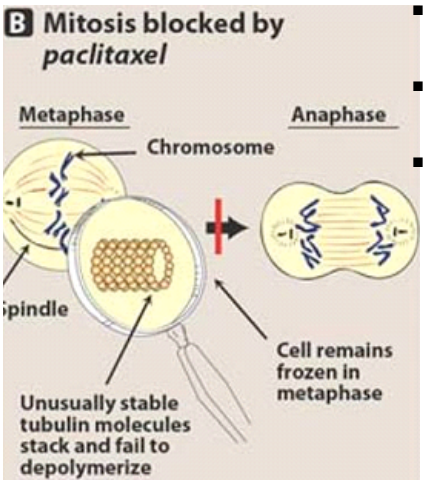


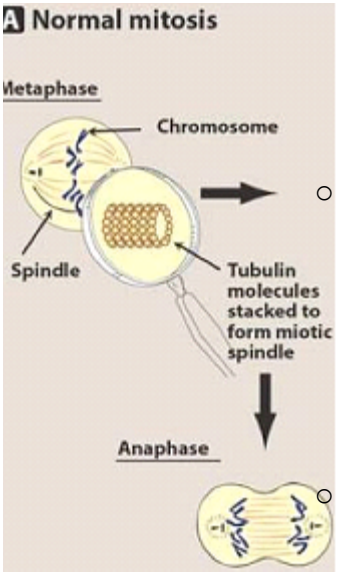
- Side fx
  - Nausea, vomiting
  - Alopecia → loss of hair from head / body
  - Stomatitis → inflammation of membs in mouth
  - Cardiotoxicity → free radical peroxidation of ♥ tissue
  - Myelosuppression → bone marrow suppression
- Mech of R
  - **P-glycoprotein** (**Pgp-170**) multidrug R **transport protein**
    - E dep → b/c efflux of drug
  - Altered **topoisomerase II**: unwinding DNA Δs
    - Pump in CM
    - Drug gets in efficiently but also removed quickly
    - Upreg w/i days of beginning of treatment

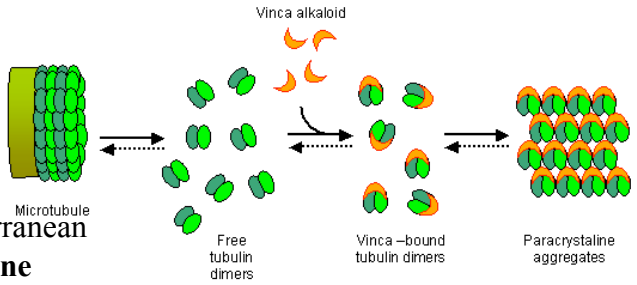
- **Bleomycin**
  - Copper chelating mlc → binds to DNA (DNA-bleomycin-Fe^{2+})
  - Undergoes oxidation to bleomycin-Fe^{3+} → like doxorubicin
    - Freed e- react w/ O_2 to form superoxides → DNA strand breaks
  - Applications: lymphomas + certain carcinomas → less widely used
  - Metab = given IV + broken down by **bleomycin hydrolase** enz
  - Mech of R
    - ↑ hydrolase activity
  - Side fx
    - Hyperpigmentation → Fe deposition in epidermis
      - Rev once stop taking drug
    - Hyperkeratosis
    - Rashes → very unusual side fx
    - Nausea + vomiting → targets dividing ¢s in gut



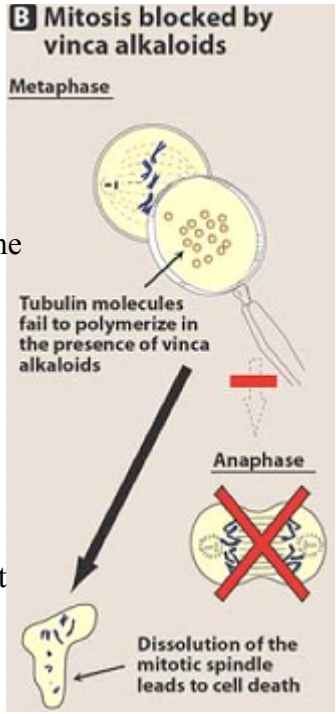
- **Microtubule inhibitors**
  - Prevent mitosis by interfering w/ mitotic spindle
    - Necessary for trafficking
    - Critical for mitosis → dynamic for movt of organelles
  - **Taxanes**
    - From back of **Pacific Yew** → challenge to syn **paclitaxel** (**Taxol injectn**)
      - Prob → remove bark = dead tree
    - **Docetaxel** (oral) = needles from **European** Yew
      - Can preserve trees while still removing needles
    - Used as *stabilizers*
      - Taxol binds to **β-tubulin**
      - Building + degradation makes microtubules dynamic
        - Depolymerization cycle necessary for movt of spindles
        - Stabilize mictrotubules to stop Xm movt to poles
          - Stays frozen → no movt possible
        - Cell death b/c ¢ can't freeze in metaphase for long



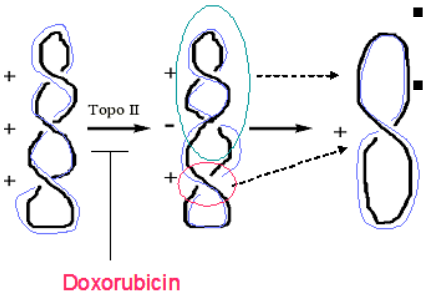




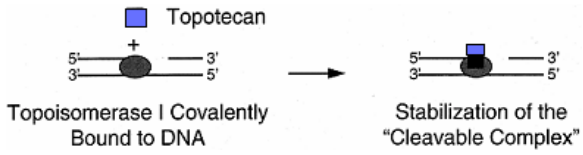
- **Vinca alkaloids**
  - Derived from periwinkle in Mediterranean
    - E.g. **Vincristine** + **vinblastine**
  - Used as *destabilizers*
    - Can't get microtubule syn
  - Prevent anaphase
    - No spindle fibres can connect to mitotic spindle
    - Can't pull Xm apart in metaphase = ¢ death
- Side fx
  - Vinca alkaloids: neurotoxicity for both vincristine + vinblastine
  - Myelosuppression = ↓ hematopoetic ¢s = vincristine only
    - Vinblastine pref
  - Taxanes = myelosuppression, alopecia, neurotoxicity
- Indications
  - Vincaalkaloids: both hematalogic cancers + solid carcinomas
  - Taxanes = metastatic carcinomas
- Mech of R
  - β-tubulin muts = don't bind as well
  - Drug efflux through **Pgp transporter** (MDR-1) = active xport
    - Non-specific
    - Stem ¢s have innate ability to pump out things
    - Reason why drugs ineffective in stem ¢ cancers

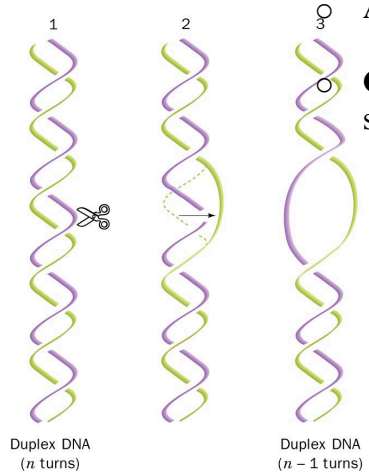


- **Other** drugs
  - Target DNA unwinding enzs = **topoisomerases** – VIDEO
    - Anthracylines, Campothecins
  - Process
    - During txn + DNA rep → need unwinding to let txn / replication machinery access DNA = copy / replicate
    - Topoisomerases I + II essential in separation of daughter strands during replication → nicking + resealing DNA helix
      - Don't want it to be supercoiled + tangled → both do unwinding
      - **Topo I** = cuts one strand → pass other strand → reseal → -1 coil
        - Inhibited by **Topotecan**
      - **Topo II** = same as 1 but cuts both strands → pass dsDNA → reanneal → -2 supercoils
        - Inhibited by **Doxorubicin**



  - **Anthracylines**: prevent resealing step cat by Topo II = only does dsDNA break
    - E.g. **Doxorubicin**
  - **Campothecins**: bind Topo I-DNA complex (cleavable complex) in intermediate step of DNA relaxation process
    - E.g. **Topotecan**
    - Results in single / double stranded break
      - Permanent w/ drug attached
    - Prevents resealing of nick
    - Cannot repair break = non-natural DNA rep / ¢ div



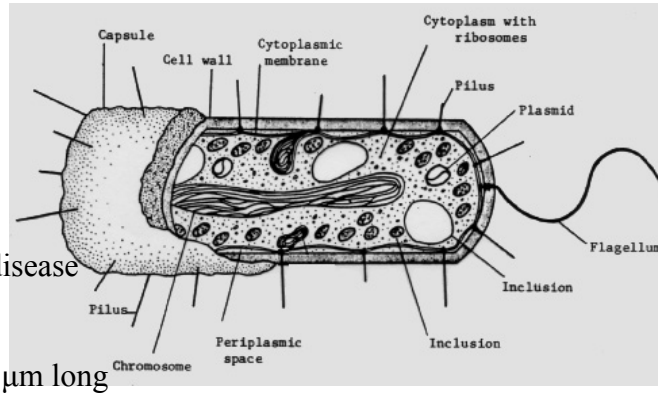


- **Podophyllins**
  - Mech similar to anthracylines = Topo II inhibition
  - Derived from Mandrake plant root = Po for Potter
  - E.g. **Etoposide**

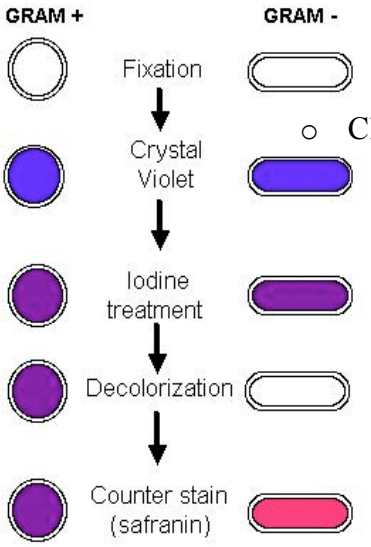
- **Cisplatin** – VIDEO
  - Part of **platinum** drugs = DNA intercalating agents
  - 3 components: cisplatin, DNA + HMG protein
  - Process for **Cisplatin**
    - Enters ¢ via active xport or passive diffusion
    - For adduct w/ **2 consecutive G bases** in strand of DNA
    - Lose Cl for Ns
      - Happens b/c balances charge better than Cl
    - HMG protein binds → insert Phe37 to minor groove
      - Tightly bound = causes destacking of nucleotide bases
      - Kinks helix = intrastrand
    - HMG stuck = no proper repair = ¢ death
    - Success dep on ratio of cancerous vs. healthy ¢ insertion
  - Applications
    - Neurological cancers, carcinomas (refractory to other treatments = not 1st line), some hematopoetic cancers
  - Metab = directly elim through kidneys
  - Toxicity
    - Renal failure
    - Severe nausea + vomiting
    - Alopecia, **ototoxicity** = dmg to ear, myelosuppression

Antimicrobial drugs

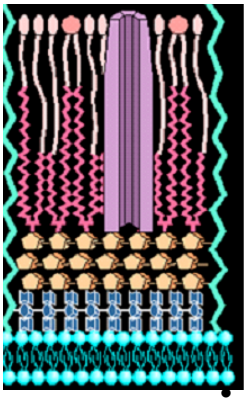
- Intro
  - **Antimicrobial**: any substance w/ sufficient antimicrobial activity = can be used in treatment of infectious diseases
    1) Antibiotics + other anti-bact drugs
    2) Antifungal agents
    3) Antiviral agents
  - Anti-bacterial
    - Modern use stems from work of Ehrlich – dev arsenical cmpds for treatment of syphilis in early 1900s
    - Discovery of penicillin by Fleming in 1929 but not ↑ used until 40s
      - During WWII b/c ↑ infections
    - Discovery of therapeutic use of sulphonamide cmpd in 1935
  - Antibiotics
    - Antimicrobials of microbial origin – most produced by fungi + bact
      - From moulds + other bact
    - Not syn w/ chem mods for R bact
    - *Streptomyces* = big producer → excrete to kill bact
    - Can be wide or narrow spec = for # bact treated



- Struc chars of bact
  - Smallest orgs capable of indep existence
    - Archaea bact not usu associated w/ disease
  - Single prok ¢s
    - Spherical = 0.5-2 μm in diameter
    - Rod shaped = 0.5-2 μm wide + 1-10 μm long
    - Single Xm + plasmid
  - Classification by **Gram Stain**
    - Def if susceptible to certain drugs
    - Process
      - Fixation = kill → add **crystal violet** → iodine treatment → decolorization → counter stain w/ **safranin** to red
        - Retain dye = *purple* = **Gram +ve**
        - Dye not retained = *red* = **Gram –ve**

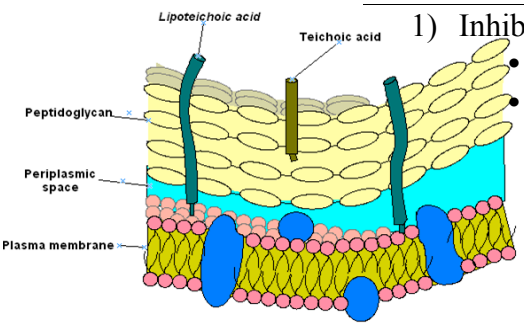


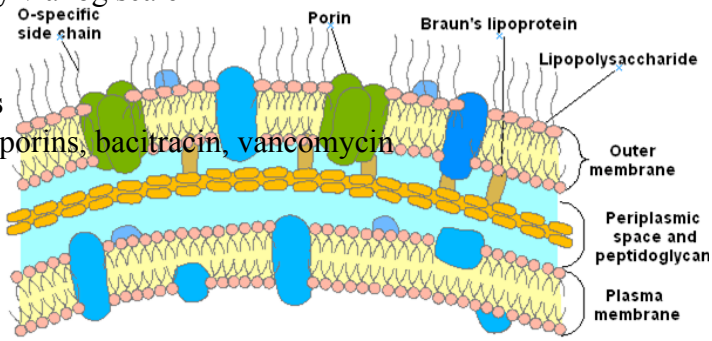
    - 1) Gram +ve
      - Peptidoglycan layer = **teichoic acid** → polysacc
        - Link via peptide bonds NAG + NAM sugars = polymer
      - Porous to abios
    - 2) Gram –ve
      - Outer memb = lipopolysaccharides (**LPS**) + porins
        - Excludes abios
        - Much less porous
        - LPS = endotoxin to trigger IS
      - Peptidoglycan CW = sig narrower + b/w 2 lipid membs
      - Lipid bilayer
    - 3) CW of **mycobacteria** = **Acid fast** staining → **3rd type** of bact
      - E.g. TB + leprosy-causing bact
      - Long chain FAs = mycolate + lipoarabinomanans (LAMs)
        - Waxy outer coat impermeable to many things
        - Extremely thick
        - Excludes antibact drugs
      - Acid fast = stain = treat w/ heat/acid to get dye in



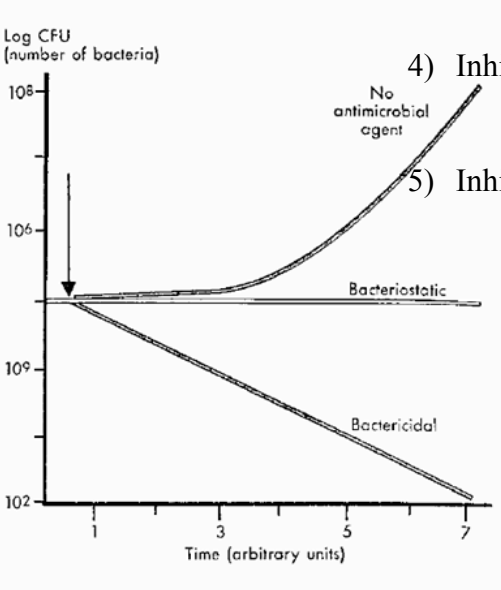
    - 4) CW deficient bact
      - *Mycoplasma* = pneumonia
      - *Spheroplasts* = stripped of CWs = not natural usu
      - Unaffected by many abios → b/c CW is target

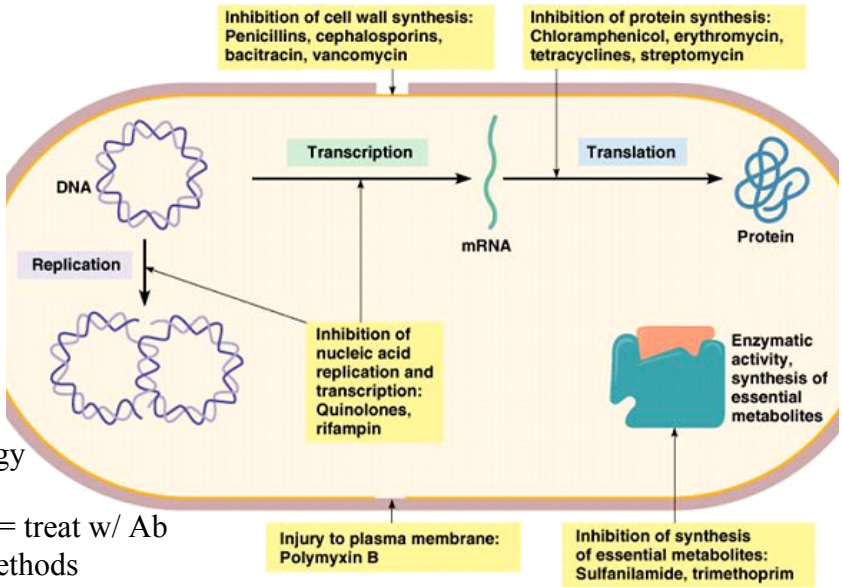
- Action of antibact drugs
  - **Bacteriocidal**: orgs killed → slope down
  - **Bacteriostatic**: orgs stop growing but not killed → no Δ in [bact]
  - No antimicrobial agent = ↑ exponentially via log scale
  - **5 sites of antibacterial drugs**
    1) Inhibition of CW syn (1)
       - Largest grp → **β-lactams**
       - E.g. Penicillins, cephalosporins, bacitracin, vancomycin





2) Injury to PM (2)
    - Rupture = dead ¢
    - E.g. Polymyxin B
3) Inhibition of nucleic acid replication + txn (3)
    - No division then
    - E.g. Quinolones, rifampin
4) Inhibition of protein syn + tln (4)
    - Attach to ribosomes = slightly diff
    - E.g. Chloramphenicol, erythromycin, tetracyclines, streptomycin
5) Inhibition of syn of essential metabs in metab (5)
    - Affect many areas in ¢
    - E.g. Sulfanilamide, trimethoprim

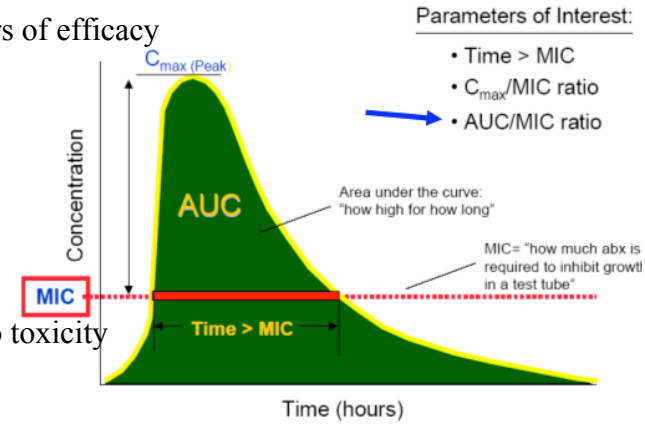




- ID / diagnosis prior to treatment
    - Examples
        - Gram stain
        - Colony morphology
        - Biochem chars
        - Toxin production = treat w/ Ab
        - Immunological methods
        - Knowledge of pathogenesis of infection → i.e. site of infection
        - Det of susceptibility to drugs
    - **Disk diffusion method**
        - Bact streaked on agar plate
        - Add drug-impregnated disks = rep of each drug class
        - Measure diameter of non-growth zones = see if inhibited or not
        - Results classified as resistant, intermediate + susceptible = qualitative
            - Large diameter of dead zone = ↑ susceptibility
    - Quantification of susceptibility
        - **Dilution test**: do dilutions of antimicro drug at certain [ ]
            - Add equal amnt of bact + measure growth w/ spectrophotometry
            - **MIC**: minimal inhibitory [ ]
                - No visible growth (e.g. in dilution tube)
                - ↓ [drug] that inhibits visible growth after 18-24 h incubation in broth culture
                - Automated = much shorter
                - MIC must be well below doses associated w/ toxicity
                - Important b/c ↑ bact R now

        - **Agar test**: plate dilutions onto plate
            - See if colonies grow in specific As
            - **MBC**: minimal bact [ ]
                - Subculture of samples from broth onto agar plates comparing # bact at beginning + end of assay
                - Least amnt of drug req to kill 99.9% of inoculum
                    - 99.9 = use to tell if drug/cleaning agent good
                    - Never 100%...
                - Used in initial testing of new drugs but not indiv cases
                    - i.e. no hospital use

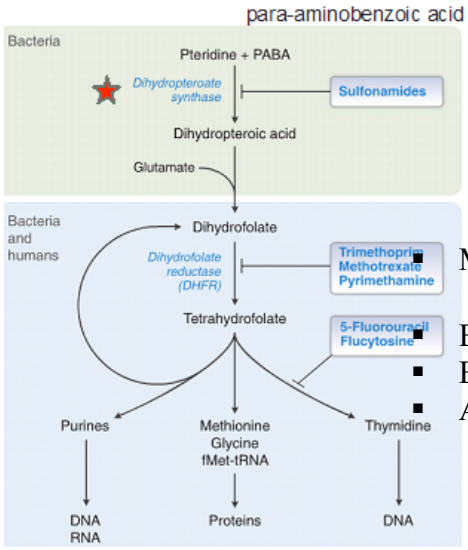
    - Pharmacokinetic/pharmacodynamic predictors of efficacy
        - Cmax = peak
        - Time = interval where at MIC
        - AUC = how high for how long
        - Parameters of interest
            - Time > MIC
            - C_{max} / MIC ratio
            - AUC / MIC ratio
            - Some drugs ↑ dose to ↑ [ ] w/o toxicity
        -



    - Treatment success
        - Not guaranteed by completing MIC
        - Bact scoring as resistant can still be susceptible w/ ↑ doses
        - Other factors
            - How drugs abs
            - Whether excreted in active form into urine = sig w/ UTIs
            - Whether pass into host ¢s
            - How rapidly metab
            - Duration of effective lvls in blood (amnt bound to albumin)
                - If use is rapid or not
            - Toxicity too

- Inhibitors of **folate** metabolism **(5)**
    - Intro
        - Bact must syn folic acid
        - Human abs it = cannot syn DNA / proteins → no metab for us
        - Drugs target enzs in metab pathway
            - Deprives bact ability to gen co-factors req for syn of purines, pyrimidines + aas
        - **Sulfonamides, trimethoprim, co-trimoxazole** = gen folic acid

    - **Sulfonamides**
        - Compete w/ PABA for enz **dihydropteroate synthase** = not in humans
            - PABA analogs dev too
        - Abs well orally w/ some exceptions



- **Sulphasalazine** = for inflammatory bowel disease = autoimmune
- To ↓ inflammation → unknown mech

Metab by acetylation + elim by kidney

- Use for uncomplicated UTIs b/c goes to kidney fast

Bacteriostatic → not killer

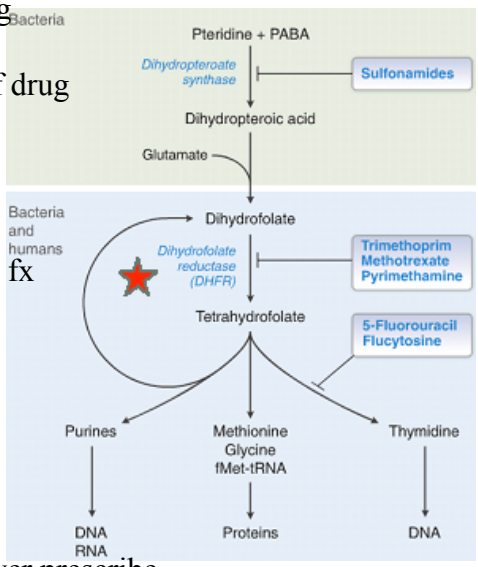
Broad activity (Gram +, –)

Adverse fx

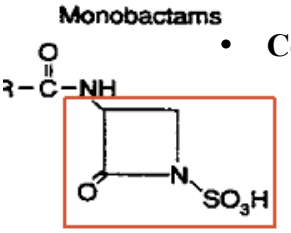
- Crystalluria + nephrotoxicity
- Hypersensitivity (rash)
- Binds albumin + can displace other drugs / **bilirubin-kernicterus**
  - Deposition of bilirubin in brain
    - Jaundice = neuro probs
    - Breakdown w/ UV light on babies

Bact R

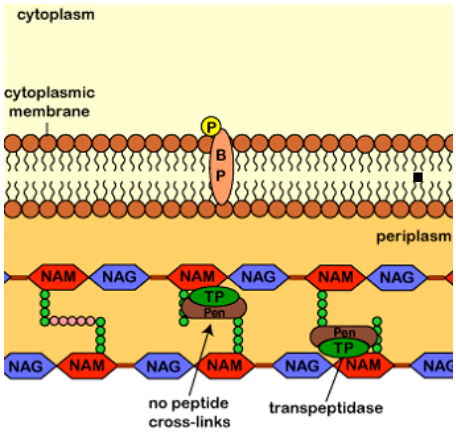
- Altered target enz
- ↑ drug inactivation → w/ enz
  - All bact have R enz but not always active / exp
  - Enz actually in bact since beginning
- ↑ PABA syn
  - Counteract / compete w/ binding of drug



- **Trimethoprim**
  - Inhibitor of **dihydrofolate reductase** (**DHFR**)
  - 20-50x more potent than sulfonamides
  - Often used in combo w/ sulfonamides
    - Mix = synergistic fx = several 1000x more fx
  - Bactericial
  - Broad spectrum (Gram +, –)
- **Co-trimoxazole**
  - Mix of sulfonamide + trimethoprim
    - Prob b/c targets humans
  - Shows synergistic fx of 2 cmpds
  - Can cause issues in patients deficient in folate
    - E.g. during pregnancy = susceptible → never prescribe
  - Used in UTIs, respiratory tract + prostate infections
    - Bact infections usu localized
    - In sites of entry / contact w/ enviro, topical, skin…
    - Esp. mucosal membs
    - Systemic = very serious but very uncommon
- **Dapsone**
  - Competes w/ PABA
  - Struc diff than sulfonamides
    - Interact w/ other components in euk though…
  - Used in combo w/ other antimicro = treat *Mycobacterium leprae* = leprosy
  - Topical use for acne, rashes → α-inflam action indep of antibact activity
  - Narrow spectrum for *mycobacterium only* (non-Gram bact)



- **Cell wall inhibitors (1)**
  - Intro
    - Gram +ve = thick CW
    - Gram –ve = thin CW but have outer memb
  - **Penicillins**
    - Discovered by Fleming as cmpd released from mould that inhibited bact growth (1928)
    - 1st used clinically several yrs later → ppl slow to adopt new sci discoveries
    - Now many variants both natural + chem syn
    - Most derives of **6-aminopenicillanic acid**



    - Fn
      - Bind to penicillin binding proteins + inhibit **transpeptidase** rxn responsible for *cross-linking* b/w peptidoglycan units
        - Last stages of CW syn
      - Bacteriocidal → rupture from incomplete CW
      - Good activity vs. Gram +ve
      - Poor activity vs. Gram –ve

Syn peptidoglycan

- Monomers of NAG-NAM peptides attached to growing end of bact CW w/ **transglycosidase** enz
  - N-acetyl glucosamine + N-muramic acid
- Transpep enz join peptide of 1 monomer w/ another to str CW
  - Penicillins + cephalosporins bind to transpep enz
  - Block formn of peptide cross-links
- Results in weak CW + osmotic lysis of bact

    - Incomplete adsorptn from GI tract but distributn throughout body = good
      - ↓ in bone + cerebral spinal fluid (CSF)
        - During inflammation = gets into CSF more easily
        - Good vs. meningitis
      - Excreted via kidney → inhibited by **probenecid**
        - Inhibition = ↑ [ ] in body
      - Considered very safe → raw rarely used though
      - Diarrhea due to disruption of normal flora
      - ~5% may show signs of allergy
    - Natural penicillins
      - Susceptible to **β-lactamases** (**penicillinase**) → R = rapid
      - Penicillin G
        - Poorly abs + ↓ further if food in stomach
        - Acid-labile
        - Admin parenterally → need i.v.
      - Penicillin V
        - Good abs via GI tract but ↓ potency

- Extended spectrum penicillins
  - E.g. Ampicillin, pipericillin / tazobactam, carbenicillin, ticarcillin
  - Broad spectrum against G+ + some G- bact
  - Penicillinase suspectible
  - Can use combo of drugs to make penicillins bacteriocidal
    - E.g. **Amoxicillin** + **Clavulanic acid**
      - Alone = not well used → together = synergistic
    - E.g. **Pipericillin** + **tazobactam**
      - Esp. effective against *Pseudomonas aeruginosa*

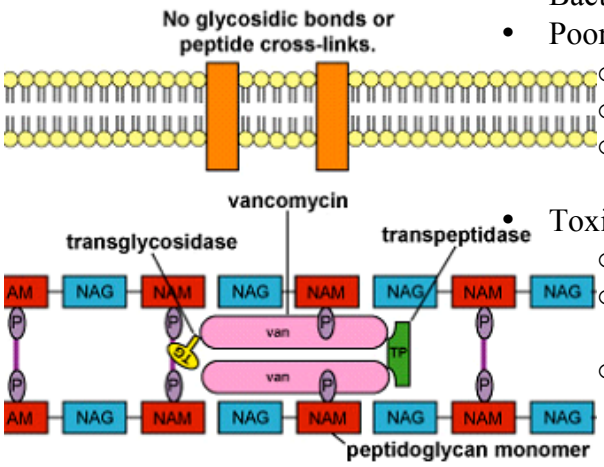
- **β-lactamase** resistant penicillins
  - a.k.a. anti-staphylococcal → narrow spectrum G+
  - Not new in bact living in isochords, uninhabited places
    - Bact always have but genes not always turned on
  - β-lactamase inactivates β-lactam ring
  - **Cloxacillin**, **methicillin** → used to be best abio
    - MRSA = methicillin resistant *Staph aureus*
  - Major reason why penicillins no longer extensively used
    - Obs R in microorganisms w/o peptidoglycan walls (mycoplasma) / w/ CWs impermeable to drug
    - Presence of β-lactamases cleave + inactivate drug

- **Cephalosporins**
  - Initially isolated from fungus = *cephalosporium*
  - Similar mech of action as penicillins but broad spectrum
    - Gram +ve + -ve effective
  - Generally admin i.v. = good distribution in body → need rapid mobilizatn
  - Elim in urine
  - Adverse fx → allergy, some induce drowsiness, headache
  - Grp based on when introduced clinically
    - 1st gen = more effective vs. G+
      - **Cephalothin**, **cephalexin**
    - 2nd gen = broad spec
      - **Cefoxitin**
    - 3rd gen = more effective vs. G-
      - **Cefoperazone** = R to β-lactamases → for vs. *P. aeruginosa*
      - Reach CSF better than others
    - 4th gen = broad spec as of March 2007
      - **Cefepime**, **cefpirome**
      - R to β-lactamases
      - Reach CSF
      - Active vs. *P. aeruginosa*
    - 5th gen = in dev
      - **Ceftobiprole**, **ceftaroline**
      - May have activity vs. MRSA
  - Grps more important than names!!!

Penicillins	Cephalosporins	Carpabenem
Gram +ve	1st: gm +ve	Broad spectrum
Extended spectrum	2nd: broader spectrum	β lactamase resistant
Resistance: β lactamases	3rd: gm -ve	
β lactamase resistant - methicillin	4th: β lactamase resistant	
MRSA		NMD1

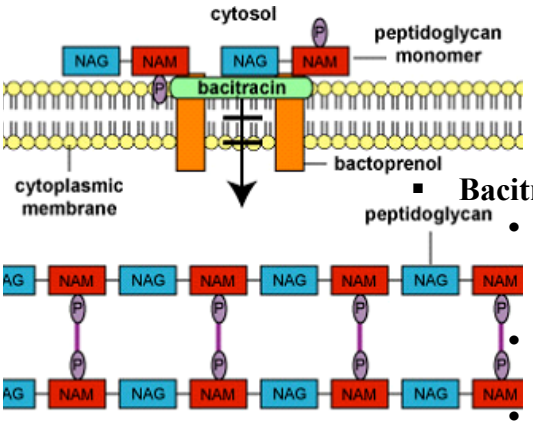
- **Carbapenems**
  - Broadest spec of all β-lactams → including anaerobes
  - R to β-lactamases
  - Cleaved in kidney by **dehydropeptidase** to yield toxic metab
    - Often admin w/ **cilastatin** to inhibit rxn
  - Admin i.v. → abio of choice for R G- bact
    - E.g. **Imipenem**, **meropenem**
  - Newly described R gene = **New Delhi** = **NDM-1** gene

- **Other** CW inhibitors
  - **Glycopeptides** = Vancomycin, Teicoplanin, Bacitracin
  - **Vancomycin**
    - Binds to peptides of peptidoglycan monomers
      - Blocks formn of glycosidic bonds + peptide cross-links
      - Results in weak CW + osmotic lysis of bact
    - Glycopeptide produced by soil bact *Streptomyces orientalis*
      - Soil bact collected in Borneo
    - Narrow spec = G+
    - Dev to treat abio R bact / for patients allergic to penicillin
      - Invasive infections
      - Treat abio R staphylococcal (MRSA) + enterococcal bact
    - Bacteriocidal
    - Poor bioavailability = i.v. admin
      - Oral form dev for *C. difficile* bowel infections
      - Usu limited by normal flora
      - Outbreak of R = can promote growth



    - Toxicity
      - Chills, fever, rashes
      - Rare nephotoxicity, thrombocytopenia, disruptions in WBCs
      - **Red-man syndrome**: erythematous rxn in upper trunk
        - Skin rxn b/c Δs in BP + hypotension
        - Flushing = get red → mediated by histamines
        - Pseudo red-man syndrome = from red clothing dyes
    - Vancomycin resistance
      - Vancomycin resistant enterococci (**VRE**) = most common
      - G+ → in normal intestinal flora
        - Outgrowth = prob
      - **Nosocomial** infections = in hospital
        - Opportunistic urinary tract infections (catheters)
        - Peritoneal infections (dialysis)

  - **Teicoplanin**
    - Similar to Vancomycin → used in Europe but not in N. Am.
    - ↓ adverse fx



- **Bacitracin**
  - Prevents peptidoglycan monomers syn in cytosol from being transported across CM
    - No building blocks available for peptidoglycan
  - Produced by *Bacillus* species isolated from girl named Tracy
    - Tracy = 1st person infected w/ bact
  - Broad spec
  - Poor bioavailability = used topically only (i.e. **Neosporin**)
    - Sometimes in combo w/ other abios (**Polysporin**)
  - Active ingredients
    - Polymyxin B sulfate 10 000 units
    - Bacitracin Zinc 500 units → in white petrolatum base

- **Isoniazid**
  - Produced from isonicotinic acid
  - Inhibits syn of **mycolic acid** by blocking activity of **fatty acid synthase**
    - Attacks 3rd type of bact = myobacteria → TB, leprosy…
    - Narrow specificity → *M. tuberculosis*
    - Also induces production of oxygen radicals like NO
  - Must be activated by bact enz **KatG**
    - Enz needed = selectivity
  - Bacteriocidal when bact growing rapidly
  - Bacteriostatic when bact growing slowly → harder to clear → ↓div
  - Oral admin often in combo w/ other drugs
    - Metab by liver
    - Good penetration in blood, CSF + granulomas
    - Isoniazid interferes w/ IR response factor → need ↑IR drug
  - Side fx
    - Headache, nausea, poor [ ]
    - Rash, abnormal liver fn + hepatitis, anemia
    - Peripheral neuropathy + CNS fx due to vit B6 depletion at ↑ doses

- **Inhibition of protein synthesis (4)**
  - **Aminoglycosides**
    - Physio fx
      - All have cyclohexane ring + amino sugars
      - Bacteriocidal
      - Active xport into bact
      - Inhibit protein syn through binding to either **30S** / **both 30S** + **50S**
        - Distortion of site of mRNA attachment, misreading of codon, blockade of initiation complex
      - Other fx → directly on CM? → unknown
      - Little / slow dev of R → b/c not as widespread

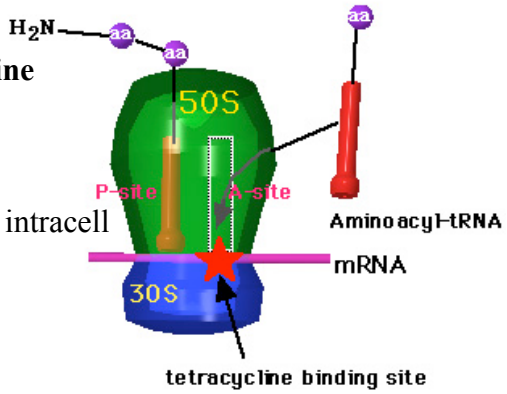
- **Streptomycin**, **tobramycin, kanamycin**
  - Syn by *Streptomyces* b/c ends in -mycin
  - For **G- aerobes**
  - Serious infections: septicemia, intraabdominal infections, UTIs
    - **Septicemia**: bact in blood → immune response = shock
    - **Pseudomonas aeruginosa** treated
      - Good b/c hard to treat → exists in **biofilms**
  - In combination w/ other drugs for mycobact infections
    - **Tobramycin** = extended spec too
- **Gentamicin,** = from related bact → *Micromonospora*
  - Sometimes used w/ ampicillin
- **Neomycin**
  - Poorly abs = topical
- Medical use
  - Admin orally, intramuscularly, i.v.
  - Poorly adsorbed, excreted by kidney
  - Blood concentrations monitored during therapy
- Side fx
  - Affects 8th cranial nerve = loss of balance, nausea, deafness
  - Allergy
  - Renal dmg

- **Macrolides**
  - Physio fx
    - **Erythromycin**, **clarithromycin**, **azithromycin**
    - Large 14-16 memb ring struc → naturally derived
    - Bacteriostatic → can be –cidal = dose dep
    - Broad spec
      - Many G+, some G-
      - Some active vs. obligate intracellular bact
    - Bind to **23S** unit of **50S** ribosomal subunit
      - Dev R via methylation of 50S subunit
  - **Erythromycin**: used for those allergic to pen + respiratory infections
    - e.g. pneumonia
    - Orally (enteric coated), parenterally, topically
    - Metab in liver
  - **Clarithromycin**: for pharyngitis, sinusitis, tonsillitis, pneumonia
    - i.e. for sore throats, rickettsia
    - Take orally = acid stable
    - Excreted in urine + bile salts
  - Side fx
    - Upset GI
    - Contraindicated in patients w/ ↓ hepatic fns
    - Inhibits **CYP3A** = can result in accumulation of drugs in liver
    - Interferes w/ statins + migraine headaches

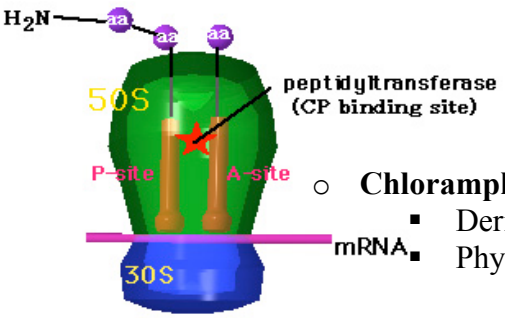
- **Other** protein syn inhibitors
  - **Clindamycin**
    - Physio fx
      - Class of abios called **Lincosamides**
      - Unrelated to macrolides → but similar mode of action
      - Greater activity vs. G-
      - Bacteriostatic
      - Used for mainly anaerobic infections
      - Can be used for pen R aerobic infections
    - Often used in combo w/ bacteriocidal agents
      - Methicillin / vancomycin
      - Some ability to inhibit production of toxins by highly pathogenic *S. aureus* + *S. pyogenes* + *MRSA* = anaerobic
      - Use associated w/ *C. difficile* diarrhea → GI tract fx
      - Used topically for acne

  - **Oxazolidinones**
    - E.g. **Linezolid** → both oral + parental admin
    - Heterocyclic cmpds
    - Binds to **50S** ribosomal unit → mech unknown
    - Against MRSA + other R G+ bact
    - Treat
      - Pneumonia
      - Soft tissue infections for R strains of cocci
        - **Staphylococci**, **pneumonococci**, **enterococci**
  - **Streptogramins**
    - 2 grps A + B act synergistically
      - e.g. **Quinupristin**, **dalfopristin** → in combo
    - Bind to diff sites on **50S** unit
    - Inhibit chain elongation + interfere w/ **peptidyl transferase**
    - Used for vancomycin R enterococci → i.v. admin
    - R dev for these too…

- **Tetracyclines**
  - Physio fx
    - e.g. **Tetracycline**, **doxycycline**, **tigecycline**
      - Doxy + tige = hospital use only
    - 4 hydrocarbon rings
    - Broad spec
      - G+, G+, mycoplasma → obligate intracell
      - For cholera before
    - Bacteriostatic
    - Active xport proteins in bact membs
    - Binds to 30S subunit
      - Blocks binding of **aminoacyl tRNA → tln**



- **Tetracycline**
  - From *Streptomyces*
  - Incomplete abs through GI tract
    - Affected by milk, antacids + Fe
  - Excreted in bile + urine
  - Widespread R now
    - Currently used to treat obligate intracell bact
    - Lyme, syphilis + acne → spirochetes
    - Valuable for exotic infections though → anthrax, plague …
  - Now semi-synthetic derivs
- **Doxycycline**
  - Similar use to tetracycline
    - Lyme disease, anthrax, acne
    - Can also be for more common G- if shown to be susceptible
- **Tigecycline**
  - Approved 2005 → still active against some R bact
  - i.v. admin
- Side fx
  - GI irritation
  - Discolouration of teeth, bone deformities in children
    - Not for pregnant women
  - Risk of **superinfections** → outgrow bact not usu pathogenic



- **Chloramphenicol**
  - Deriv from *Streptomyces*
  - Physio fx
    - Bacteriostatic
    - Broad spec including intracell bact + anaerobes
    - Binds **50S** ribosomal unit blocking **peptidyl transferase → tln**
  - Admin orally + i.v. + topically
    - Readily abs = diffuses into all body compartments including CSF
    - Cheap
  - Used to be used for typhoid (*salmonella*) but R has dev
  - Used for cholera, bact meningitis, bact conjunctivitis
  - Adverse fx
    - GI disturbances
    - Depresses bone marrow (BM)
      - Rev but rarely see fatal aplastic anemia
      - Can now be treated w/ BM treatment
    - In neonates
      - Affect resp + circulatory sys → **gray baby syndrome**
  - Resistances
    - **Acyltransferases** that inactivate them

- **Inhibition of nucleic acid synthesis (3)**
  - **Quinolones**
    - Synthetic drugs
    - Used for serious hospital acquired infections → e.g. pneumonia, *C. diff*
    - Contain 2 6-memb rings
      - Sub w/ F to gen fluoroquinolones
      - E.g. **Nalidixic acid**, **Ciprofloxacin**, **norfloxacin**, **ofloxacin**
    - Bactericidal + broad spec
      - Not active against streptococci, *mycoplasma* + anaerobes
      - Obligate intracell
    - Targets **DNA topoisomerases**
      - For nicking, supercoiling + sealing DNA during replication
    - Oral admin
      - Good distn to all body compartments
      - Penetration into **phagocytes** → mycobact survive in them = killed
      - Prolonged serum half-life → evades secretion
    - Some secreted by kidney + liver → some kidney only
    - Side fx
      - Adverse fx mild = generally well tolerated w/ some exceptions
        - GI upset, rashes, arrhythmias, CNS toxicity
        - Not used in pregnancy + young due to tendon injury
      - Considered ↑ risk for dev of *C. diff*
        - Hard to elim b/c spore forming = quiessent
      - R against earliest quinolones = **nalidixic acid**
        - Nalidixic = 1st one for G- UTIs
        - Less R against newer drugs

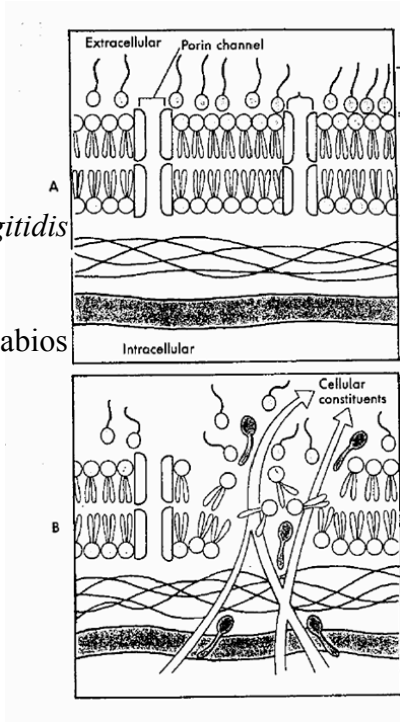
  - **Metronidazole**
    - Narrow spec
      - Against anaerobic bact
      - Also action against **fungi** + **parasites** = euk ¢s
    - Action req reduction of nitro grp under anaerobic conds to fn
    - Disrupts DNA struc = induces breaks in DNA strands
    - Oral / topical admin
    - Mild C. diff infections, pelvic inflammatory disease, H. pylori
      - **H. pylori** = bact in stomach that makes ulcers → cancer long-term
    - Anaerobic bact
    - Often used in combo w/ 2nd antimicrobial
    - Side fx
      - Nausea, vertigo, metallic taste in mouth
      - **Disulfiram**-like effect = ↑ fx of alcohol → sensitivity

  - **Nitrofurantoin**
    - Reduced in bact to reactive intermediates which inactivate / alter bact ribosomal proteins + other macromlcs

        - Both NA + **CW syn** inhibited
        - Disrupts **DNA syn**, **RNA syn** → nucleic acid inhibition
        - Multiple actions = harder to dev R bact
    - Not well adsorbed → poor tissue distn
        - Bacteriocidal / static = dep on [ ] achieved
    - Mostly used in UTIs

- **Telithromycin**
    - New class = **ketolide**
        - Acid stable = admin orally
    - Treats community acquired **pneumonia** = *S. pneumoniae*
        - Use limited by association w/ liver failure = ↓ value
    - Innovative mech of action
        - Unlike macrolides = has **2 binding sites** on bact ribosome
        - Reduces R strains of *S. pneumoniae* in community

- **Rifampin** (**Rifampicin**)
    - From soil bact
    - Inhibits **DNA dep RNA pol**
    - Broad spec = bacteriocidal
        - Active vs. G+, some G-, mycobact
        - Used alone for chemoprophylaxis of *N. meningitidis*
    - Combo w/ other drugs for treatment of tuberculosis
        - **Dapsone**, **clofazimine**
        - Sometimes used for MRSA in combo w/ other abios



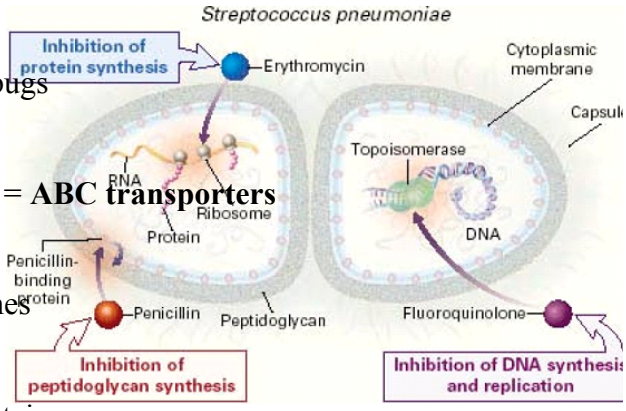
- **Inhibitors of CM (2)**
    - **Polymyxins**
        - E.g. **Polymyxin B**, **colistin**
    - Bacteriocidal
    - Narrow spec = G-
    - Cationic detergent
        - -ve effect on CM = loss of memb integrity
    - Only used topically b/c of nephrotoxicity, neurotoxicity

Antimicrobial resistance

- Variety of muts can lead to abio R in bact
- General mech of abio R
    1) Enz destruction of drug
    2) Prevention of penetration of drug + ejection of drug
    3) Alteration of drug's target site
- **Enz destruction (1)**
    - Enz have diff spectra of activities
    - 1 of most robust mech of abio R
    - 100s of enz produced by bact

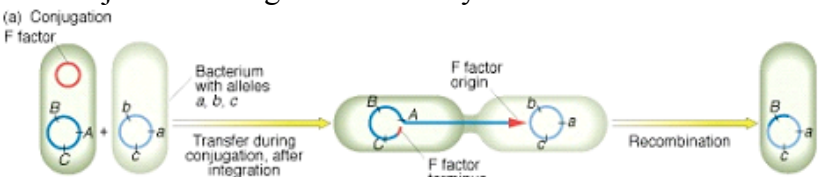
        - **β lactamases** = cleave β lactam ring (**penicillinase**)
        - Modding enzs = acetylation, +P ...
    - **β lactamases**
        - G+
            - R = 1st gen pens
            - Little activity against cephalosporins, methicillin
            - Bound by **clavulanic acid** = killed activity
        - G- = outer memb + CW
            - Upreg enz to R
            - Act against penicillins + cephalosporins
            - Pre-existing + induced
        - Extended spec
            - Inducible enzs
                - Not usu in absence of drug
                - Broad activity
            - Activity against multiple cephalosporins
    - Modding enzs
        - Give R to **aminoglycosides**
            - 50+ enzs
            - Acetylation, adenylation, phosphorylation all done
        - Similar enzs inactivate **erythromycin** + **chloramphenicol**

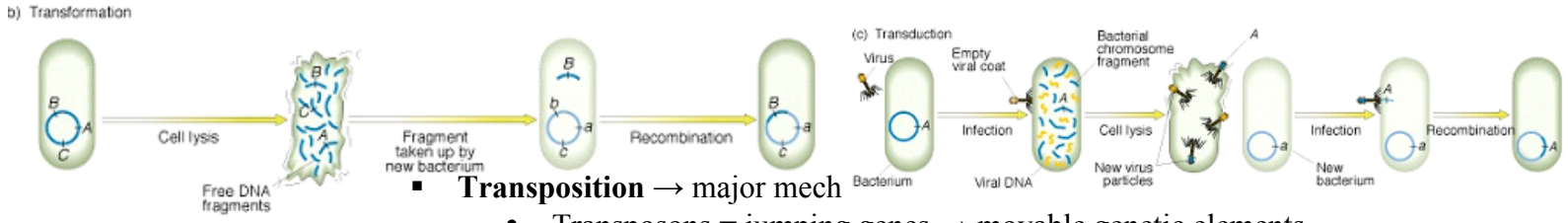
- **Prevention of penetration / efflux (2)**
    - For bact lacking active xport sys
    - **Muts in porin proteins** of outer memb of G- bugs
        - Most abios prevented into ¢
        - E.g. *P. aeruginosa* = biofilms = prob
    - Active efflux pumps that move drugs out of ¢s = **ABC transporters**
        - Use to pump out abio
        - Bact = diff from human = diff fn
        - E.g. R to tetracyclines + fluoroquinolones



- **Alterations in target (3)**
    - Pt muts, seq substituents, exchange w/ new protein
    - Δs in susceptibility small, build up over time → can be sudden too
    - Responsible for early R to aminoglycosides + nalidixic acid (quinolone)
        - Δs in pen binding proteins (PBPs) responsible for MRSA
            - E.g. w/ transpep = no CW syn
        - Some vancomycin R bact, sulfonamides, trimethoprim
        - Methylation of ribosomal RNA confers R to clindamycin, erythromycin + other macrolides → upreg +Me of cmpds

- Genetics of resistance
    - Muts = pt, seq subs or recombination
    - Acquired from another org
        - **Conjugation** – plasmid → major mech → genetic diversity





- **Transposition** → major mech
  - Transposons = jumping genes → movable genetic elements
  - Jump w/i Xm, plasmid-plasmid, or plasmid-Xm / rev
    - E.g. can xfer MDM-1 New Delhi gene for R
  - Rarer in nature
  - **Defensins** = at mucosal membs → esp. gut
- **Transformation**
  - Cell lysis → Free DNA frags
  - Taken up by other bact
- **Transduction**
  - w/ **phage** = attack back only = less common in nature

- Ways to ↓ R
  - Decreased demand of abios = best
  - ↓ generalized usage (agricultural)
    - Major prob b/c find yrs later in soil + land
  - Improve education / compliance of patient
  - Dev new agents structurally diff
    - Target R pathways → i.e. multi-drug R pumps

Antifungal & Antiviral drugs

- Antifungal drugs
  - Fungi = euk ¢s, drugs more toxic for host
    - Indiv ¢ = yeast = ¢ div
    - Hyphae / branches = moulds
  - Detoxification sys acts on antibios
    - Most effective drugs act on memb / CW
    - Extract sterols / prevent syn / target **chitin synthase**
  - Admin topically for athlete's foot, vaginal candidiasis, ringworm → local
    - Parenterally / orally for systemic infections → meningitis, aspergillosis
    - **Ringworm**: mould that leaves ring on skin = uncomfortable
  - Cytoplasmic membrane → many = renal dysfn
    - **Polyenes**
      - **Nystatin** = topical
      - **Amphotericin B** = parenteral → highly toxic
        - Use only if systemic mould → life/death sit = no prob then
    - **Azoles**
      - Convert sterols to ergosterols
        - Limit enz earlier = defective memb
        - Prob = may effect hormones
      - **Clotrimazole**, **miconazole** = topical
      - **Fluconazole**, **itraconazole**, **voriconazole** = oral for meningitis
    - **Allyamines**
      - **Naftifine** = topical for dermaphytes = rashes
      - **Terbinafine** = oral
        - *Candida* = yeast for mouth, throat + vaginal infections

        - *Aspergillus* = yeast on mucosal sites like lungs
            - **Pneumocystosis** = pneumonia caused by yeast
            - Found in HIV ppl → weakened IS
            - Get mouldy brains + spores
    - **Other** antifungal drugs
        - Nucleic acid syn
            - **Flucytosine** (**5FC**)
                - Oral, well abs
                - Active vs. yeasts (Candida) but not moulds
            - Rev inhibition of BM
        - CW syn
            - Broad spec
            - **Echinocandins**: caspofungin, micafungin, andiulafungin
            - **Nikkomycins**: nikkomycin Z, X

- Antiviral drugs
    - Viruses
        - More common in ppl immunosuppressed like HIV + cancer
        - Obligate intracellular pathogens
            - Do not replicate outside living ¢
        - All viruses reliant on cellular *ribosomes*
            - Must hijack ¢ + syn proteins but genes = protected
            - Disrupting ¢ fning = harder to deal w/ w/o affecting host
                - Treat w/ vaccines / leave alone
                - But few cause ↑ diseases
                - Dangerous if humans unnatural host
        - Vary in dependence on other cellular factors
            - RNA pol II
            - DNA pol
            - Cytoskeletal elements
    - DNA genome viruses → harder to treat
        - Herpes viruses (HSV, CMV, EBV, VZV)
        - Hepatitis B virus
        - Papillomaviruses → warts, cervical cancer
    - RNA genome viruses → treatable
        - Hepatitis C
        - Influenza virus
        - HIV → integrates cDNA into host Xm

    - Drug interfering w/ virus rep = most successful
        - **Nucleoside analogues**
            - Analogues converted by **viral TK** to monophosphate
                - Then by cellular enz to triphosphates
                - Inhibit activity of viral DNA pol
            - **Gancyclovir** = CMV → cytomegalovirus
                - Prob w/ transplants + immunosuppression usu

- **Acyclovir** = HSV 1, 2, VZV
    - Interferes w/ ability to syn new genes
    - New derivs = **valacyclovir**, **famcyclovir**
    - HSV-1 = cold sores → prob in infants = encephalitis
    - HSV-2 = genital herpes
    - VZV = for chickenpox
        - Usu don't treat unless get shingles
        - Virus for life but activate if immunosuppressed
            - Shingles in elderly usu
- Other drugs
    - **Foscarnet** = drug R CMV, HSV → but kidney toxicity
        - Inhibits DNA pol
        - Very toxic → only R virus

- **Hepatitis B virus**
    - No treatment for acute infection unless rapid deterioration
        - RT = target for most drugs
        - Treat if have liver probs
    - Treatment for chronic diseases
        - **Nucleoside analogues**
            - Inhibit activity of reverse transcriptase activity
            - **Entecavir**, **tenofovir**, **telbivudine**
        - **Reverse transcriptase inhibitor**
            - **Lamivudine** (3TC) → also for HIV
        - **Interferon alpha 2a + 2b**
            - Antiviral activity, promotes IR
    - **Interferon**
        - Humans produce when infected w/ viruses
            - Makes ¢ inhospitable for viral infection
        - Various preps of type I IFNs = licensed for treatment of virus infections in US
        - IFN α 2a, 2b → for chronic Hep C
        - IFN α 2b → for chronic Hep B
        - IFN α n3 → for genital, laryngeal warts (papilloma virus)
            - Use vaccines
        - Side fx
            - Flu-like symptoms
            - Aching muscles
            - Depression

- **Hepatitis C virus**
    - Not related to Hep B → just causes liver dmg too
    - **Viral RNA pol inhibitor**
        - **Ribavirin** = resembles ribonucleotides → bad b/c inhibit enz fning
            - Get haemolytic anaemia though
            - Better if in combos

        - **Protease inhibitors**
            - **Telaprevir**, **boceprevir** (**NS3/4a inhibitors**)
            - Very ↓ side fx
        - **Pegylated Interferon**
            - ↑ [ ] = less doses req if this drug combos w/ other 1

- **Influenza virus**
    - Virus entry / uncoating
        - **Amantadine**, **rimantadine**
        - Virus must go in at ↓ pH → drug prevents Δ in pH
        - Modest fx when admin w/i 12-24 hrs of symptoms
        - R = no longer used routinely
    - Virus release
        - Neuraminidase inhibitors
            - **Oseltamivir** (**Tamiflu**), **Zanamivir** (**Relenza**)
        - Active vs. Flu A + B + C
            - A = Δs regularly but B = serious infection
            - Prob = must treat in few hrs
        - Must be admin early → R dev now though
    - **Neruaminidase inhibition** process
        - HA binds sialic acid
            - NA cleaves to let ¢ leave
        - Inhibition = prevents virus from escaping + spreading to other ¢s
- **HIV**
    - Life cycle
        - Gp120 binds to T4
        - Gets in as genomic RNA → must use RT to get cDNA
        - Get into nucleus to integrate into host Xm → uses integrase
        - Txn to mRNA + tln to proteins → need to use protease
        - Bud out as mature virion
    - Antiviral HIV drugs
        - **RT** inhibitors
            - Nucleotide analogues (**NRTIs**)
                - **AZT**, **3TC** (Lamivudine)
            - Non-nucleoside RT inhibitors (**NNRTIs**)
                - **Nevirapine**, **rilpivirine**
        - **Protease** inhibitors (**PI**)
            - For life cycle prevention
            - **Indinavir**, **ritonavir**, **darunavir**
        - Inhibition of entry
            - Fusion inhibitor → **Fuzeon** (**enfuvirtide**) → block binding
            - **CCR5** antagonist → **Maraviroc**
        - **Integrase** inhibitors (**II**)
            - Block enz that integrates into ¢ → patients only to ↓ R
            - **Raltegravir**, **elvitegravir**

        - **HAART** (highly active anti-retroviral therapy)
            - Can prevent transmission from mother to child
            - Also from infected to uninfected partner
            - Common therapy = 3 drugs → combo therapy
                - 2 NRTIs
                - 1 PI or NNRTI or II
                - i.e. 2 RT inhibitors + 1 other
                    - Keeps ↓ viral replication

Antidepressants

- Prevalence
    - Very common in society
- Clinical presentation
    - Must be sig Δ from prev fn
    - ONE symptom must be either:
        - Depressed mood
        - Lack of interest in activities
    - FIVE+ more symptoms during 2 week period
        - Acronym = **SIG SCAPE**
            - Sleep – Insomnia
            - Interest ↓
            - Guilt ↑↑↑
            - Suicidal thoughts
            - Concentration Δs
            - Appetite ↓ = ↓ weight
            - Psychomotor agitation / retardation
            - Energy – Fatigue
    - Antidep fn on **monoamine hypothesis**
        - Dep due to deficiency in 1+ of 3 **catecholamines**
            - **Serotonin** (**5-HT**)
            - **Norepinephrine** (**NE**)
            - **Dopamine** (**D**)
        - Mech of antidep = ↑ lvls of 1+ of the 3
            - Block reuptake pumps
            - Inhibit destruction by monoamine oxidases

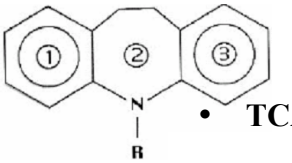
- **SSRIs** (selective serotonin reuptake inhibitors)
    - Pros
        - Newer class
        - Most widely used drug for treating dep
        - As effective as TCAs but has ↓ side fx
        - Safer in OD
    - Cons
        - Drug interactions possible
        - ↑ $$$
    - Process
        - Serotonin deactivated in synapse by reuptake into presyn neuron usu
        - Prozac blocks reuptake of serotonin → ↑ activation of 5-HT receptors
    - Drug names
        - **Fluoxetine** (**Prozac**), Citalopram (Celexa), Escitalopram (Cipralex), Sertraline (Zoloft), Paroxetine (Paxil)

- Mode of action
  - Short-term = inhibitor neuronal reuptake of **5-HT** → stay in synapse
  - Long-term = down-reg of presyn autoreceptors → detect 5-HT
    - ↑ firing rate of 5-HT neurons b/c const ↑ lvl
- Pharmacokinetics
  - Well abs from gut
  - Extensive **CYP450** metab
- Adverse fx = **HANDS**
  - Headache / dizzy
  - Anxiety → nervousness → insomnia
  - Nausea
  - Diarrhea
  - Sexual dysfn

- Examples of SSRIs
  - **Fluoxetine**
    - Other indications: bulimia + anorexia
    - Longest $t_{½}$ → parent = 2.5 days + active metab = 8 days
    - Most drug intns
  - **Fluvoxamine**
    - Other indications: OCD + panic disorder
    - Has sedative fx
  - **Paroxetine**
    - ↑ bioavailability
    - Most sedating + most weight gain
  - **Sertraline**
    - Pref in elderly → ↓ side fx + take w/ other drugs
    - Fewer drug intns
  - **Citalopram** + **Escitalopram**
    - Escitalopram more potent than citalopram

- **Serotonin syndrome**
  - Occurs when SSRIs used in combo w/ other serotonergic drugs
    - MAOIs, TCAs, dextromethrophan
    - Triptans = for migraines, Demerol = for pain
  - Symptoms
    - ↑BP, ↑HR, ↑RR → tachycardia
      - Agitation
    - ↑T → Diaphoresis = XS sweating
    - Diarrhea → ↑ bowel sounds
    - In lower extremities = hallmark***
      - Tremor → oscillations + twitching
      - **Clonus** → involuntary muscle contractions + relaxations
      - **Hyperreflexia** → XS NS response to stims (like seizures)
    - Myadriasis

- **Discontinuation syndrome**
  - Occurs when SSRIs stopped abruptly
  - Symptoms = **FINISH**
    - Flu-like symptoms
    - Insomnia
    - Nausea
    - Imbalance
    - Sensory Δs
    - Hyper



- **TCAs** (tricyclic antidepressants)
  - 2nd line treatment → limited b/c of side fx
  - Drug names
    - **Amitriptyline**, **clomipramine**, **desipramine**, **imipramine**, **nortriptyline**
  - Mode of action
    - Short-term effect = inhibits neuronal reuptake of **NE** + **5-HT**
    - Long-term effect = down-reg of presyn autoreceptors
      - ↑ firing rate of NE + 5-HT neurons
  - Pharmacokinetics
    - Liver metabs TCAs into active + inactive metabs
    - Long $t_{½}$ = 18-70 hrs
  - Adverse fx
    - Muscarinic antag → **α-cholinergic**
      - Can't see = pupil dilation → no accommodation = blurred vision
      - Can't pee = urinary retention
      - Can't sh*t = constipation
      - Can't spit = dry mouth
    - α1 antag → orthostatic hypertension
    - Histamine antag → weight gain
    - Sedation
    - Toxic lvls
      - ↓ seizure threshold
      - Cardiac conductance disturbances
        - Arrhythmias, tachycardia, hypotension

- **MAOIs**
  - Normally for refractory depression → i.e. unresponsive to other treatment options
    - Limited use b/c of interactions → must limit food intake
  - Types
    - **MAO-A** = metab 5-HT
    - **MAO-B** = metab D
    - B = not used in dep
  - Drug names
    - 1st gen = **phenelzine**, **tranylcypromine**
    - 2nd gen → **RIMAs** (reversible inhibitors of MAO-A) = **moclobemide**
    - **MAO-B inhibitors** = **Selegiline** → used in Parkinson's

- Mode of action
  - Irrev bind to monoamine oxidase
    - No degradation of biogenic amine NTs → NE, 5-HT + D
  - ↑ [D, NE + 5-HT] in storage sites
- Pharmacokinetics
  - Relative ↓ $t_{½}$
  - Pharmacologic effect persists for many hrs after serum lvls ↓
- Drug intns
  - **Tyramine** foods
    - Aged cheeses, beer, some wine
    - Some fruits + vegetables → raisins, avocados, canned figs
    - Chocolate + coffee → if consumed in large quantities
- Adverse fx
  - **Hypertensive crisis**
    - Headache, palpitations, neck stiffness, sweating, photophobia

- **SNSRIs** (serotonin norepinephrine reuptake inhibitors)
  - Drug names
    - **Venlafaxine** (**Effexor**) + **Duloxetine** (**Cymbalta**)
  - Mode of action
    - Selective + potent inhibitor of both 5-HT + NE
  - Indications
    - Major depressive disorder
    - **Diabetic** peripheral neuropathic pain
    - Generalized anxiety disorder
  - Side fx
    - Similar to SSRIs

- Other antidepressants
  - **Bupropion**
    - Mode of action = weak reuptake inhibitor of D, NE, 5-HT
    - Adverse fx = agitation, insomnia, nausea + weight loss
    - May help quit smoking
  - **Mirtazepine**
    - Adverse fx = ↑ weight/appetite + sedation
  - **Trazodone**
    - Mode of action = inhibits reuptake of 5-HT
    - Adverse fx = sedation + orthostatic hypertension
      - Usu use this only for sedation fx
- Other treatment options
  - Psychotherapy
    - Enhances response to pharmacologic treatment
    - ↑ compliant to meds
  - Electroconvulsive therapy
    - Alternative to antideps
    - Ineffective + not well tolerated…

- Treatment considerations
  - 1st 2 weeks side fx may ↑
  - Usu takes 2-4 weeks for antideps to elevate mood (some up to 6 weeks)
  - Antideps usu continued for 4-9 months after depressive symptoms gone
    - Prevents relapse + weans off drugs

Antipsychotics (APs)

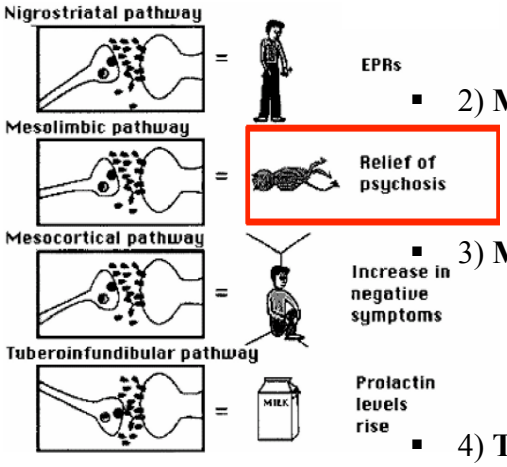
- Indications + clinical use
  - Exact mech unknown
    - Works diff / person
    - Inexact science → need to try many to get right effect
  - Use for following disorders
    - Schizophrenia
    - Bipolar disorder
    - Depression
    - Dementia
    - Acute agitation + delirium
    - Autistic disorder
- Schizophrenia
  - Mental illness that affects 300 000 Canadians + approx 1% of pop
  - Form of psychosis often present as:
    - Delusions, hallucinations, disorganized thoughts + emo abnormalities
    - Some dangerous + violent but not all → have stigma
  - Symptoms can occur at any age but often present in early adulthood
    - Detached from life = hard to keep jobs
  - Examples of behavs:
    - Preoccupation w/ delusions, hearing voices, slovenly appearance
  - Classification of symptoms
    - No single defining features present in all patients
    - Each person has variety of symptom combos + exps
    - Often 1st presents as **prodromal** period
      - Ppl have unusual behavs + ideas followed by acute episode
      - Overwhelming thought + ↓ rationale
    - Affects multiple cognitive + emo sys
      - Positive symp = present / added to normal behav
        - Antipsychotics = moderately / very effective
      - Negative symp = Taken away from normal behav
        - Antipsychotics = mildly / not effective

Positive Symptoms	Negative Symptoms
Agitation	Alogia (poverty of speech)
Delusions	Avolition (apathy)
Disorganized speech	Affective flattening
Disorganized thinking	Anhedonia (lack of pleasure)
Hallucinations	Attentional impairment
Insomnia	Social isolation
	Lack of motivation

Antipsychotics: moderately/very effective

Antipsychotics: mildly/not effective

- Bio basis of psychosis
  - **Dopamine hypothesis**
    - +ve psychotic symps linked to overactivity of **mesolimbic dopamine pathway** → delusions + hallucinations
    - Drugs that ↑ dopamine produce +ve psychotic symps
      - E.g. **Amphetamines**, **cocaine**…
    - Neuroleptic drugs act as antags at brain **dopamine receptor D2**
    - Very ↑ correlation b/w therapeutic potency + affinity for binding to dopamine receptors
    - Brains from schizophrenic patients have abnormally ↑# dopamine receptors
      - **D2** + **D4** subtypes
  - Mechanism of APs
    - Not completely understood b/c interacts w/ multiple receptor types
    - Therapeutic fx maybe from competitive antagonism of D2 + 5-HT Rs
      - **Typical** APs = ↑↑ affinity for D2 (or =)
        - **Haloperidol** = ↑ binder to remem
      - **Atypical** APs = ↑↑ affinity for 5-HT (or equal)
    - Receptor specificity varies w/ diff antipsychotics
      - Creates varying risks of adverse fx for each agent
      - Δ affinities = Δ side fx
  - Effects of AP on major dopamine pathways in brain
    - 1) **Nigrostriatal**
      - Substantia nigra → basal ganglia
      - Ctrls movts
      - Parkinsonism induced when D pathway blocked = ↓ D
      - Inability to initiate movt
        - **Dystonia** = rigidity in face + neck, tremor, rigidity
        - **Akinesia** = loss of ctrl of voluntary movts
    - 2) **Mesolimbic** DA pathway
      - Midbrain ventral tegmental → nucleus accumbens
      - Produces delusions when overactive
        - **+ve** symptoms = XS dopa → want to ↓ D
    - 3) **Mesocortical**
      - Tegmentum → brain cortex
      - Reg mesolimbic pathway
      - Perhaps associated w/ **–ve** symptoms
      - Underactive, deep apathy …
    - 4) **Tuberoinfundibular**
      - Hypothalamus → pituitary
      - **Prolactin** release at pituitary
        - Breast dev + milk production in women
      - ↑ release = ↑ lactation, menstrual cycle Δs, sex dysfn
      - Happens in men too → impotence

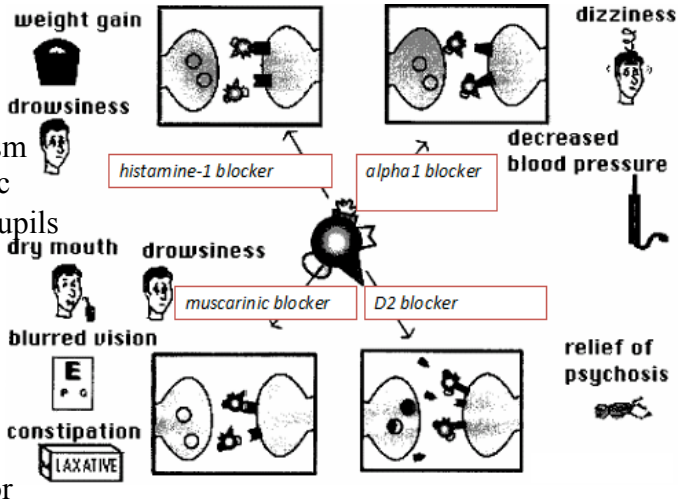


- Dopamine hypothesis **revisited**
  - If abnormality of D physiology completely responsible for pathogenesis of schizophrenia → APs would have ↑ efficacy
    - Only partially effective for most + ineffective for some
  - **NMDA receptor** antags like **phencyclidine** make more schizophrenia-like symptoms than dopamine agonists → in non-psychotic ppl
  - Cloning + char of multiple dopamine receptor types
    - May permit more direct testing of dopamine hypothesis if drugs dev to act selectively on each receptor type
    - Can't block D selectively yet
  - Several atypical APs much ↓ fx on D2 but still effective on schizo
  - Direction of research changed to focus on cmpds that act on several transmitter-receptor sys
    - Hope to syn drugs w/ greater efficacy + ↓ adverse fx
    - Esp **extrapyramidal toxicity**

- Changes in dopamine neurotransmission
  - D receptors blocked immediately → therapeutic fx of APs = take weeks to see
  - Time-dep Δs in dopamine tmn
    - 1) ↑ in dopamine syn, release + metab → Brain compensates
    - 2) Inactivation of dopaminergic neurons producing depol blockade
      - Neurons tired on syn dopamine
    - 3) Receptor up-reg + supersensitivity to dopamine agonists
      - ↑dopa + upreg = problems → need to wean

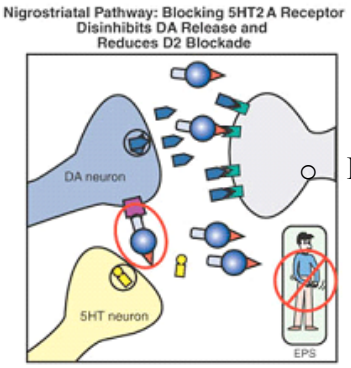
- Adverse fx of antipsychotics
  - **Extrapyramidal rxns** (EPRs) → movt disorders like Parkinson's
    - Side fx associated w/ blockade of **nigrostriatal pathway**
      - Can happen early in course of treatment / w/ dose ↑
      - Very upsetting side fx → ppl embarrassed, discriminate…
    - Restlessness → tremors
    - Balance off → slow speech / mouth open
  - Hypothetical action of conventional APs over time
    - Add dose = still have no psychosis or EPS
    - Later = get α-psychosis + EPS
    - Years later = can get α-psychosis, EPS + tardive dyskinesia
  - **Tardive dyskinesia**
    - Involuntary repetitive hyperkinetic body movts w/ ↓ onset
      - E.g. lip smacking, chewing, tongue protrusion, grimacing, rapid limb movts
    - Treatment of schizophrenia = trade-off w/ side fx
      - EPRs, tardive dyskinesia
      - **Galactorrhea**: spont flow of milk from breast
      - **Neuroleptic malignant syndrome** (rare)
        - Muscular rigidity, fever, coma, death…

- **Neuroleptics**
  - ↓ +ve psychotic symptoms
  - Most differ in terms of side fx profile instead of efficiency
    - Histamine-1 blocker
      - Weight gain + drowsiness
    - α-1 blocker
      - ↓ BP → dizziness
      - Also done w/ D2 antagonism
    - Muscarinic blocker = ↑sympathetic
      - Blurred vision → dilated pupils
      - Constipation
      - Dry mouth, drowsiness
    - D2 blocker
      - Relief of psychosis



- Receptor affinities
  - Diff receptor affinities of APs
    - Δ rate of dissociation from receptor
    - Δs risk of adverse fx
  - ↓ Ki = more drug binds to R
  - ↑ Ki = ↓ % bound to R
    - Fast on, fast off → will have less movt probs

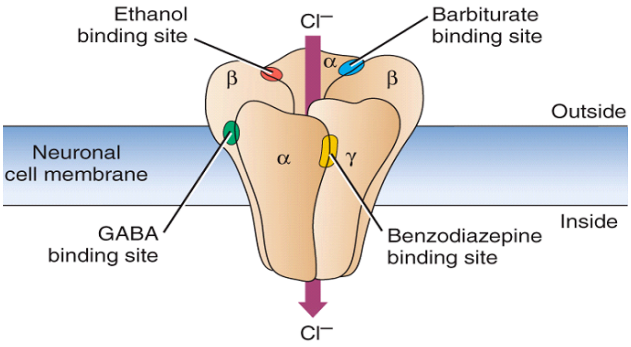
- **Typical** APs → for D2
  - Classified based on chem struc + pharmacologic props
  - Adequately abs from GI tract after oral admin
  - Several agents can be admin parenterally
    - Including long-acting depot preps for IM injection
      - Ppl forget to take pills = use this
  - Differ in terms of side fx profile + potential for drug intns
  - **Rule**: ↑ anti-cholinergic activity tend to display ↓ extrapyramidal side fx
    - E.g. Chlorpromazine vs. haloperidol
- **Atypical** APs → for 5-HT
  - Comparable efficacy to typical APs for treating +ve symps of schizo
    - Advantage in treatment of –ve symps
  - Distinguished from typical APs by greater affinity for 5-HT2 receptors + faster dissociation from D2 receptors
    - ↓ movt probs then
  - Most highly bound to plasma proteins + metab in liver by CYP-450 enz
  - Available in oral, short-acting + long-acting IM injections + under tongue
  - Tend to
    - 1) Display ↓ EPR side fx
    - 2) **Clozapine** 1st atypical dev → many fnal grps
      - Prob = leads to **agranulocytosis**: ↓ granulocytes
        - Dangerously ↓ WBCs = ↑ risk of infection
      - Used as last resort b/c need ↑ monitoring
    - 3) **Olanzipine** designed to elim association w/ agranulocytosis



- **Risperidone** (**Risperdal**) + **Sertindole**
  - Work as 5HT-2 + D2 antags
  - 5HT-2 antag = thought to remove –ve feedback on release of DA in **nigrostriatal pathway** → ↑DA there
  - D2 antag = serves to block overactive **mesolimbic pathway**
  - Other atypical APs like **quetiapine** (**Seroquel**) act on multiple receptors
- **3rd gen** antipsychotics
  - Only available agent in class = **aripiprazole**
    - Unique mech of action
      - **Partial agonist** at pre + post syn D2 + 5-HT1A receptors
      - Antag at 5-HT2A receptors
    - Partial ag of D2 +/ antag of 5-HT2 in tuberinfundibular tract explains lack of ↑ prolactin
    - ↓ activity at histamine receptors = ↓ sedation

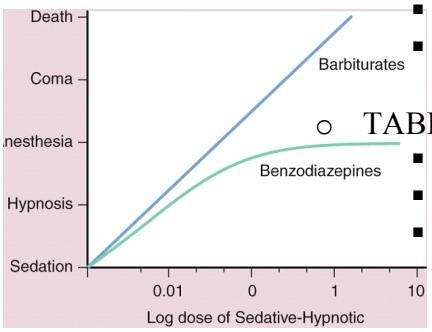
Anxiolytics and Street drugs

- **Anxiety**
  - Normally adaptive response
  - Char by Δs in mood (apprehension + fear), symp NS arousal + hypervigilance
  - Chronic anxiety can dev GI, CV, neuro symptoms
    - Diarrhea, tachycardia, tremor, sweating, dizziness
  - Neuronal pathways involved in anxiety
    - Sensory sys, cortical processing + memory
      - Interpret stimulus to be dangerous + create heightened arousal
    - Motor sys + autonomic
      - Exaggerated responses to anxiety state
  - Classification of anxiety disorders
    - **Acute** Anxiety: illness, fam, stressful event = self-limiting
    - **Panic** Disorder: severe anxiety, sweating, impeding DOOM
    - **Phobic** Disorder: stim causes anxiety
    - **Obsessive-Compulsive** Disorder: Persistent thoughts, actions …
    - **Generalized Anxiety** Disorder: chronic worrying
    - **Post-traumatic Stress** Disorder: military, flashbacks to see assaults
  - Treatment for anxiety disorders
    - Use SSRIs → 4 weeks til starts fx
    - Anxiolytics + sedative-hypnotics include: → see in 1st 4 weeks
      - Benzodiazepines
      - Barbiturates
      - Anti-Histamines
      - Non-sedating anxiolytic drugs
      - Other sedative-hypnotic drugs
    - Sedative-hypnotic drugs
      - Benzodiazepines → Lorazepam (Ativan) …
      - Barbiturates → Phenobarbitol …
      - Zolpidem → Ambien
      - Zopiclone → Imovane
      - Eszopiclone → Lunesta
      - Antihist → Dimenhydrinate (Gravol), Diphenhydramine (Benedryl



- GABA
  - GABA = gamma-aminobutyric acid
  - Most common inhibitory NT in CNS
  - GABA receptor
    - Most common receptor in CNS
    - GABA receptor-ion channel complex = made up of **5 subunits (α, β, γ)**
      - **Chloride** channels → stim = hyperpolarize ¢
    - Binding sites for benzodiazepines, barbiturates, alcohols, steroids, + inhalational anaesthetics

- **Benzodiazepine**
  - Bind at interface of α + γ subunits
    - ↑ ability of GABA to bind to GABA receptors → allosteric binding
  - Benzos ↑ **freq** w/ which Cl^- channel opens
  - GABA ↓ excitability of CNS neurons + ↓ ntmn + induces effects of benzos
  - Effects
    - Sedative, hypnotic (sleep-inducing)
    - Anxiolytic
    - Anticonvulsant → Muscle relaxant
  - Uses
    - ↓ anxiety + aggression
    - Sedation + induction of sleep → not best…
    - Muscle relaxants (central action) → restless leg syndrome
    - Anti-epileptic drugs
    - **Anterograde amnesia** → can't create mems post-event → for surgery
  - Side fx
    - XS drowsiness
    - Ataxia = loss of muscle ctrl → in elderly
    - Dependence, tolerance (14 days) + abuse
    - ↑ adverse fx when combo w/ alcohol
    - Possible amnesia
    - Prolonged usage → results in withdrawal = get abuse of drugs
      - i.e. rebound insomnia, anxiety, tremors, ↑ HR… symp NS stuff
  - TABLE + DIAGRAM



    - Prob in elderly → renal dysfn = accumulate metabs → use Oxazepam
    - Fast onset = important
    - Duration of action = longer if have more active metabs → more tfns
      - E.g. **Chlordiazepoxide** = 4 before conjugation + excretion = long
      - E.g. **Oxazepam** = short → conj right away

- **Barbiturates**
  - Includes: amobarbital, pentobarbital, phenobarbital, thiopental
  - Bind to allosteric site on GABA A receptor **distinct** from benzos site
  - ↑ affinity of receptor for GABA + **duration of time** Cl- channel opens
  - Also directly ↑ Cl^- influx in absence of GABA → benzos don't
    - **No ceiling effect** → can coma + death at ↑ doses

- **Other sedative-hypnotic** drugs
  - **Non benzodiazepines**
    - E.g. **Zolpidem** + **Zopiclone** + **Zaleplon**
    - Newer anxiolytics that do not share same struc as benzos
    - Rapidly becoming 1st-line treatment for insomnia
      - Induce sleep but not disrupting sleep cycle → like benzos
    - Agents demonstrate ↓ unwanted cog, mem + motor side fx
    - Better pharmacokinetics + well rapid onset + short duration of action
  - Graphs
    - Only have rapid eye movts in REM sleep
    - **Benzodiazepines**
      - Induce sleep
      - ↑ stage 1 + 2 length
      - ↓ stage 3 + 4 + REM length
    - **Zolpidem** + **Zaleplon**
      - Induce sleep
      - Little change in EEG otherwise (monitors sleep stages)

- **Other non-sedating anxiolytics**
  - **Seritonergic anxiolytics**
    - **Hypothesis** of **serotonin dysreg** → ↑ 5-HT = anxiety
      - **Buspirone** = **5HT-1A** partial agonist that interacts w/ *somatodendritic –ve feedback*
        - ↓ release of 5-HT by stim –ve feedback but ctrlled
    - In general = less sedative
      - But ↓ interactions w/ alcohol
      - ↓ potential for abuse
      - Not fast acting = delay in onset of action
    - Side fx
      - Vertigo
      - "Woozy" feeling → likely b/c interactions w/ postsyn 5HT-1A Rs
  - **Noradrenergic anxiolytics**
    - **α-2 agonist**
      - **Clonidine**
      - ↓ NE = ↓ symp NS + ↓ emotional aspects of anxiety
    - **β** adrenergic **antags**
      - **Propranolol**
      - Treats social phobia, stage-fright, anxiety w/ stressful event mems
      - Not always emotional = good too
    - In general → ↓ anxiety, tachycardia, dilated pupils, tremor + sweating

- **Antihistamines**
  - Cross BBB (esp. 1st gen) → producing varying degrees of sedation
  - Sedation caused through binding to H1 receptors in CNS
    - ↓ ACh released by neurons in reticular activating sys

- Often found in OTC sleep preps (over-the-counter)
- E.g. anything with **Diphenhydramine** → Nytol, Unisom, Sleepeze
  - Delayed for a few days

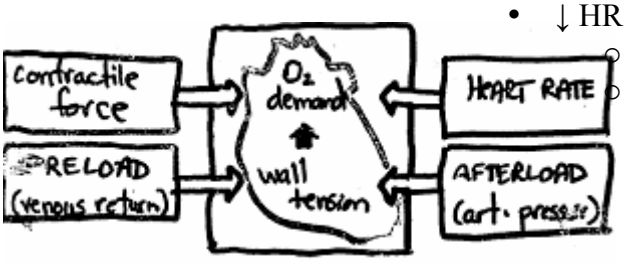
- Drugs of abuse
  - Cond in which indiv feels compelled to repeatedly admin psychoactive drug
  - **Physical dependence**: w/o drug = physical signs of withdrawal present
    - E.g. nausea, vomiting, sweating, chills …
  - **Psychological dependence**: need for stim / pleasure / escape reality
  - CNS depressants
    - *Alcohols + glycols*
      - **Ethanol**, methanol, ethylene glycol, isopropyl alcohol
    - *Barbiturates + benzodiazepines*
      - Pentobarbital (Nembutal), Flunitrazepam (**Rohypnol**)
      - γ-hydroxybutyrate (**GHB**)
        - ↑ use in sex assaults + thefts
        - Both have effects like GABA
        - Combined w/ alcohol = ↑↑ loss of consciousness + amnesia
    - *Opioids*
      - **Heroin**, Oxycodone (**Oxycontin**) → ↓ RR, coma, death…
  - CNS stimulants
    - *Amphetamine + derivs*
      - Amphetamine, methamphetamine, 3,4-methylenedioxy-methamphetamine (**MDMA**)
    - *Other stims*
      - **Cocaine**, caffeine, nicotine → appetite suppressant
  - Other psychoactive drugs
    - *Cannabis + derivs*
      - **Marijuana**, dronabinol (Marinol) → THC R, Nabilone (Cesamet)
    - *Hallucinogens*
      - Lysergic acid diethylamide (**LSD**), mescaline + psilocybin, phencyclidine (**PCP**)
- Examples of drugs of abuse
  - **Rohypnol** (**roofies**) / Flunitrazepam → opioid
    - Benzodiazepine for short-term treatment of insomnia
    - Sedative hypnotic
    - Preanesthetic med
    - Physiological fx similar to diazepam but *10x more potent*
  - **GHB** → opioid
    - Occurs naturally in mammalian brain
    - Acts on *GABA receptors* + GHB receptors
      - Either directly or through conversion GHB → GABA
    - Syn = mixing γ-butyrolactone (paint remover) + NaOH in proper amnts
    - Tinted blue w/ food colouring
      - *Biggest dangers* of GHB lies in possibility of ingesting impurities / unreacted substrates → e.g. NaOH …

        - Adverse fx
            - CNS = amnesia, coma, unconsciousness
            - CV = bradycardia, hypotension
            - Respiratory = depression
            - Other = ↓ muscular tone
    - **MDMA** → CNS stim
        - Aka Ecstasy, XTC, E, Adam → 3,4-MethyleneDioxyMethAmphetamine
        - Psychedelic amphetamine
            - Produce strong feelings of comfort, empathy + connectn to others
        - Substantial ↑ BP + ↑ HR = cardiac injury
            - Feel extremely drained day after use → hangover
        - Can die if in combo w/ alcohol
    - **Methamphetamine** → CNS stim
        - Poor-man's cocaine
        - ↑ HR, ↑BP, ↑T°, ↓ appetite
        - Chronic use = **amphetamine psychosis**
            - Paranoia, auditory + visual hallucinations, self-absorption, irritability, aggressive + erratic behav + picking at skin
        - **Methylphenidate** (**Ritalin**) used as CNS stim w/ similar fx
            - For **ADHD**, ↓ appetite…
        - **Meth mouth** symptoms
            - **Dry mouth**
                - Saliva acts as buffer vs. acidic subs
                - Meth dries out salivary glands
                - Acidic sub eat away at minerals in tooth enamel
                    - Causes holes / weak spots that become cavities
            - **Tooth decay**
                - Meth users notorious for trying to treat **cottonmouth** w/ lots of sugary soda
                - Bact feed on sugars → secrete acid = more tooth decay
                - Meth users less likely to floss, brush, + rinse when high
                - Meth also made from HCl
                - Users smoke meth → acid in drug erodes tooth enamel
            - **Cracked teeth**
                - Drug makes them feel anxious / nervous
                - Users clench / grind teeth → dev cracks in teeth
            - **Gum disease**
                - Meth causes BVs that supply blood to oral tissue to shrink
                - Repeated shrinking = BVs don't recover + tissues die
    - **Ketamine** (**Special K**)
        - Dissociative anaesthetic for human + veterinary
            - Physical fx similar to PCP
            - Visual fx of LSD
        - ↓ doses produce exp called **K-Land** → mellow, colourful "wonder world"
        - ↑ doses = fx called **K-Hole** / out of body / near-death exp (dissociated)
        - Can cause delirium, amnesia, dep + long-term mem + cog difficulties

Anti-Anginals

- **Angina pectoris**
  - **Angina**: crushing chest pain caused by accumulation of metabs in ♥
    - Basically have ↑ symp NS fx
    - **Ischemia**: lack of flow
    - **Arteries**: pipe that supplies nutrients to body
    - Stim nerve endings w/ ↑ metabs
      - ↓ [metab] = ↓ pain = slower contractions
      - Main therapy = ↓ *work of* ♥
  - **Atherosclerosis**
    - Most common cause → 80+% angina patients
    - Patients w/ atherosclerosis = **Stable angina** → const atherosclerosis
      - Predictable, recurrent = ↑ metabs that stim neurons
      - Precipitated by exertion
    - Patients normal / atherosclerosis = **Prinzmetal's angina**
      - Variant = BVs constrict anywhere / anytime
        - ↓ diameter = ↓ flow = build up of metabs
    - Largest grp = b/w both sample
  - **Unstable angina**: rapidly progressing w/ + freq + severity
    - ↓ O_2 = send out pain → death if untreated
    - Danger of myocardial infarction
      - Subset of ¢s = w/o O_2
      - Complain have pain = ¢s die → ♥ attack

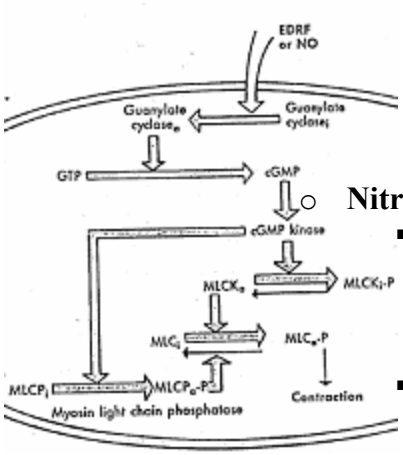
- Successful therapy
  - ↑ **O_2 supply**
    - Pharmacogenomics
      - Drugs fn diff in ppl b/c of genetics
        - E.g. ↑ O_2 in haemoglobin
    - **Extraction** of O_2 by ♥ = near maximal → even at rest
      - O_2 content of blood cannot be ↑ at normal P
    - **Delivery** of O_2 to ischemic zones can be ↑ by
      - 1) **Reversing vasospasm** (variant angina) → spont constrict = ↓d
      - 2) ↑ **coronary perfusion** = more blood in
      - 3) **Revascularization** = reorg pipes
    - Most pharm agents seek to ↓ O_2 REQs instead of above
  - ↓ **myocardial O_2 demand** = ↓ w
    - 40$ ♥ = mito → syn ATP = use O_2
    - Anti-anginal drugs will
      - ↓ preload = amnt of blood in
        - Set by wall tension → amnt of blood in ♥ chamber
          - E.g. 100 mL in α T of chamber
      - ↓ HR / contractility = ↓w = ↓ O_2
        - ↑ blood into ♥ req ↑w
        - Δ by ↓ blood in → ↓ F contraction = ↓ O_2



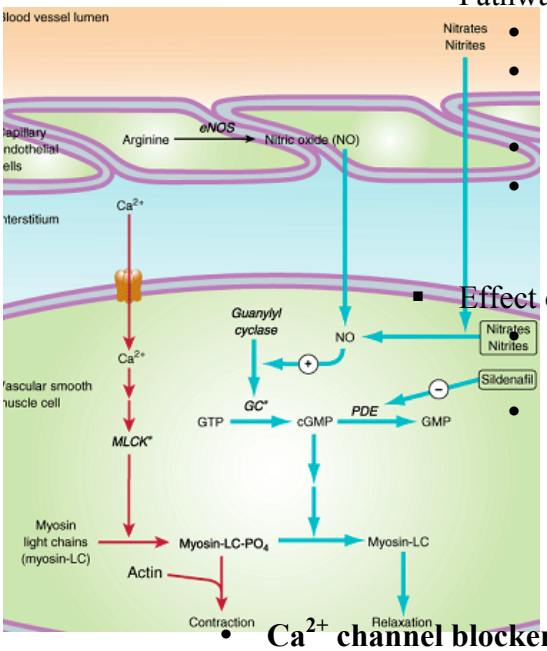
- ↓ after load = BP outside valve
    - Open aortic valve
    - Build up P = valve opens
    - ↑ BP outside
        - Need ↑F b/c P outside must be overcome
        - ↓ peripheral BP = ↓w needed
- 3 major classes
    - **Nitrates**
    - **β-blockers**
    - **Ca channel blockers**
        - ↓ contraction stim = ↓w
        - ↓ BP lots too
            - Symp ↑ then
            - Need combo therapy
    - Do combo of above 3 to treat angina → also relieve ischemia

- **Nitrates**
    - NO grps to syn nitrous oxide (N_2O) = boosts health of pipes
    - **Amyl Nitrite**: inhaled, very short duration of action (3-5 min)
        - For severe acute pain → gas = finished quickly
    - **Nitroglycerin**: well abs from GI tract but metab by liver
        - Can avoid w/ sublingual + aerosols (<1h $t_{½}$)
        - Well abs through skin (ointment / transdermal) (8-10hrs)
        - Also use i.v.
    - **Isosorbide dinitrate**: longer lasting b/c of active metabs
        - Have oral / sublingual preps
    - Major effect on venous capacitance vessels = pooling of blood
        - ↓ venous return + ↓ pre-load
        - Dilation of large epicardial vessels = ↑ blood flow to ischemic As
            - Supply ♥ w/ blood ↑ O_2 = ↓ metabs
        - At ↑ doses, dilation of arterioles ↓ BP = ↓ preload = ↓w
            - Mixed actions
    - Nitrates in **angina**
        - Action
            - ↓ O_2 req
            - ↓ preload / after-load (peripheral fx) = ↓w to open aortic valve
            - Reversal of vasospasm = stop ischemia
        - Useful for
            - Prophylaxis / acute treatment of angina
            - Stable + exertional angina
                - Prevent attack PRIOR to activity
            - Vasospastic angina
            - Basically any angina
                - Relieve pain of already established attack
        - Economics: inexpensive + proven safe

- Side fx
  - Headache = ↓BP to ♥ = ↓ blood to brain
  - Hypotension → stim symp NS
  - Reflex tachycardia → ↑HR = must ctrl otherwise useless therapy
  - Tolerance (**tachyphylaxis**)
    - Variable + unpredictable dev
    - Dev = **sulfhydryl** → proteins + aas ↓ = bad b/c must replenish to syn active metab
    - Need ↑ amnt of drug
    - Neuro-hormonal reflex + intravascular V = less of a reason

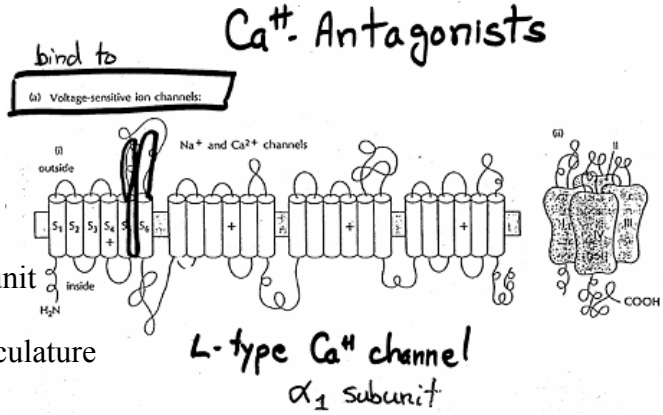


- **Nitrate *physiology***
  - Have **nitroglycerin** → nitrates → use cysteine stores to convert to s-nitrosothiol → NO → cGMP
    - Cys = depleted w/ ↑ [drug]
    - Get tolerance of nitroglycerine b/c no conversion to active metab
  - Or **nitroprusside** → nitrate ester → NO → cGMP
    - **cGMP** important for vasodilation = stats fx
  - Pathway

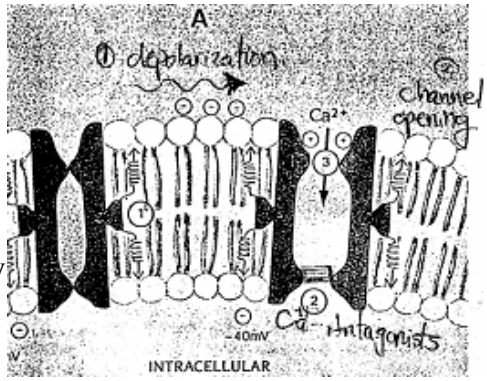


    - Contract / relax smooth muscles
    - **Myosin light chain kinase** (**MLCK**) interacts w/ actin = +P
      - Occurs = constrict
    - Relax w/ **myosin light chain phosphatase** (**MLCP**) = remove +P
    - cGMP in ¢ = stim cGMP kinase
      - ↓ intn w/ actin
      - ↑ stim MLCP = relax → ↓ contraction
  - Effect of nitrates on smooth muscle [ ]
  - Endothelium syn NO in ¢ w/ **NO synthetase** from **Arginine**
    - Stim syn of cGMP = for relaxation
  - **Ca^{2+} voltage-channels** open b/c depolarization of CM
    - Stim MLCK for contraction
    - Can block to ↓ MLCK = ↓ contraction
      - Prob = in cardiomyocytes too for contraction
      - But good b/c ↓ contraction = ↓w + vessels dilate

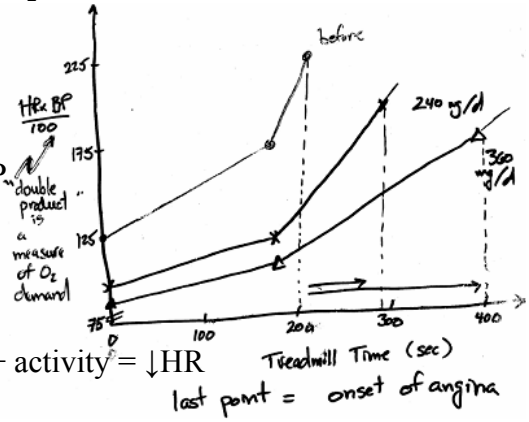
- **Ca^{2+} channel blockers**



  - Ca2+ channel
    - 6 TMDs
    - 4 motifs
    - α1 = where antags bind
    - L-type channel on right
  - 3 classes w/ all diff binding sites on α1 subunit
    - Can gauge how much want in
    - Tissue selective too → i.e. ♥ vs. vasculature
    - All have interactions w/ each other
      - Alkylamine bad w/ both but pyridine + thiazepine = synergists



- 1) **Phenylalkylamine**
  - Block depol of Ca channel = Δ conformn
    - ↓AV conduction = ↓ impulse + ↓ activity
      - ↓ contraction = ↓w
    - e.g. **Verapamil**
  - Moderate vasodilator = ↓w
    - Dilation of coronaries = ↑ flow to ischemic zones
    - Peripheral vasodilation = ↓ afterload of O_2 demand
- 2) **Dihydropyridine**
  - Ca^{2+} antag
    - No fx on AV conduction = ↓ fx of fns
    - E.g. **Nifedipine**
  - Potent vasodilator = pool blood in veins = ↓ BP
  - May ↑HR = ↑ affinity
- 3) **Benzothiazepine**
  - Block depol of Ca channel = plug
    - E.g. **Diltiazem** → graph
  - Mild slowing of AV conduction = ↓ impulses + activity = ↓HR
  - Moderate peripheral/coronary vasodilation
    - ↓ BP = takes care of **vasospasms** = ↓w
  - **Diltiazem** + **Verapamil** also ↓ rate + ↓F to further ↓ O_2 demand
    - Good b/c blocks Ca^{2+} from entering
    - w/ NO to ↓HR
    - Diltiazem on angina of effort = prolongs t of symp appearance



- **Ca channel blocker *physiology***
  - Well abs orally → 90% protein bound in plasma
  - Hepatic metab important
    - Diltiazem + verapamil have active metabs
  - Side fx
    - Peripheral edema (N > V > D)
    - Flushing, dizziness (N) = rapid ↓ BP
    - Constipation (V)
  - Toxicity
    - AV block, hypotension, ♥ failure
    - Block Ca^{2+} = *no contraction* done
  - Clinical fx
    - Prevent focal coronary artery spasm
      - b/c ↓ contraction
    - Management of angina
    - Superventricular tachycardia
      - Atrial arrhythmia = ¢ not getting O_2 supply
      - To threshold of finding = send out impulses
      - ¢s do their own b/c diseased = ↓ O_2 → chain w/ healthy ¢s
    - Improvement of exercise endurance

- **β blockers**
  - β1 receptors in cardiomyocytes
    - Stim w/ NE = ↑F contraction
  - β in SA node = ↑ stim = ↑HR
    - Have β-blockers for these
  - Block **β1 receptors**
    - ↓ F of contraction of ♥
    - ↓ HR
    - ↓ Renin secretion
    - But all ↓w of ♥
  - Block **β2 receptors**
    - ↑ airway resistance in bronchioles = constrict airway → ↑ anxiety too
    - ↑ vascular resistance in capillary beds

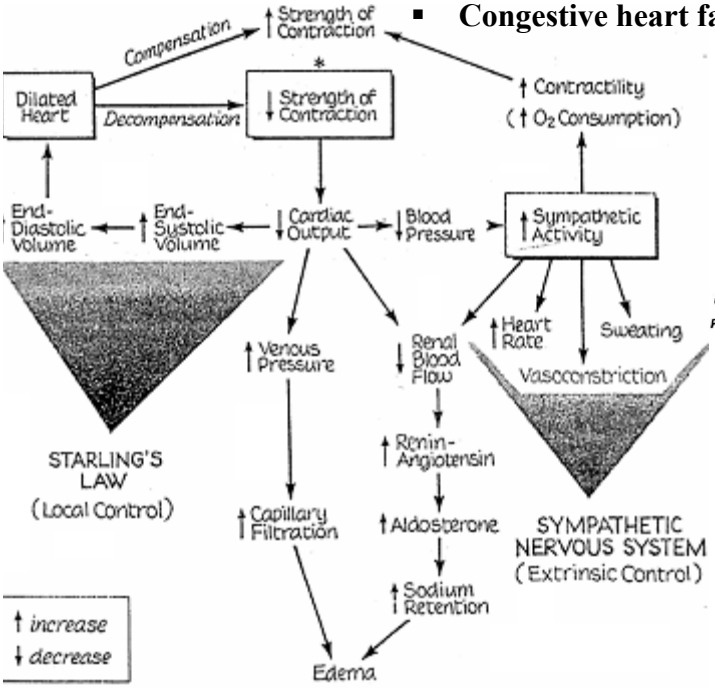
Organ	Adrenergic Response	Receptor
Heart rate	↑↑↑	β1
F of contraction	↑↑↑	β1
Blood vessels	Vasoconstriction	α1 + α2
	Vasodilation	β2
Lungs (bronchi)	Bronchodilation	β2

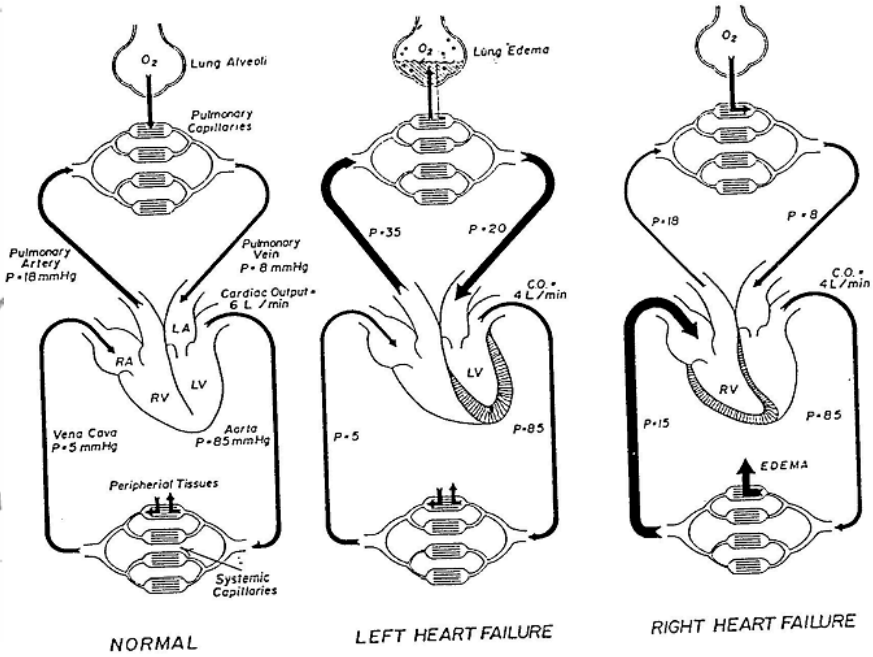
  - **β-blockers**
    - Physio fn
      - ↓ myocardial O2 demand by:
        - ↓ HR + ↓ contractility
      - But does vasoconstriction of BVs = must combo w/ other drugs
    - **β2 receptors**
      - Affect glycogenolysis
      - Affect lipid profiles
    - **β1 blockers**
      - **Atenolol**
      - **Metoprolol**
    - Non-selective β blocker → **Propanolol**

Inotropes

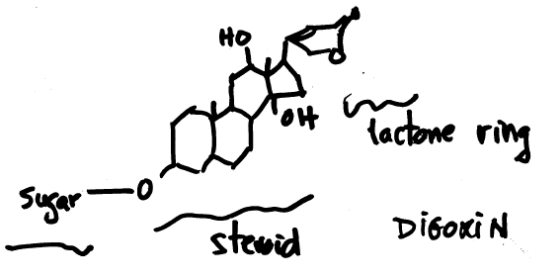
- Compensatory mechanisms → no actual treatment for ♥ failure → drugs minimize dmg
  1) **Sympathetic activity**
     - ↓ in CO (5.5L) = ↓BP b/c ↓ body V
     - ↑symp NS = ↑ vasoconstriction + contractility to ↑BP
     - **Starling's law**
       - **Local ctrl**: sense P + exert P to push blood out
         - Blood pools in ventricles
         - ↑ blood in = better sense P = easy to push out = ↑ contractn
       - No dmg = compensation
       - ♥ failure = decompensation
         - No sensing = bad contraction → blood stays in
         - Can be b/c of genetic defects → myosin, actin…
         - ↓Ca^{2+} = ↓F contraction → also genetic defect
  2) Activation of **renin-angiotensin** system
     - ↑ venous P = pooling of blood outside ♥ → ↑BP peripheral
     - Aldosterone further ↑ BP = prob → get edema
  3) **Myocardial hypertrophy**
     - ↑ load = muscle like bicep gets big → same in ♥
     - Compensatory mech = try to work harder = bad if not dev athletically

4) **Long term remodelling of ♥ + vasculature**
   - ♥ remodelling = compensation too
   - ↑ blood in ventricles
   - Hypertrophy + remodelling in athletes = good mechs
     - Bad if not like that → e.g. genetic defect, unhealthy…
   - May exacerbate CHF by ↑ load on failing ♥
   - **Congestive heart failure**: ♥ unable to pump enough blood for whole body

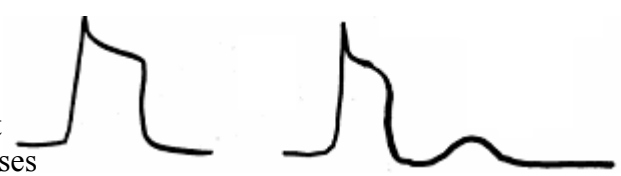




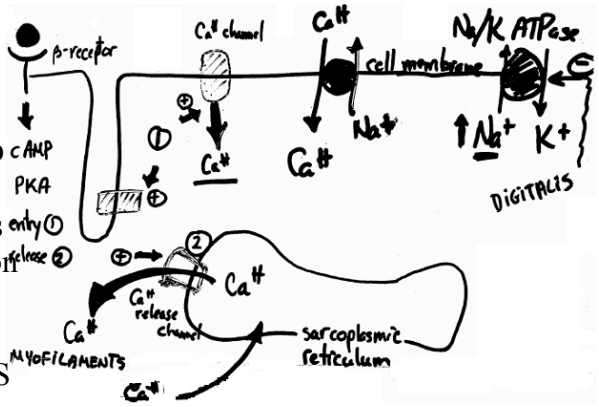
   - **Left ♥ failure**
     - ↓CO → ↑ blood in left side
     - Blood remains in lungs = lung edema
       - Can't breathe as well
     - Load ventricles = hypertrophy
   - **Right ♥ failure**
     - Back-up into venous side
     - Blood can't get into heart easily = stays in body
     - Pool blood in ankles, feet, legs = ankle edema
   - #1 goal = ↑ cardiac output GRAPH
     - Can measure ventricular fn via **ventricular end diastolic P**
       - End of relaxation = time just prior to contraction → CO
       - Blood goes in to a max V
       - Greater EDP = ↑F contraction in healthy ♥ = ↑CO
     - Can't just ↑V
     - ♥ muscles stretch ↑ = Starling curve ↓
       - Can keep trying but ineffective past certain point
     - Symptoms of XS pressure
       - **Fatigue** =↓O2 to brain
       - **Dyspnea** = rapid shallow breath → lung edema
       - Also edema



- **Cardiac glycosides**
  - Used for over 200 yrs in treatment of CHF
  - Obtained from **foxglove** (**Digitalis**) plant
  - **Digoxin** → thought to ↓edema = diuretic
    - Hydrophilic
    - Excreted by kidney
    - Rapid onset
    - $t_{½}$ = 1.5 days
  - **Digitoxin**
    - Lipophilic
    - Highly protein bound
    - Metab by liver
    - Longer $t_{½}$ = 5 days
  - Mech of action
    - 1) Mechanical effect
      - ↑F of contraction
      - Inhibition of **Na^+/K^+ ATPase**
    - 2) Electrical effects
      - ↓ AV conduction = direct effect
        - Atria → ventricle impulses
      - Stim of vagus = indirect
        - Innervates ♥ = ↓ HR
      - After depol + ectopic beats = toxic
        - Arrhythmias gen
        - Normal depol
          - Resting memb pot = -90 mV
          - Na^+ in, Ca^{2+} in, K^+ in
        - Ectopic beat = ↑ resting memb pot to -60 mV
          - ↑% get impulse = arrhythmia
    - Present use controversial b/c ↑↑↑ risk of toxicity → ↓ therapeutic index

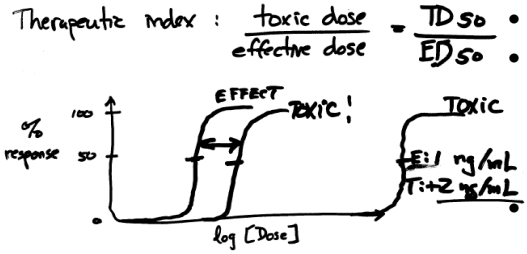


  - Physiology of cardiac glycosides
    - **Digitalis** blocks K^+ in / Na^+ out
      - Na^+ builds up in cardiomyocytes
      - Get Na^+ out = via **Na^+/Ca^{2+} pump**
    - Ca^{2+} to sacroplasmic reticulum
      - Now release Ca^{2+} to myofilaments
    - Intn of actin/myosin happens = contraction
    - Reuptake to SR afterwards
    - End effect = ↑ F of contraction
      - As result = ♥ ↓dilated + ↓symp NS
      - ↓ HR + ↓ peripheral R
    - Prob = XS Ca^{2+} stays = Δ resting memb pot
      - More likely to arrhythmia → dose very narrow

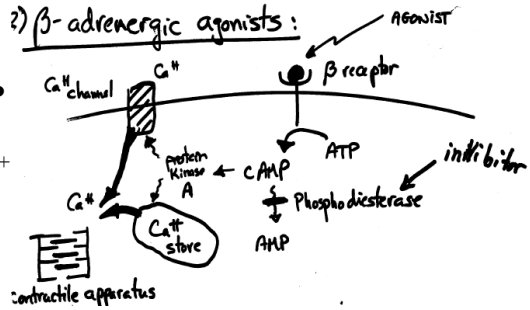


  - Toxicity
    - Nausea, vomiting, arrhythmia
    - Often associated w/ ↓ K^+ → block Na^+/K^+ pump
      - Cardiac glycosides bind to same site as K = competitive inhibitor
      - ↑ K^+ outside = drug less effective
      - Electrolyte imbalance = need to Δ dose b/c competition

- Treatment = supplement K^+ digoxin antibodies → **Digibind**
- Watch for
  - Diuretics that ↓ $[K^+]$ plasma
  - Drug interferes w/ clearance / metab = **quinidine** / **verpamil**
    - Watch dose b/c ↓ metab
    - Major diff = good
    - Want diff of 10+ → Digoxin = 1 = very narrow
  - Renal/liver dysfn

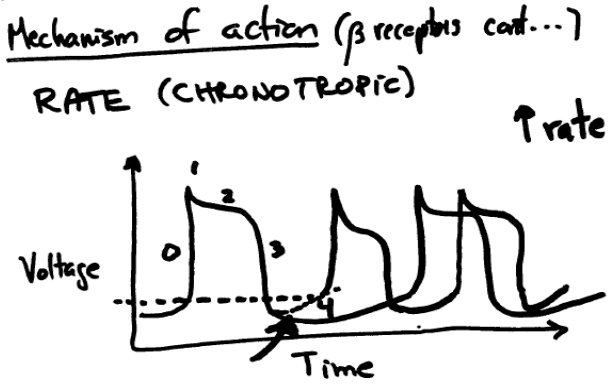


- **β-adrenergic agonists**
  - In CHF = stim cardiac performance by +ve inotropic effect
    - α1 + α2 = constrict BVs
    - β1 + β2 = dilate BVs
  - Physiology of β-adrenergic receptors
    - Bind to β-receptor = convert ATP → **cAMP**
    - ↑cAMP → ↑**PKA**
      - Stim Ca^{2+} into ¢ + SR to release Ca^{2+}
    - ↑Ca^{2+} = to contractile apparatus

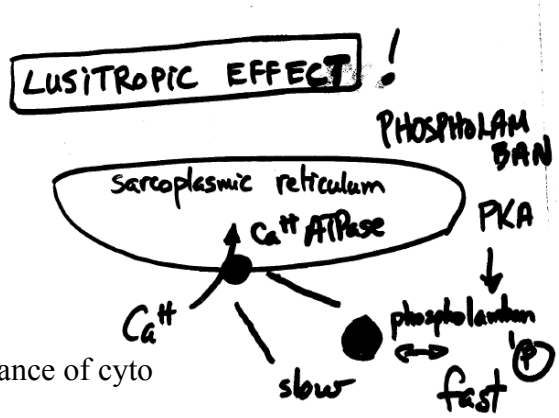


  - **Dopamine**
    - Binds to β receptor
    - ↑ HR + contractility
    - ↑ dose → vasoconstriction through α receptor activation
    - ↓ dose → ↑ renal blood flow
      - Na^+/H_2O excretion through dopamine receptor → restore kidney fn
    - Drug of choice for shock/acute ♥ failure
  - **Dobutamine**
    - Synthetic β1 agonist
    - No vasoconstrictor activity
    - ↑ CO w/ little effect on HR
    - Can enhance AV conduction = worsen atrial *arrhythmias*
    - Use of both limited by arrhythmogenic props → short $t_{½}$ + tolerance
      - Useful if want to ↑CO + not Δ anything else
      - E.g. patient symp activity ↑↑
  - **Prenalterol**, **Xamoterol**
    - Partial β1 agonist that stim receptor
      - Blocks out effect of endogenous catecholamine
    - Prevents NE binding
    - ↓ stim = not whole thing

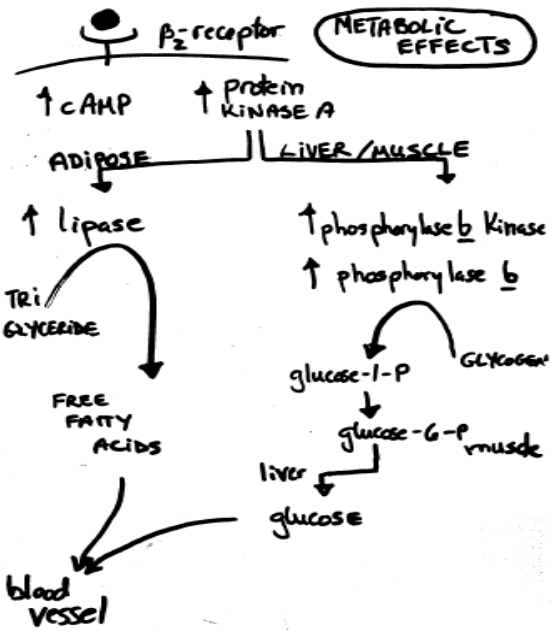
- Mech of action of β receptors
  - β stim = ↑HR
    - +ve inotropes = ↑F contraction
    - –ve inotropes = ↓F contraction
      - Like Ca^{2+} channel blockers
  - Rate = chronotropic
    - β stim = ↑ rate of contraction



- Phase 4 = upstroke before Na^+ opens
  - ↑AP b/c ↑ depol
- All abt cAMP generation
- Can use drug to Δ HR



- **Lusitropic effect**
  - = relaxation of ventricles
  - ↑ contraction # = must relax faster too
    - Governed by rate of Ca^{2+} clearance of cyto
  - Use **phospholamban**
    - Part of subunit of **Ca^{2+} ATPase pump** to SR
    - Usu inhibits pump
    - **PKA** quickly phosphorylates pump
    - +P = remove intn = ↑ Ca^{2+} reuptake



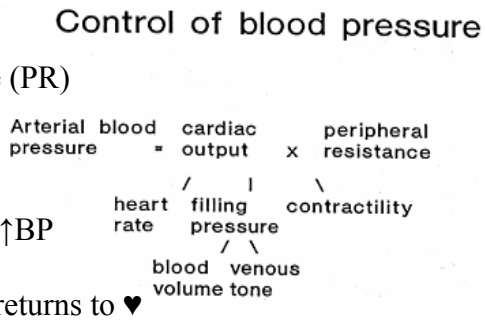
- **Metabolic effects**
  - ↑cAMP → ↑PKA
  - In adipose
    - ↑ lipase activity
    - Breakdown TGs to free FAs
      - Mobilized in BVs
    - #1 fuel of cardiomyocytes = fats
    - 70% metab of body = fat
  - In liver / muscle
    - ↑ Phosphorylase kinase B (PKB)
    - ↑ Phosphorylase B
    - Converts glycogen into glucose-1-P
    - To G6P in muscle
    - To glucose in liver → to BVs

- Cyclic nucleotide phosphodiesterase inhibition
  - Bipyridines → **Amrinone**, **milrinone**
  - ↑ cAMP lvls by inhibiting PDE in BVs
  - ↑ CO by contractility
    - Also relax smooth muscle = ↓ afterload
  - Numerous adverse fx associated w/ non-cardiac fx of amrinone
    - Nausea
    - Thrombocytopenia
    - ↓ platelets
    - XS Bleeding
- Calcium sensitizers
  - E.g. **Sulmazole**, **Pimobendan**
  - ↑ affinity off Troponin C for Ca^{2+} leading to ↑ contractility
    - Sensitizes contractile apparatus
  - Advantage = tend not to get Ca^{2+} overload
    - Sensitizing as opposed to mobilization

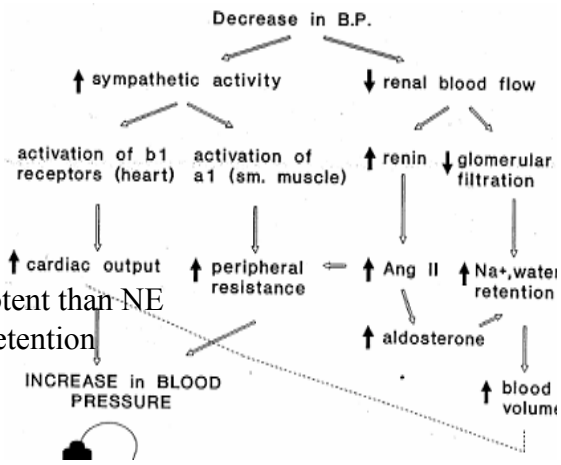
Antihypertensive

- **Hypertension**
  - BP ctrlled by vascular, hormonal + kidney health
    - ♥ needs ↑w to pump out blood
    - ↑ hyperT prevalence = esp. in elderly
      - Have = forever / very long-term
  - = Risk factor for
    - Cardiac hypertrophy = bad if not athletic
    - Congestive heart failure = inefficient cardiomyocytes
    - Stroke = burst BVs
    - Coronary artery disease = ♥ circulation probs
  - **Essential hypertension**
    - No specific etiology
    - 95% cases
    - Factors: hormones, vascular dmg, rxn to diff factors
  - **Secondary hypertension**
    - Cause = clear → usu cancer
    - 5-10% cases
    - E.g. pheochromocytoma: stim adrenaline = ↑ constriction
    - E.g. Aldosterone-producing carcinomas ↑ H_2O retention = ↑BP
  - **Mild hypertension**
    - 140-150 / 90-104 mm Hg → want 120/80
      - Systolic / diastolic pressure
    - 80% all patients treated
    - Take 3 readings on 3 occasions → b/c BP Δs based on excitability

- **Ctrl of BP**
  - **Arterial BP** = cardiac output (CO) x peripheral resistance (PR)
    - i.e. V of blood x R of fluid
    - CO = based on 3 factors:
      - **HR** ↑ = ↑CO = ↑BP
      - **Contractility** → ↑ preload = ↑blood out = ↑BP
      - **Filling P**: based on blood V + venous tone
        - **Venous tone**: how effective blood returns to ♥



  - ↓BP restored via 2 mechs
    - ↑ symp activity
      - Brain senses ↓ in glucose
      - Activates β1 receptors in ♥ = ↑CO
      - Activate α1 receptors = ↑PR
      - ↑ in BP → absent in ppl w/ hyperT
    - ↓ renal blood flow
      - ↑renin → ↑ Ang II = ↑ aldosterone
        - Angiotensin II = 40x more potent than NE
      - ↓glomerular filtration = ↑ Na^+/H_2O retention
        - ↓ urine production = ↑BP



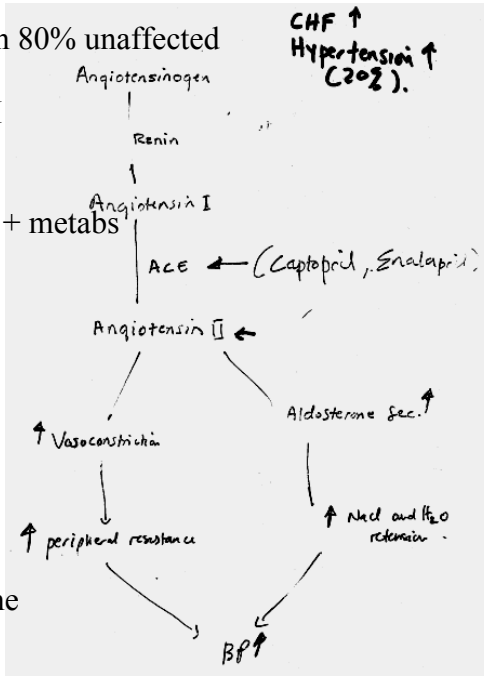
- Antihypertensive drugs summary
  - All relieve P
  - Diuretics = manipulate kidney to remove salts
  - β-blockers = ↓w of ♥
  - ACE inhibitors = ↓ aldosterone to ↓ H_2O retention
  - Ca-channel blockers = ↓ contractility + dilating pipes
  - Others: Prazosin, Hydralazine, Minoxidil, Nitrates …
    - Know classes, mech + big picture

- **Diuretics**
  - ↓BP + remove Na^+
    - Also ↓electrolytes in general like K^+, Cl^-
  - Classes of diuretics
    - Loop = high-ceiling → e.g. **furosemide**
      - ↑ potency for 200+ BP
      - Work on loop of Henle
    - Thiazide = moderate → e.g. **hydrochlorothiazide**
    - Potassium-sparing → e.g. spironolactone, triamterene
      - No K^+ removal = retain H_2O
  - **Loop** diuretics
    - Most potent of natriuretic agents
    - Rapid onset + intense diuresis → short duration of action
    - Enhance excretion of Na, Cl, K, Ca, Mg → inhibition of Na/K/2Cl reabs
    - Site of action = entire thick ascending limb
      - e.g. **Furosemide**
    - Side fx
      - **Ototoxicity** = affect hearing + balance
      - Hypotension, hypo K+, arrhythmias
  - **Thiazide** diuretics
    - Weakly natriuretic → but most common
    - Prolonged duration of action
    - ↑ excretion of Na, Cl, K → inhibit Na/Cl
      - e.g. **Hydrochlorothiazide**
    - Side fx
      - ↑K^+, hypotension, uric acid (gout), Ca^{2+} build-up

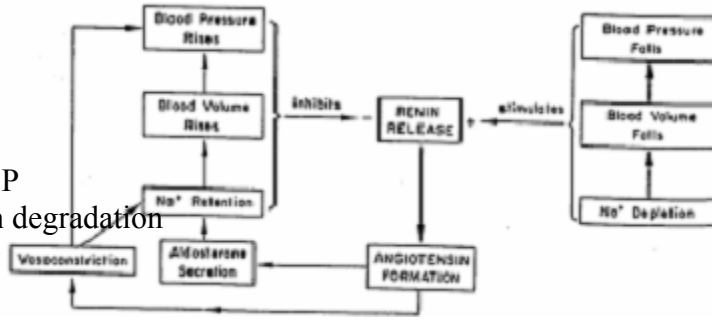
  - **Potassium-sparing** diuretics
    - Weakly natriuretic
    - Potent anti-**kalluretic** agent
      - Prevents loss of K^+
      - Inhibits aldosterone mediated reabs of Na
    - **Spironolactone**
      - Effective if aldosterone elevated
      - Delayed onset → prolonged action (2-3 days)
      - Side fx: menstrual irregularities
        - **Gynecomastia** = ↑ in breast size in men

        - **Triamterene**
            - Effective regardless
            - Rapid onset → long duration (12-18 hrs)
        - Side of action
            - Last ½ of distal tubule + cortical collecting duct
    - Complications of thiazide / loop agent therapy
        - Extracellular fluid volume depletion = XS
        - K depletion → digoxin toxicity
        - Hypochloremia = $\downarrow Cl^-$
        - **Deafness** → loop agents only
        - **Hypocalcaemia** = $\downarrow Ca^{2+}$ → loop agents only
    - Therapeutic uses
        - **Loop** diuretics
            - ↓ acute edema in CHF
            - Rapid onset of action + rapid, intense diuresis
        - Thiazides
            - α-hypertensive after 3-7 days
                - BP stabilizes at ↓ lvl w/o further major diuretic fx
            - ↓excretion of Ca^{2+} in hypercalciuria = kidney stones (need ↑t)
        - K^+ sparing
            - Protects vs. K^+ loss (combo w/ other diuretics)

- **Angiotensinogen** pathway
    - Upreg system in 20% cases
        - CHF↑ + ↑Hypertension
        - If block = ppl unaffected here → still get benefit in 80% unaffected
    - Angiotensinogen → Angiotensin I via cat of Renin
    - Ang I cat by **ACE** (Angiotensin converting enz) to Ang II
        - ACE inhibitors = Captopril, Enalapril
    - Ang II = ↑ BP
    - To make products = peptides degraded to syn active mlcs + metabs



- ACE **inhibitors**
    - E.g. Captopril, Enalapril
    - Renin = rate limiting step
    - **Ang II**
        - Preload
            - ↑ Aldosterone release
                - Na^+/H_2O retention + K^+ excretion
            - **Arteriole dilation** = direct fx
            - **Venous dilation** = withdrawal of symp tone
        - Afterload
            - ↑ Vasoconstriction via receptors
        - KO = ↓ constriction + aldosterone = ↓ BP
        - Also facilitates symp outflow → ↓symp to ↓BP
            - Slight ↓ in HR = ↓ stim of SA node



- **ACE**
  - Helps to cat syn of Ang II → ↑BP
  - Also responsible for **bradykinin** degradation
    - Bradykinin = vasodilator
    - ACE degrades it
    - Inhibit ACE = ↑bradykinin = ↓BP b/c ↑dilation
  - Inhibit = ↓ACE II syn
- ↓BP by ↓PR
  - No reflex ↑ in symp activity / HR
  - Patients w/ ↓Na^+ (serum) = ↓ response to inhibitors
    - B/c drug ↓ Na retention
    - Ineffective b/c not much Na to retain = little ↓ in BP

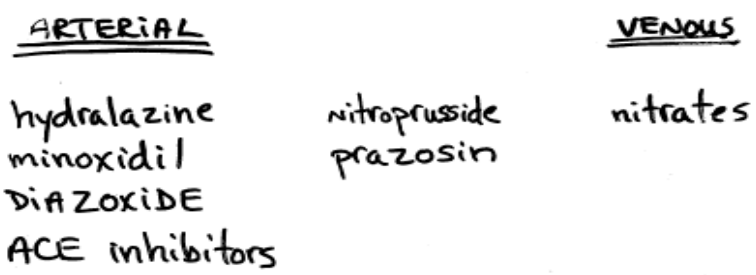
- **Captopril**
  - Rapidly abs but abs ↓ by food (1h before meals)
  - Max response = 2-4h after dose
  - Metab by liver
  - 50% excreted by kidney (unchanged)
  - Side fx / toxicity = rare → only in long-term
    - Rash
    - Dry cough
    - ↓ taste sensation
    - Severe hypotension (1st dose) → ↑diameter of pipes
    - Proteinurea
- **Enalapril**
  - Metab by liver to active cmpd prodrug → **enalaprilate** = active
  - Longer $t_{½}$ (10x)
  - Others = **lisinopril**, **fosinopril** = NOT TESTED
- ACE in **CHF**
  - ♥ failure = nothing going out
  - ACE allows cardiomyocytes to ↓w = good
  - ↓ afterload
    - ↑CO
    - ↓preload (b/c ↓ symp NS activity)
    - ↓HR
  - Hypertension
    - Mild / severe = renin-dep
  - 1st drugs of choice
    - ACE inhibitor = ↓BP little = usu combo w/ diuretics
    - Combine w/ diuretic / other antihypertensives

- **Vasodilator** effects
  - For both sys / diastolic → need combos
  - **Arterial**
    - Relax arterial smooth muscle preferentially = ↑ diameter to ↓BP

- Result in ↓ afterload
- Little venous dilation ↑preload + ↑return
- ↓BP results in reflex ↑HR

- Venous
  - Results in pooling of blood = in veins
  - ↓preload = ↓w

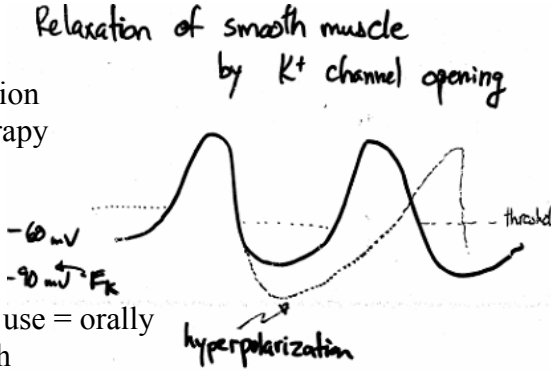
- Drugs
  - Arteriolar dilators
    - Hydralazine
    - Minoxidil
    - Diazoxide
    - ACE inhibitors
  - Mixed dilators
    - Nitroprusside
    - Prazosin
  - Venodilators
    - Nitrates



- **Arteriolar vasodilators**
  - Relax arterial smooth muscle preferentially
    - For mechs that normally work → normal
    - ↑dosage = makes BP worse
      - Useful = potent at ↓BP → brain ↑HR to reg
    - Potent reduction of arteriolar resistance = ↓ afterload
  - Sig reflex stim of adrenergic outflow
  - Renal fx
    - Na^+ + H_2O retention
    - ↑renin = ↑Ang II = ↑aldosterone
    - Counteracts antihypertensive fx

  - **Hydralazine**
    - Moderately effective
    - Used in hypertensive crisis
      - E.g. had stroke → nothing else worked
      - Use b/c person in life or death sit
    - Highly metab → N-acetylation, glucuronidation, hydroxylation
    - Unknown mech of action
    - Side fx
      - Genetically slow acetylators more susceptible → ↑ side fx
      - Reflex cardiac stim
      - Na^+ + H_2O retention
      - **Lupus-like syndrome**
        - Autoimmune disease → Abs attack own body

- **Diazoxide**
  - Powerful non-diuretic thiazide
  - Usu reserved for hyper emergency
  - Side fx
    - Reflex cardiac stim
    - $Na^+ + H_2O$ retention
    - **Hyperglycemia** = Δs in glu build up
- **Minoxidil**
  - Powerful oral vasodilator
  - Usu reserved for refractory hypertension
    - Not responding to normal therapy
  - Activated by liver metab (sulfate)
  - Side fx
    - Reflux cardiac stim
    - $Na^+ + H_2O$ retention
    - **Hypertrichosis** w/ prolonged use = orally
      - Main use = hair growth

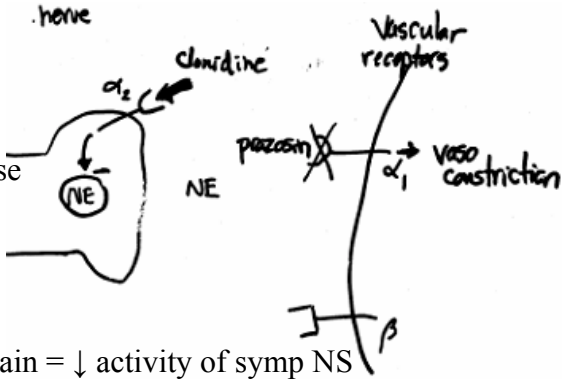


- **Pinacidil**
  - K^+ channel opening → memb hyperpolarization
    - Same for mech of diazoxide + minoxidil
    - More K^+ leaves ¢ = more –ve
    - Need ↑ stim to Δ
  - Doesn't let smooth muscle constrict

- Mixed action vasodilators
  - **Nitroprusside** → $NOFe(CN)_5$
    - i.v. treatment for severe hypertension
    - 1st choice in life-threatening hypertension
      - Rapid onset, consistent fx, ↓ toxicity
    - Relaxes both arteriolar / venous beds
    - Generates nitric oxide in circulation (like nitrates)
    - Toxic fx
      - Excessive vasodilation
      - **Thiocyanate poisoning**
        - Get cyanide poisoning → no O_2 into erythrocytes
        - i.e. confusion, delirium

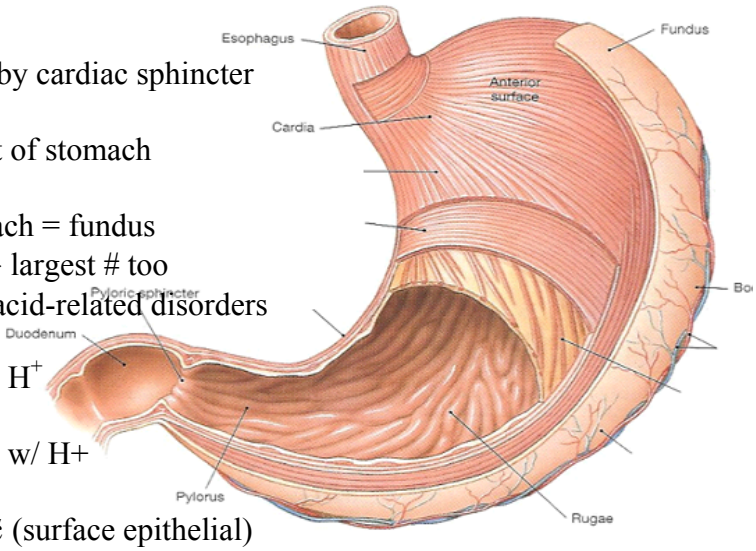
  - **Prazosin**
    - Fx similar to nitroprusside → mech Δs
    - Blocks post-syn α1 receptors (no α2 blocking)
      - NE + Epi = no action → dilation
      - Rebound effect of adrenergic-receptor blockers (agonists)
    - Tolerance dev w/ continued admin
      - B/c of renin-angiotensin sys
      - ↑ constriction

- **β blockers**
  - Do hypotension
    - ↓ CO = ↓HR + ↓ contractility
  - ↓ renin release in kidneys = ↓Ang II = ↓ constriction → can get R
    - ↓aldosterone = ↓Na^+ + H_2O retention = ↓BV
  - May take several weeks to dev full fx
  - Non-selective = **propanolol**
  - β1 selective = **atenolol**
  - Understand comboing
    - Diuretics, ACE + β = most exp w/ use
    - Newer = ↑ side fx
  - **Clonidine**
    - Centrally acting adrenergic drug
    - α2 agonist
    - ↓ central adrenergic outflow from brain = ↓ activity of symp NS
    - Causes Na^+/H_2O retention → used w/ diuretic
    - Side fx
      - Sedation, dry nasal mucosa
    - Use
      - Test for pheochromocytoma
        - Block central comm = from NS
        - If no fx after using drug = know fx not syn by brain
      - Does not ↓ renal blood flow / glomerular filtration rate
        - Good for concomitant renal disease
        - No kidney fx
    - Also **α-methyl dopa** = ↓ adrenergic output formn in CNS

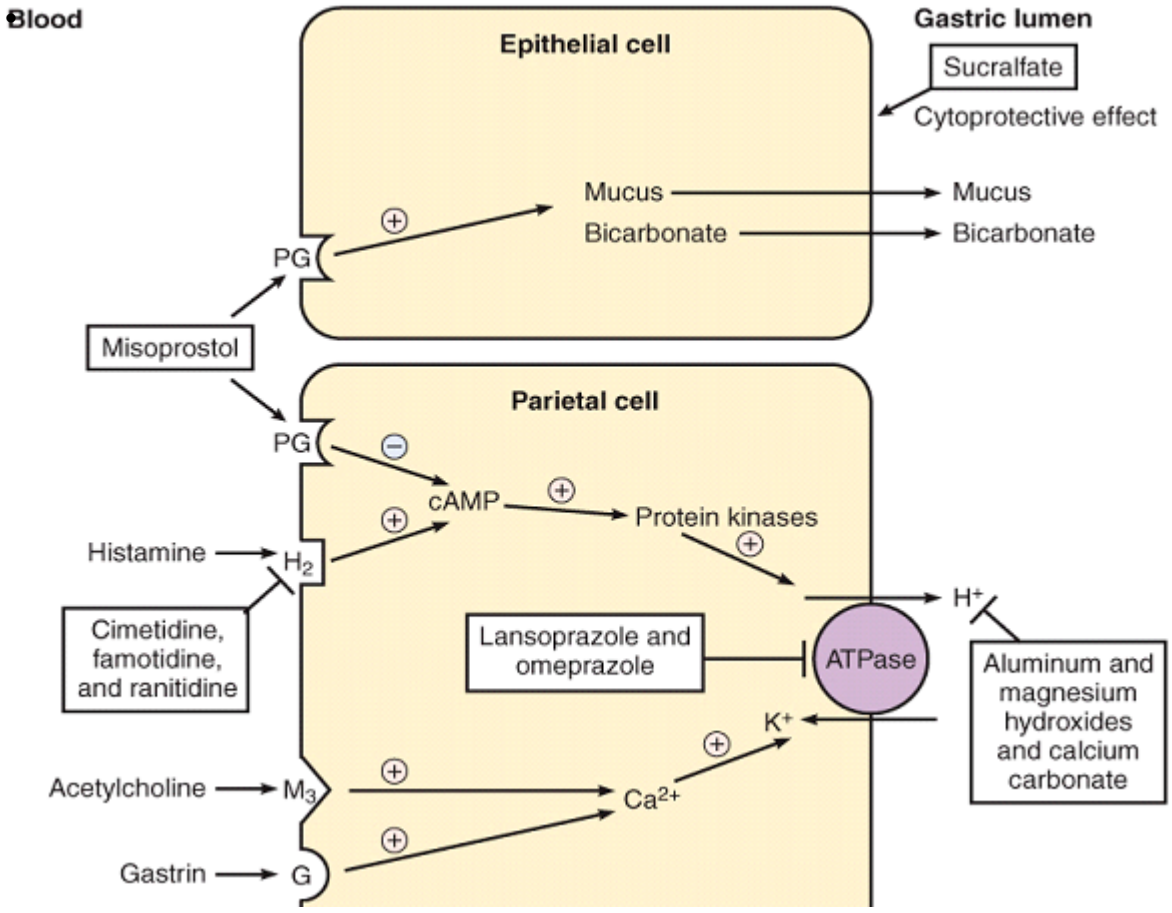


Gastrointestinal Pharmacology

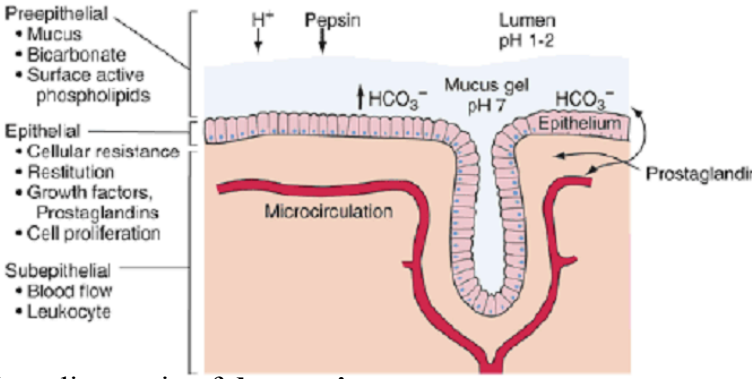
- Stomach
  - 3 parts: Fundus, Body, Antrum
  - 3 fnal areas each w/ specific glands
    - **Cardiac zone**: uppermost A by cardiac sphincter
      - Has **cardiac** glands
    - **Pyloric zone**: lowermost part of stomach
      - Has **pyloric** glands
    - Greater part of body of stomach = fundus
      - Has **gastric** glands → largest # too
      - Play most sig role in acid-related disorders
  - Cells of gastric gland
    - **Parietal ¢**: produce + secrete H^+
    - **Chief ¢**: secrete pepsinogen
      - Pepsinogen → pepsin w/ H+
      - Pepsin = proteolytic
    - **Mucoid ¢**: mucus-secreting ¢ (surface epithelial)
      - Protective mucous coat = protect self-digestion by HCl



- **Parietal cell** acid regulation
  - Gastric acid stim by 3 endogenous cmpds
    - 1) **ACh** at muscarinic (**M**) receptors
      - From **vagus nerve** terminals
      - Mediates **cephalic** phase of gastric acid secretion
        - From smell, taste + thought of food
      - Directly stim H^+ + stim histamine release
    - 2) **Histamine** at histamine2 (**H_2**) receptors
      - Released from **paracrine** ¢s (enterochromaffin-like)
      - For both cephalic + gastric phases
      - Mediates **basal** acid secretion in fasting
      - Provoke cAMP → stim pump
    - 3) **Gastrin** at gastrin (**G**) receptors
      - Hormone secreted by **G** ¢s into gastric antrum
      - Mediates **gastric** phase of H^+ secretion
        - From presence of food in stomach
      - Directly stim H^+ + stim histamine release
    - All intracellular msgers
      - To Ca^{2+} or cAMP
      - ↑ activity of **H^+/K^+ ATPase**
    - **Intrinsic factor**: glycoprotein that facilitates gastric abs of **vit B12**
  - Process
    - Gastric acid secreted by **H^+/K^+ ATPase** (H^+ pump) at luminal memb
      - In **parietal ¢s** of gastric mucosa
    - Stim by histamine, ACh, gastrin



- **Peptic ulcer**
  - Deep defect of mucosa related to action of HCl + pepsin in gastric juice
  - Peptic ulcer locations
    - **Duodenum** 1st → **stomach** 2nd → **esophagus** 3rd
    - Main cause of both duodenum + gastric ulcers = H. pylori
      - NSAIDs = #2 in gastric
      - Idiopathic causes = #2 in duodenum
  - Caused by imbalance b/w dmging factors + protective factors
    - **Protective** factors
      - Bicarbonate = stop hyperacidity = base
      - **PGs** = α-inflam, ↑ blood flow, mucus + bicarb → coating
      - Growth factor = ↑ blood flow
      - Mucus = coating
      - Mucosal blood flow
    - **Dmging** factors
      - ↑HCl = acid digestion
      - Pepsin = lyse proteins
      - Helicobacter Pylori infection
      - NSAIDs
      - Prolonged use of glucocorticoids
      - Stress
      - Smoking
      - Alcohol
  - Stomach lining + location of protective + dmging
    - **Pre-epithelial**
      - Mucus gel secretion from ¢s = barrier
      - Secrete bicarb into mucus layer
      - Intrinsic resistance of CMs to H^+ diffusion
        - Phospholipid hydrophobic barrier
    - **Epithelial**
      - Cellular R, GFs, PGs
    - **Sub-epithelial** = blood flow
      - Last line of defence = lets gastric ¢s evacuate H^+ that are through other defences



- Treatment of peptic ulcer disease
  - Antacids
  - Mucosal protective (coating) agents
  - H_2 receptor blockers
  - Proton pump inhibitors
  - Prokinetics (↑GI motility)
  - Anti-microbial agents for H. Pylori
- **Antacids**
  - Act primarily in stomach by ↑ GI pH = relieve pain of **dyspepsia**
    - ↓ pepsin activity

- Common = mixtures of both:
  - **$Al(OH)_3$** → alone = constipation
  - **$Mg(OH)_2$** → alone = diarrhea
- **$CaCO_3$**
  - Also causes constipation
  - Large doses = rebound in H^+ secretion
- Formerly used to treat peptic ulcers
  - Taken in large doses at ↑# intervals
  - Nocturnal acid secretion = hard to ctrl w/ these → ↓ compliance
- Interaction
  - ↓ abs of other drugs
- Short duration of action

- **Mucosal protective (coating) agents**
  - **Sucralfate**
    - = sucrose octasulfate + aluminum hydroxide
    - MOA
      - Forms protective barrier on surface of ulcer
      - Inhibits pepsin
      - Stim PG syn
      - For ppl who can't tolerate H_2 blockers / PPIs
    - Side fx = constipation
    - Interaction = impair abs of other drugs → for 2 hrs
      - E.g. Digoxin, fluoroquinolones, ketoconazole, phenytoin
  - **Bismuth salts**
    - e.g. **Bismuth Subsalicylate** = **Pepto-Bismol**
    - MOA
      - Coats ulcer
      - α-secretory effect
        - Stim abs of fluid + electrolytes across intestinal wall
      - α-microbial action
        - Binds to E. coli toxins
        - Via **bismuth oxychloride** + **bismuth hydroxide**
      - α-inflam after converting to salicylic acid → inhibits PG syn
        - ↓ inflam + hypermotility
    - Indication
      - **Gastric distress** = symp relief of upset stomach + ♥ burn
      - Diarrhea = symp treatment
      - Treatment of *H. pylori* → gastritis + duodenal ulcer (w/ abios)
    - Side fx
      - Darkened tongue + stools
      - Tinnitus
    - Contraindication
      - Salicylate allergy i.e. viruses
      - **Reye's** in children = acute febrile illnesses → influenza + varicella

- **Misoprostol**
  - **Prostaglandin E1 analogue**
  - MOA
    - Cytoprotective by inhibiting gastric acid secretion
    - Promote secretion of mucus + bicarb
    - ↑ blood flow
    - Block pro-secretory fx of histamine
  - Indication
    - Prevent gastric + duodenal ulcers w/ taking NSAIDs long-term
    - For ppl for ↑ risk NSAID-induced ulcers → elderly, history of...
  - Side fx
    - Diarrhea + Intestinal cramping
  - Contraindication
    - Pregnancy → uterine contraction → abortions…

- Acid reduction = α-secretory
  - ↑intragastric pH above 3 for a few hrs = promote healing of most ulcers
  - **H2 receptor blockers**
    - E.g. **Cimetidine**, **Ranitidine**, **Famotidine**, -tidines
    - MOA
      - Similar struc of histamine = *competition* for binding to H_2
      - Potent inhibitor of both meal-stim secretion + basal secretion of H^+
      - ↓V + $[H^+]$ = ↓ pepsin (no conversion)
    - Indication
      - Peptic ulcer disease (PUD) → PPI = better b/c heals faster
      - Prevention + treatment of dyspepsia + ♥urn
        - ♥burn = fullness, bloating, distension, nausea post-meal
        - Use 30 min before meals
      - **Gastro Esophageal Reflux Disease** (**GERD**)
      - ~70% acid suppression → esp nocturnal
    - Side fx
      - Gynecomastia w/ Cimetidine in men → not in other H_2 blockers
        - Get b/c is **weak anti-androgenic** activity
      - Non-toxic = OTC med
    - Drug intns
      - Cimetidine = **cytochrome P450** isozymes

  - **Proton pump inhibitors (PPIs)**
    - E.g. **Omeprazole**, **Esomeprazole**, Lansoprazole, Dexlansoprazole, Pantoprazole, Rabeprazole
    - MOA → best 1
      - **Irrev** bind to **H^+/K^+ ATPase pump** on parietal ¢ apical memb
      - Accumulation in parietal ¢ = acts as prodrug → activated w/ pH↓
        - Must syn new enz to overcome inhibition = ↑ t
      - ↓ gastric acid 95+%

        - Indication
            - Healing of all grades of **erosive esophagitis** (EE)
            - Treating ♥burn associated w/ reflux
        - Side fx
            - Diarrhea
            - Dizziness
            - Headaches

- **Prokinetics** (↑ GI motility) / **anti-emetics**
    - E.g. **Domperidone**, **metoclopramide**
    - MOA
        - **Centrally** = dopamine receptor-blocking agent
        - **Peripherally** = ↑ lower esophageal sphincter tone + stomach motility
            - Stomach-duodenal coordination
            - Stim ACh release
        - **Metoclopramide**
            - Blocks dopamine D2 + serotonin 5-HT3 receptors (↑ dose)
            - Prevents relaxation of gastric body
            - ↑phasic contractions of antrum
            - Relaxes proximal duodenum
                - Accepts gastric material as antral contractions arrive at pyloric sphincter
                - ↑ resting P of lower esophageal sphincter
                - ↓ reflux of acid from stomach into esophagus
            - Passes BBB
        - **Domperidone**
            - ↑milk production by blocking D2 receptors in breast-feeding moms
            - Doesn't pass BBB
    - Indication
        - GERD
            - XS secretion of H^+ + ↓P in lower esophageal sphincter b/c ↑H^+
            - i.e. reflux of gastric acid into esophagus
        - **Diabetic gastroparesis** → delay in gastric emptying
            - Acute = recovering from surgery, trauma, abdominal infections
            - Chronic = neuropathies that affect stomach (**diabetes mellitus**)
    - Side fx
        - Drowsiness
        - EPR fx → ↑ACh in nigrostriatal pathway = Parkinson's like (Meto)
        - ↑ prolactin release
        - ↑ aldosterone release

- **Laxatives**
    - MOA
        - Stim intestinal peristalsis
        - ↑ movt of material through bowel

        - **Irritant**: **castor oil, cayenne, bisacodyl, sennosides**
        - **↑V: psyllium, fibre**
    - Indications
        - Treat constipation
        - Evacuate bowel before surgery / diagnostic exam
        - Prob in elderly = dependence
        - Elim drugs / poisons from intestinal tract → if drug OD / poisoning
    - *Classification*
        - **Bulk-forming**
            - Indigestible hydrophilic sub
            - Abs / retain H_2O in lumen = ↑ mass = ↑ GI motility = peristalsis
                - Need full glass of water for adequate hydration
                - Also to avoid intestinal obstruction
            - For chronic constipation
            - E.g. **Psyllium**
        - **Surfactant** (**stool softeners** / **emollient**)
            - Bring more H_2O to fatty intestinal materials + soften feces
            - Mainly for **hemorrhoids** when passing dry stool = irritating
                - ↓ dry stool by ↑ H_2O
            - Should avoid straining after abdo surgery
            - e.g. **docusate sodium** + **docusate calcium**

        - **Osmotic**
            - MOA = **hyperosmotic** → stim peristalsis
                - ↑osmotic P b/c salt ↑ in lumen
                - Retain H_2O in intestinal lumen = ↑ intraluminal P
            - **Sodium phosphate**
                - Evacuate bowel in patients scheduled for surgery / diagnostic exams / patients that OD / poison
            - **Magnesium oxide**
                - Prevent constipation in patients receiving opioid analgesics
                - Not for chronic constipation b/c ↓↓↓ fluid + electrolytes
            - **Lactulose**
        - **Stimulant**
            - MOA = Stim peristalsis
                - Work directly on intestinal mucosa to alter fluid secretion
            - Natural products
                - **Lubrification**: w/ mineral oil
                    - Can ↓ bioavailability of lipid-soluble vits (A D E K)
                - E.g. **castor oil** / plant extracts of **senna** / **cascara**
            - Synthetic cmpds such as **bisacodyl**
                - Evacuate bowel before surgery / exams
                - **Opioid antag**: methylnaltrexone
                    - For constipation associated w/ narcotics use
            - Adverse fx = abdominal cramping + sig electrolyte + fluid depletn

- **Antidiarrheals**
  - Opiates derivs
    - E.g. **Diphenoxylate**, **Loperamide** (**Imodium**)
  - MOA
    - Prevents rhythmic waves of contraction + relaxation of smooth muscle by activation of opioid receptors
    - i.e. **opioid agonist**
  - Long-term = constipation
  - E.g.
    - **Psyllium hydrophilic mucilloid** + **Calcium polycarbophil**
    - **Bismuth subsalicylate**

- Anti-microbial agents for Helicobacter Pylori
  - **Helicobacter pylori**
    - 1982 → 2 physicians confirm link b/w gastritis + bact in stomach
      - In almost all ppl w/ duodenal ulcers
      - 80% patients w/ gastric ulcer
    - G- spiral-bacillus w/ unipolar flagella
    - Fecal/oral or oral/oral tmn
    - Colonize gastric mucosa of humans, water supplies
    - Attach to epithelial ¢s of stomach + duodenum = stops washing out
      - Cause dmg to ¢s by secreting degrading enzs, toxins
        - Dmgs mucosal ¢s
      - Inflammation + tissue destruction → self-destructive IR
  - Treatment
    - Hp PAC kit = PPI + 2 abios → 3 combo
      - Lansoprazole, Clarithromycin, Amoxicillin (2 pills)
    - α-secretory agents to assist in wound healing + pain ↓
    - Eradication of H. pylori ↑ healing + prevents recurrence
    - Quadruple therapy
      - PPI, tetracycline, bismuth salt, metronidazole
      - For 7-14 days = eradicate 85-95%

- **Toxicology**
  - Definitions
    - **Toxic**: having chars of producing undesirable / adverse health effect
    - **Toxicity**: any toxic (adverse) effect that chem / physical agent might produce w/i living org
    - **Toxicology**: science that deals w/ study of adverse effects (toxicities) chems / physical agents do in living orgs under specific conds of exposure
      - Attempts to qualitatively det exposure conds where induced
      - Occurrence, nature, incidence, mech, risk factors for adverse fx
    - Types of toxicities
      - Dermal / ocular, hematologic, hepatotoxicity, immunotoxicity, neurotoxicity, renal, respiratory sys

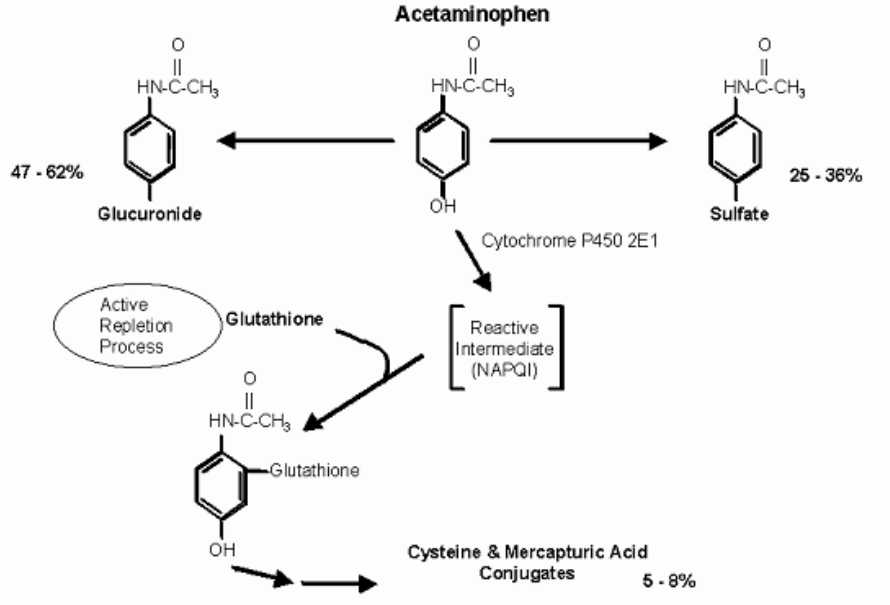
- **Modifiers** of toxicity
  - Young / old → for receptors, enzs + xporters, renal fn
    - Toxic ↑ by ↓ activity in pathway of elim
    - Newborns = ↓ renal fn + enz to metab drugs
      - Less Tylenol toxicity b/c ↓bioactivation of Tylenol to toxic reactive intermediate
      - More susceptible to AG toxicity b/c renally excreted
  - Route of admin
  - Duration + freq of exposure
  - Male / female → gastric emptying, fat %
    - Slower gastric emptying in women
    - Women have ↑ fat % = larger V of distn
  - Nutrition → affects abs + metab
    - β blockers, diazepam, li, carbamazepin = ↑ drug abs
    - Grape fruit juice = ↑ ccbs drug lvls
  - Genetic diffs → Δ lvl of isoforms
    - E.g. CYP450 + N-acetyltransferases enz
  - Coexisting disease
    - E.g. CVD = ↓ liver blood flow + inhibit lidocaine metab
    - Also ↓ renal blood flow

- Mech of toxicity
  - 1) Rev binding of parent mlc +/ stable metabolite to cell receptor
  - 2) Bioactivation of non-toxic chem to highly EL / free rad reactive int
    - Irrev bind to DNA, protein + lipid
- Risk assessment
  - ID whether or not chem causes adverse fx
  - Assess whether there is relationship b/w dose / [chem] + toxicity
  - Det whether sufficient exposure to cause harm
- 2 values in risk assessment
  - **LOAEL**: Lowest-observed adverse effect lvl
    - ↓ [chem] in study that **produces** sig ↑ in freq/severity of adverse fx
  - **NOAEL**: No-observed adverse effect lvl
    - ↑ exposure lvl where **no bio** sig ↑ in freq / severity of adverse fx
    - Some fx may be produced but not considered adverse / precursors of adverse fx

- **Acetaminophen** toxicity (**Tylenol**)
  - Toxicity case = IN NOTES
  - Evo of injury in 3 phases
    - Stage I = minor non-specific bindings (0-24h) = minimum symps
      - Nausea, vomiting, pallor, malaise
    - Stage II = clinical signs of hepatotoxicity (day 2-3) = moderate symps
      - Abdominal pain, hepatomegaly, right upper quadrant pain
      - AST / ALT / Bili / PT / lipase elevation

- Stage III = liver dmg / failure (day 3-4) = severe symps
  - Usu death at this stage → need liver transplant
- Stage IV = death or rapid + complete hepatic recovery (day 4-10)
  - Clinical recov usu begins by day 4 + complete day 7-10

- Pathways of acetaminophen metab
  - **Acetaminophen liver toxicity**: metab creates toxic metabs
    - Cause **hepatic necrosis** at lvls exceeding liver's detox capacity
    - 150+ mg/kg in acute dose
    - 7.5g in 24 h = chronic
  - **NAPQI** = N-acetyl-p-benzoquinone imine = TOXIC metab
  - In OD sits
    - Liver enz saturated to make glucuronide + sulfate
    - Must go through NAPQI = need ↑ glutathione = ↓ toxicity
      - NAPQI = toxic to hepatocytes → renal later
    - **Glutathione** (**GSH**) normal does detox
      - OD = glutathione overwhelmed
    - Can use NAC to disable
  - Reported freq = 0.2-21%
  - Symptoms
    - Nausea / flushing / chills / fever
    - Urticarial rash (hives) / hypotension
    - Bronchospasm
    - Hemolysis
    - Cardiovascular collapse
  - Treatment = **N-acetylcysteine** (**NAC**)
    - MOA = glutathione substitute → ↑stores
      - Enhances **gluthathiolation** of NAPQI directly
      - ↑sulfation pathway
      - May supply inorganic sulfur = alter metab
    - Route of admin = orally / i.v.
      - W/i 1st 8h = 100% effective to prevent hepatotoxicity
      - Dose + rate-dep usu occur in 1st hr of rxn



Drugs List

Drug	Effects / Facts	Side effects
Corticosteroids / Adrenocorticoids		
Glucocorticoids • **Hydrocortisone** • Cortisol	Carbs + protein metab • ↑syn of glucose + metab of aas • ↓use Lipid metab • ↑lipolysis of adipose Ca^{2+} balance • ↓Ca^{2+} abs in GI • ↑Ca^{2+} excretion in kidney Replace nonfnal adrenals (**Addison's**) **Anti-inflammatory** • Direct = 3 • 1) Inhibits activation of T ¢s + **IL-2** • 2) Inhibits **PLA_2** = ↓AA syn • 3) Inhibits **NF-kappa B** Use • Acute disease like **asthma** • Localize when possible (inhalants) • Refractive **arthritis** • Many skin conds • Opthalmopathy w/ **Grave's** disease	**Anti-inflammatory** • Indirect = immunosuppressant • 1) ↓monocytes • 2) ↑neutrophil release • 3) Lymphopenia • 4) Lymphoid tissue atrophy **Osteoporosis** if long term
Mineralocorticoids • Aldosterone	Regulate Na^+ / H_2O	Discussed later
NSAIDs • Inhibit COX-1 + COX-2 → interact reversible w/ Arg120		

Carboxylic acids
• Salicylic acid (**ASA**)
• Acetic acid
  • **Indomethacin**
• Propionic acid
  • Naproxen
  • Ibuprofen
	ASA = acetylates serine in active site
	• Blocks AA via covalent bond
	
	Indomethacin = reg vasoconstriction/dilation
	• In babies post both
		NSAIDs:
		Hypertension + acute renal failure
		• ↑ **vasoconstriction**
		• Also b/c shunt to **lipoxygenase**
		
		PGs
		• ↓**Na^+ retention** in kidney

Enolic acids = Oxicams • Piroxicam • **Meloxicam**	For chronic inflammation issues Meloxicam = ↑ specificity over COXs	
Para-aminophenol • **Acetaminophen** • Paracetamol • Phenacetin	Just pain relief (not α-inflam) Unknown mech → COX-3? Liver toxicity b/c ↑metabs	

COX-1 inhibitors • **Flubiprofen** • NSAIDs + Aspirin • **Mesoprostol**	**Iso 523** selectivity (small pocket) COX-1 = physiological fns ↓risk of stroke (platelets have COX-1) Mesoprostol = same fx as NSAIDs but blocks uptake of PGE2	↑acidity of stomach • Proton pumps ↑ b/c no PGE2 to block signals **Bronchospasms** (asthma) Can get **urticaria** • i.e. hives + rashes
COX-2 inhibitors • DuP697 • **Meloxicam** • Etodolac • Celecoxib • Rofecoxib	**Val 523** selectivity (large pocket) Irrev covalent bond Is actually effective	Stroke + renal failure Both NSAIDS + COXibs • GI upset • Asthma • **Reyes** syndrome • Urate accumulation • ↑BP / renal failure / stroke • Bleeding

DMARDs
• Humanized antibodies
  • **Ifliximab** (Remicade)
  • **Adalimumab**
• Recombinant protein
  • **Etanercept** (Enbrel)
  • **Lenercept**
	TNFα
	• Promote adhesion + retention of WBCs
	• ¢s respond = syn cytokines
	• Activate **osteoclasts** = eat Ca
	• Activate **chondrocytes** = proteases
	Treat arthritis, psoriasis
	• Bind to **TNFα + IL-1**
	• Prevent signalling of ¢ death	

Cancer drugs Cell cycle specific • Antimetabolites • Bleomycin • Peptide antibiotics • Vinca alkaloids • Etoposide	**Cancer drugs** Cell cycle non-specific • Alkylating agents • Antibiotics • Cisplatin • Nitrosoureas	
Alkylating agents • **Cyclophosphamide** • → **Phosphoramide mustard** • **Bis(clorethyl)amine** • **Nitrogen mustards**	Attach alkyl grp to **guanines** at N7 of **imidazole** • Attempt to repair = strand breaks • Get ¢ death = DNA mismatch repair Affects RNA pol = can be effective w/o cell div Metab by CYP450 to active ingredient Also metab by **aldehyde dehydrogenase**	Nausea Vomiting **Alopecia** (hairloss) Bone marrow depression Secondary malignancies Get **glutathione**-mediated reduction = resistance • ↑repair activity • ↓¢ permeability

	= less effective	

Antimetabolites
• 1) Inhibit syn of purine + pyrimidine
  • **Methotrexate**
  • **5-fluorouracil**
• 2) Direct competition w/ normal DNA/RNA syn mlcs
  • **Gemcitabine**
	MTX
	• Inhibits **DHFR**
	• Can't syn thymidine, other bases
	• **Leucovorin** rescue to fix
	5-FU
	• Inhibits **thymidine synthase** enz
	• Interferes w/ conversion of dUMP to dTMP
	• Blocks S phase
	Gem
	• Deoxycytidine pyrimidine analogue
	• Compete for **deoxycytidine kinase**
	• Add into DNA = chain termination
		R
		• ↓ influx of drug
		
		For 5-FU
		• Myelosuppression
		• GI irritation
		• Stomatitis
		• Hepatotoxicity

Antibiotics • **Doxorubicin** • **Bleomycin**	Doxo • 4 ring struc reg ROS • Break DNA strands • Intercalation b/w bases = uncoiling Bleo • Cu chelating mlc = binds to DNA • Free e- interact w/ O2 = ROS • Broken down by **bleomycin hydrolase**	Hepatotoxicity Nausea, vomiting Alopecia Stomatitis (mouth inflam) **Cardiotoxicity** Myelosuppression R • **P-glycoprotein** = transport protein • Altered topo II Bleo • Hyperpigmentation • **Hyperkeratosis** • Rashes • Nausea, vomiting

Microtubule inhibitors
• **Taxanes**
  • Paclitaxel
  • Docetaxel
• **Vinca alkaloids**
  • Vincristine
  • Vinblastine
	Taxanes
	• Prevent mito = interfere w/ mitotic spindles
	• Binds to **β-tubulin**
	• **Stabilizes** MTs = stop Xm movt
	• ¢ death b/c bad in metaphase long
	Vinca
	• **Destabilizers** = no anaphase
	• Can't pull Xm apart
	• No fibers connect to mito spindles
	• Aggregate tubulin dimers too
		Vinca
		• Neurotoxicity
		• Myelosuppresion
		Taxanes
		• Myelosuppresion
		• **Alopecia**
		• Neurotoxicity
		
		R = drug efflex via **Pgp transporter MDR-1**

Other drugs	Anthra = prevent resealing cat by **Topo**	

• **Anthracylines**
  • Doxorubicin
• **Campothecins**
  • Topotecan
	II
	  • For dsDNA breaks
	
	Campo = bind to **Topo I-DNA complex**
	  • Prevent resealing of nicks	

Other drugs
• **Podophyllins**
  • Etoposide
• **Cisplatin**
  • Oxaliplatin
	Podo = topo II inhibition = from Mandrake
	Cisplatin
	• From adduct w/ 2 consecutive Gs
	• Lose Cl for Ns
	• **HMG protein** binds to **Phe37** minor groove = kinks helix
	• Stuck = no proper repair = ¢ death
		Renal failure → elim metabs through kidneys
		Severe nausea + vomiting
		Alopecia
		Ototoxicity = ear dmg
		Myelosuppresion

Antimicrobials		
Inhibitors of **folate metab** • **Sulfonamides** • Sulfasalazine • **Trimethoprim** • **Co-trimoxazole** • **Dapsone**	Compete w/ PABA for **dihydropteroate synthase** → not in humans • For uncomplicated UTIs • Static • Broad activity G+ G- Inhibitor of **dihydrofolate reductase** (**DHFR**) → 20-50x more potent • Cidal • Broad spec G+ G- Mix of sulfonamide • UTIs, resp, prostate → localized Competes w/ PABA • For leprosy • Acne, rashes • Mycobacterium only	Metab by acetylation Crystalluria Nephrotoxicity Hypersensitivity **Bilirubin-kernicterus** • Jaundice

CW inhibitor
• **Penicillins**
  • Penicillin **G**
  • Penicillin **V**
  • Ampicillin
  • Pipericillin + tazobactam
  • Carbenicillin
  • Ticarcillin
  • Amoxicillin + clavulanic acid
  • Cloxacillin
  • Methicillin
• **Cephalosporins**
  • Cephalothin = 1
  • Cephalexin = 1
	Inhibits **transpeptidase** = rupture CM
	• NAG + NAM attached to growing bact end w/ **transglycosidase**
	  • Binds to penicillin bind proteins
	  • Cross-links peptidoglycan units
	• Cidal
	• Weak ¢ = osmmotic lysis of bact
	• Excretion inhibited by **probenecid**
	• Susceptible to **β-lactamases**
		↓ distn in bone + CSF
		Diarrhea b/c disruption of normal flora
		
		High resistance now
		Esp in microorgs w/o peptidoglycan walls (mycoplasmas)
		
		Allergy
		
		Allergy
		Drowsiness

• Cefoxitin =2 • Cefoperazone = 3 • Cefepine = 4 • Cefpirome = 4 • Ceftobiprole = 5 • Ceftaroline = 5 • **Carbapenems** • Imipenem • Meropenem • **Other** CW inhibitors • **Glycopeptides** • **Vancomycin** • Teicoplanin • **Bacitracin** • Neosporin • Polysporin • **Isoniazid** **Clavulanic acid** • Counters **β lactamases** •	Use these 2 for MRSA (R bact) Similar mech as penicillins Admin i.v. 1 = for G+ 2 = for broad spec 3 = for G- • Reach CSF better 4 = broad spec • R to β-lactamases • Reach CSF 5 = in dev • Activity vs. MRSA? Broadest spec of all β-lactams • Cleaved in kidney by **dehydropeptidase** = toxic • Often admin w/ **cilastatin** Bind to peptides of peptidoglycan monomers • Blocks syn of **glycosidic bonds** + peptide cross-links • Cidal • G+ only • For ppl w/ R bact or allergy to Pen • For **nosocomial** infection Similar to Vanco b/c in Europe Prevents **peptidoglycan** monomers syn in cyto from being xported across CM • Broad spec • ↓bioavailability • Active ing = **polymyxin B sulfate** • Also **Bacitracin Zinc** Inhibits syn of **mycolic acid** by blocking **fatty acid synthase** • For mycobact • Produces oxygen radicals like NO • Activated by bact enz **KatG** • Cidal = when culture grows fast • Static = grows slow	Headache Newly described R gene = **New Delhi** = **NDM-1 gene** Chills, fever, rashes Rarely nephrotoxicity, thrombocytopenia, disruptions in WBCs **Red-man syndrome** • Skin rxn + flushing • Δs in BP + hypoT Interferes w/ **IR response** factor = need ↑IR drugs Headache, nausea, poor [ ] Rash, abnormal liver fn Hepatitis, anemia **Peripheral neuropathy** **Vit B6** depletion at ↑ doses

Inhibition of **protein syn**
• **Aminoglycosides**
  • Streptomycin
  • Tobramycin
  • Kanamycin
  • Gentamicin
  • Neomycin
	Inhibit protein syn through binding to **30S** or both **30S + 50S**
	• Distort mRNA attachment = misread codon + block initiation complex
	• Cyclohexane ring + amino sugars
	• Cidal
	• Active xport in
	Use
	• G- aerobes
	• Septicemia
	• P. aeruginosa → **biofilms**
	• Admin orally + IM + i.v.
	• Gentamicin = Micromonospora
	• Tobramycin = extended spec
		Affect 8th cranial nerve
		• Loss of balance
		• Nausea
		• Deafness
		Allergy
		Renal dmg

• **Macrolides**
  • Erythromycin
  • Clarithromycin
  • Azithromycin
	Bind to **23S** unit of **50S** ribosomal subunit
	• 14-16 memb ring struc
	• Static
	• Broad spec
	• Erythro = resp infections + allergy
	• Clarithro = sore throats, rickettsia
		Inhibits **CYP3A**
		• Accumulation of drugs in liver
		• Contraindicated in ppl w/ ↓ hepatic fns
		• Interferes w/ statins + migraines
		Upset GI too

• **Tetracyclines**
  • Tetracycline
  • Doxycycline
  • Tigecycline
	Binds to **30S** subunit = block **aminoacyl tRNA** from doing tln
	• 4 rings
	• Broad spec = obligate intracell
	  • Mycoplasma too
	• Static
	• Active transport in
	• Treat spirochetes
	• Lyme, syphilis, acne
	• Good for exotic infections b/c no R
		Incomplete abs through GI
		• Excreted in bile + urine
		• GI irritation
		Discolouration of teeth
		Bone deformities in kids
		Risk of **superinfections**

• **Chloramphenicol**	Binds to **50S** subunit = block **peptidyl transferase** • Static • Broad spec → intra¢ bact + anaerobe	GI disturbances Depressed bone marrow • **Fatal aplastic anemia** (rare) **Gray baby syndrome** • Affect resp + circ Inactivated by **acyltransferases**

• Other
  • Lincosamides
  • **Clindamycin**
 	
  • **Oxazolidinones**
  • Linezolid
 	
  • **Streptogramins**
  • Quinupristin
  • Dalfopristin
	• Admin orally + i.v. → into CSF
	Use
	• Typhoid
	• Cholera, meningitis, conjunctivitis
	
	Like macrolides = **23S** of **50S** binding
	• Bacteriostatic
	• Better activity vs. G-
	Use
	• Anaerobic infections
	• Inhibit production of toxins in *S. aureus*, *S. pyogenes*, *MRSA*
	• *C. diff* diarrhea
	• Topical acne
	
	Binds to **50S** subunit → unknown mech
	• Against other R G+ bact
	Use
	• Pneumonia
	• Soft tissues infections = -cocci
	• Staphylo, pneumono, enterococci
	
	Bind to diff sites on 50S subunit
	• Inhibit chain elongation = interfere w/ **peptidyl transferase**
	• 2 grps = act synergistically	

Inhibition of nucleic acid syn
• **Quinolones**
  • Nalidixic acid
  • Ciprofloxacin
  • Norfloxacin
  • Ofloxacin
 	
• **Metronidazole**
	Target **DNA topoisomerases**
	• Only serious hospital acquired infections
	• 2 6 memb rings
	• Cidal
	• Broad spec
	• Penetrates phagocytes
	
	Disrupt DNA struc = induce breaks in strand
	• Req reduction of nitro grp in anaerobic conds to fn
	• For mild *C. diff*, *H. pylori*, pelvic inflam disease
		GI upset, rashes, arrhythmias, CNS toxicity
		Not for pregs + kids b/c **tendon injury**
		↑ risk of dev R w/ *C. diff*
		
		Nausea, vertigo,
		Metallic taste in mouth
		Disulfiram-like effect
		• ↑sensitivity to alcohol
		
		Not well abs == poor distn

• **Nitrofurantoin** • **Telithromycin** (**ketolide**) • **Rifampin** (**Rifampicin**)	Disrupts DNA + RNA syn = nucleic acid inhibition • Reduced in bact to metabs = inactivate ribosomal proteins • NA + CW inhibited • Cidal or static → dep on [ ] • For UTIs **2 binding sites** on bact ribosomes • Treat pneumonia • ↓ R *S. pneumoniae* in community Inhibits **DNA dependent RNA polymerase** • Cidal • Broad spec = G+, G-, mycobact • For chemoprophylaxis of N/ meningitidis • Combo w/ other drugs to treat TB + MRSA (dapsone, clofazimine)	Liver failure
Inhibitors of cell membrane • Polymyxins • Polymyxin B • Colistin	**Cationic detergent** • Loss of memb integrity • Cidal • Only G-	Nephrotoxicity Neurotoxicity
Antifungals		
Polyenes • Nystatin • Amphotericin B	Only use if molds are systemic b/c ↑ toxicity Topical usu	
Azoles • Clotrimazole • Miconazole • Fluconazole • Itraconazole • Voriconazole	Convert sterols to ergosterols • Limit early = defective memb Topical or oral Clo, mico = topical Flu, itra, vori = oral for meningitis	May affect hormones
Allyamines • Naftifine • Terbinafine	Topical for dermaphytes → rashes Oral → for *Candida* + *Aspergillus* yeast • Treat pneumocystosis • In HIV → weakened IS	
Other antifungals • Nucleic acid syn	5FC = active vs. yeasts but not moulds	Rev bone marrow inhibitn

• Flucytosine (5FC)
• CW syn
  • **Echinocandins**
  • Caspofungin
  • Micafungin
  • Andiulafungin
  • **Nikkomycins**
  • Nikkomycin Z
  • Nikkomycin X
	Inhibit chitin syn	

Antivirals		
Interferon • Alpha 2a • Alpha 2b • Alpha n3 **Pegylated interferon**	Humans produce when viral infection • ¢s inhospitable for virus • IFN α 2a = chronic Hep C • IFN α 2b = chronic Hep C + Hep B • IFN α n3 = genital + laryngeal warts (papilloma virus)	Flu-like symptoms Aching muscles Depression
Nucleoside analogues • **Gancyclovir** • **Acyclovir** • **Valacyclovir** • **Famcyclovir** • **Foscarnet**	Converted by **viral thymidine** kinase Inhibit viral activity of viral DNA pol • Interfere w/ ability to syn new genes Use • CMV, HSV-1, HSV-2, VZV • Shingles = VZV • Foscarnet = for R CMV, HSV	Kidney toxicity

Reverse transcriptase inhibitor
• Nucleotide-based (**NRTIs**)
  • Lamivudine (**3TC**)
  • AZT
• Non-nucleoside (**NNRTIs**)
  • Nevirapine
  • Rilpivirine
	Inhibit RT = **no cDNA** syn from RNA
	• For HIV
	• Bind to growing DNA / RNA
	• Stop txn b/c missing 3' component that RT recogs	

Viral RNA pol inhibitor • Ribavirin	Resemble ribonucleotides	Hemolytic anemia
Protease inhibitors • Telaprevir • Boceprevir (NS3/4a inhibitors) • Indinavir • Ritonavir • Darunavir	Stops proteins from being cleaved from tln • Cannot proceed in life cycle b/c no proteins to syn virus	
Inhibit viral entry/uncoating • Amantadine • Rimantadine	Virus must go in at ↓ pH • -tadines = prevents Δ in pH	

• Enfuvirtide (Fuzeon) • Maraviroc	Fuzeon = fusion inhibitor to block binding Maraviroc = CCR5 antag	
Neuraminidase inhibitors • Oseltamivir (Tamiflu) • Zanamivir (Relenza)	Inhibit virus release Active vs. Flu A + B + C • B = serious infection	
Integrase inhibitors • Raltegravir • Elvitegravir	Block enz that integrates into ¢	
Antidepressants		
Selective Serotonin reuptake inhibitors (SSRIs) • **Fluoxetine (Prozac)** • Fluvoxamine • Citalopram (Celexa) • Escitalopram (Cipralex) • Sertraline (**Zoloft**) • Paroxetine (Paxil)	Serotonin deactivated in **synapse** by reuptake into presyn neuron • ↑ activation of **5-HT** receptors • Short-term = inhibit reuptake • Long-term = down-reg presyn autoreceptors → ↑ firing rate Use • Most widely used drug to treat dep • Effective like TCA but ↓ side fx • Prozac = bulimia + anorexia • Fluvox = OCD + panic disorder • Parox = weight gain • Sertra = for elderly	Headache / dizzy Anxiety → nervousness Nausea Diarrhea Sexual dysfn → insomnia **Serotonin syndrome** • In combo w/ other ↑5-HT drugs • ↑BP, HR, RR • ↑T → Diaphoresis • **Tremor, clonus, hyperreflexia** • Myadriasis **Discontinuation** syndrome • Flu-like symps • Insomnia • Nausea • Imbalance • Sensory Δs • Hyper
Tricyclic antideps (**TCAs**) • Nortriptyline Amitriptyline • Clomipramine • Imipramine • Desipramine	2nd line treatment • Short-term = inhibit reuptake of 5-HT + **NE** • Long-term = down-reg presyn autoreceptors → ↑ firing rate of both	**Muscarinic antag** • Pupil dilation • Urinary retention • Constipation • Dry mouth α1 antag • Orthostatic hyperT Histamine antag = ↑weight Sedation ↓seizure threshold **Cardiac conductance** disturbances • Arrhythmias

		• Tachycardia • Hypotension

MAO inhibitors (MAOIs)
• 1st gen
  • Phenelzine
  • Tranylcypromine
• 2nd gen = Rev inhibits of **MAO-A** (**RIMAs**)
  • Moclobemide
• **MAO-B** inhibitors
  • Selegiline
	Irrev bind to **monoamide oxidase (MAO)**
	• No degradation of biogenic amine NTs → NE, 5-HT, D
	• ↑[NTs] at storage sites
	Drug intns
	• **Tyramine** foods
	• Aged cheeses, beer, wine
	• Fruits + veg = raisins, avocados, fig
	• Chocolate, coffee in ↑ amnts
	Selegiline = used in Parkinson's
		Hypertensive crisis
		• Headache
		• Palpitations
		• Neck stiffness
		• Sweating
		• Photophobia

Serotonin norepinephrine reuptake inhibitors (SNSRIs) • Venlafaxine (Effexor) • Duloxetine (Cymbalta)	Selective potent **inhibitor** of both **5-HT** + **NE** reuptake • Major depressive disorder • Diabetic peripheral neuropathic pai • Generalized anxiety disorder	Like SSRIs
Other antidepressants • Bupropion • Mirtazepine • Trazodone	Bupropion = **weak reuptake inhibitor** of D, NE, 5-HT • May help quit smoking **Inhibits reuptake** of **5-HT** • More useful as sedative	Agitation, Insomnia Nausea ↓ Weight ↑weight/appetite Sedation Sedation Orthostatic hypertension
Other treatment options • Psychotherapy • Electroconvulsive therapy	Enhances response to pharm treatment • ↑ compliance Ineffective Not well tolerated	
Antipsychotics		

Typical antipsychotics
• Chlorpromazine
• **Haloperidol**
	↑↑ affinity for **D2** → ↓ for 5-HT
	• **Block dopamine**
	• Takes weeks to see effects
	  • Treats +**ve** symps
	• ↑ D syn, release + metab
	• Inactivate D neurons
	• Receptor up-reg + ↑ sensitivity to D agonists
	• Admin parenterally
	  • IM injection = long-acting
	• ↑an**ti-cholinergic** activity = display
		Extrapyramidal rxns (EPRs)
		• Movt disorders
		• Parkinson's tremors
		• Restlessness
		• Off balance
		• Slow speech/mouth
		Tardive Dyskinesia
		• Involuntary repetitive

	↓ EPR side fx	hyperkinetic movts • Lip smacking • Chewing • Tongue protrusion • Grimacing • Rapid limb movts **Galactorrhea** **Neuroleptic malignant syndrome** • Muscle rigidity • Fever • Coma, death **Clozapine** = ↓ granulocyte = **agranulocytosis** = ↓WBCs • ↑risk of infection
Atypical antipsychotics • Clozapine • Olanzipine • Risperidone (Risperdal) • Sertindole • Quetiapine (Seroquel)	↑↑ affinity for **5-HT** → ↓ for D2 • Treats +**ve** symp • Treat –**ve** symp too • ↓ movt probs b/c ↑ dissociation from D2 = ↓ EPRs • Metab in liver by CYP-450 enz • Oral, short, long-acting IM inj, sublingual **5-HT-2 + D2 antag** • 5-HT-2 = thought to remove –ve feedback on DA release in **nigrostriatal** pathway • D2 = block overactive **mesolimbic** pathway	
Neuroleptics • Histamine-1 blocker • α-1 blocker • Muscarinic blocker • D2 blocker	↓ **positive** psychotic symps D2 blocker = relief of psychosis	Hist-1 blocker • weight ↑ + drowsy α-1 blocker = ↓BP Muscarinic ↑ symp • Blurred vision b/c dilated pupils • Constipation • Dry mouth • Drowsiness
3rd gen APs • **Aripiprazole**	Unique • **Partial agonist** at pre + post synaptic D2 + 5-HT-1A receptors • **Antag** at 5-HT-2A • ↑D2 + ↓5-HT-2 in **tuberoinfundibular tract** explains ↓ prolactin	↓ activity at histamine receptors • ↓ sedation
Anxiolytics and Street drugs		
Benzodiazepine • Alprazolam • Chlordiazepoxide • Diazepam • Oxazepam	↑ ability of GABA to bind receptors • Binds at **α + γ subunits** of chloride channels • ↑ freq of Cl- channel opening • Sedative, hypnotic • Anxiolytic • Anticonvulsant	Excessive drowsiness **Ataxia** = lose muscle ctrl Dependence, tolerance + abuse ↑ adverse fx when combo w/ **alcohol** Amnesia

	Uses • ↓anxiety + aggression • Sedation\Muscle relaxant → restless leg syndrome • Anti-epileptic • **Anterograde amnesia**	Prolonged usage = **withdrawal** • Rebound insomnia • Anxiety • Tremors **Disrupt sleep cycle**
Barbiturates • Amobarbital • Pentobarbital • Phenobarbital • Thiopental	↑duration of time Cl- channel **opens** • Directly ↑Cl- influx in absence of GABA • **No ceiling effect** → i.e. line not square root curve	
Other sedative-hypnotics • Zolpidem • Zopiclone • Zaleplon	1st-line treatment for insomnia • Induce sleep **w/o** sleep cycle disruption • ↓ unwanted cog, mem + motor fx	
Other **non-sedating** anxiolytic • **Seritonergic** anxiolytic • Buspirone • **Noradrenergic anxiolytics** • Clonidine • Propranolol	**5-HT-1A partial agonist** • Interact w/ somatodendritic –ve feedback receptors • ↓ release of **serotonin** by stim – ve feedback in ctrlled fashion ↓ sedative • ↓ intns w/ alcohol • ↓ potential for abuse **α-2 agonist** – clonidine • ↓NE = ↓symp NS = ↓emo anxiety **β adrenergic** use – propranolol • **Social phobia**, **stage-fright** • Anxiety w/ mem of stressful event • ↓anxiety + tachycardia	Vertigo **Woozy feeling** b/c intn w/ 5-HT-1A Dilated pupils Tremor Sweating
Antihistamines • Diphenhydramine containing OTCs • Nytol, Unisom, Sleepeze	Sedation via binding to **H1** receptors in CNS • ↓ACh released by neurons in **reticular activating sys**	Delayed onset **Cross BBB** = varying degrees of sedation
Drugs of abuse **CNS depressants** • **Alcohols + glycols** • Ethanol • Ethylene glycol • **Barbiturates + benzodiazepines** • Pentobarbital (Nembutal)	**Rohypnol** (roofies) → Benzodiazepine • Short-term treatment of insomnia • Sedative hypnotic • 10x more potent than diazepam	

• **Flunitrazepam** (**Rohypnol**) • **γ-hydroxy-butyrate (GHB)** • Opioids • Heroin • Oxycodone (Oxycontin) CNS stimulants • **Amphetamine** + derivs • **Methamphetamine** • **MDMA** • **Other stim** • Cocaine • Caffeine • Nicotine **Other psychoactive** • **Cannabis** + derivs • **Marijuana** • Dronabinol (Marinol) • THC R • Nabilone (Cesamet) • **Hallucinogens** • Lysergic acid diethylamide (LSD) • Mescaline • Psilocybin • Phencyclidine (**PCP**)	**GHB** → barb / benzo • Naturally in mammalian brain • On GABA + GHB receptors • Directly or via conversion GHB → GABA • ↑ use in sexual assaults + thefts w/ alcohol **MDMA** → CNS stim • Ecstasy, XTC, E, Adam • Psychedelic amphetamine • Strong feelings of comfort, empathy + connection to others **Methamphetamine** → CNS stim • ↑HR + ↑BP • ↑T + ↓ appetite • **Methylphenidate** (**Ritalin**) similar **Meth mouth** • Dry mouth → dries salivary glands • Tooth decay → bact + poor hygiene • Cracked teeth → anxious / nervous = clench + grind teeth • Gum disease → constricted BVs **Ketamine (Special K)** → hallucinogen • Dissociative anaesthetic • Physical fx like **PCP** • Visual fx like **LSD** • ↓ doses = **K-Land** • Mellow, colourful **wonder world** • ↑ doses = **K-Hole** • Out of body / near death exp	**CNS** = amnesia, coma, unconsciousness, death • Combo w/ alcohol CV = bradycardia, hypoT ↓RR ↓ muscular tone Cardiac injury = ↑BP + HR **Hungover** after → drained Death if w/ alcohol **Amphetamie psychosis** • Paranoia • Auditory + visual hallucinations • Self-absorption • Irritability, agg + erratic behav • Picking at skin Delirium Amnesia Depression Long-term memory + cognitive difficulties
Anti-anginals		
Nitrates	Major effect = **pooling** of blood in	Headache b/c ↓blood to

• Amyl Nitrite = inhaled • **Nitroglycerin** = sublingual + aerosol • Isosorbide dinitrate = sublingual + oral	veins • ↑ venous capacitance of vessels • ↓ **venous return** = ↓ preload = ↓w • Dilation of large **epicardial vessels** • Supply ♥ w/ O_2 better = ↓ metabs • Reversal of vasospasms • ↑ dose = dilate arterioles • ↓BP = ↓preload = ↓w of aortic valve = ↓ O_2 reqs Use • Prophylaxis / acute treatment of ang • Stable + exertional angina • Vasospastic angina • … Any angina See notes for physiology pathway	brain Hypotension **Reflex tachycardia** = ↑HR to compensate **Tachyphylaxis** (tolerance) • **Sulfhydryl** metabs (proteins + aas) • Neuro-hormonal reflex • Intravascular V
Ca channel blockers • **Phenylalkylamine** • Verapamil • **Dihydropyridine** • Nifedipine • **Benzothiazepine** • Diltiazem	Block depol of Ca channel = **Δ conformn** • ↓ AV conduction = ↓ impulse + ↓ activity • ↓ contraction = ↓w • Also moderate vasodilator • Dilation of coronaries = ↑ flow to ischemic zones • Peripheral vasodilation = ↓ afterload of O_2 demand **Ca^{2+} antag** • No fx on AV conduction = ↓ side fx • Potent vasodilator = pool blood in veins to ↓ BP • ↑HR = ↑ affinity Block depol of Ca channel = **plug opening** • Mild slowing of AV conduction = ↓ impulses + activity = ↓HR • Moderate peripheral / coronary vasodilation • ↓BP = no prob w/ vasospasms = ↓w	Toxicity • AV block • Hypotension • ♥ failure → no contraction done Constipation = V Flushing, dizziness (N) = rapid ↓BP Peripheral edema (↑ in N, then V, then D)

	• + Verapamil = ↓rate + ↓F = ↓O_2 • + NO = ↓HR Use • Prevent **focal coronary** artery spasm • Management of angina • **Superventricular tachycardia** • Improvement of exercise endurance	

β-blockers
• **β1 blockers**
  • Atenolol
  • Metoprolol
• **Non-selective β-blocker**
  • Propanolol
	β1 receptors in cardiomyocytes = ↑F
	β in SA node = ↑ stim = ↑HR
	• NE = ↑F of contraction
	• Block = ↓ F, ↓HR, ↓ Renin secretion
	• All ↓w = ↓myocardial O_2 demand
	Block β2
	• Affect glycogenolysis + lipid
	• ↑ airway resistance = constrict
	• ↑ vascular resistance in capillaries
		Vasoconstriction of BVs = must combo w/ other drugs
		• ↑ anxiety

Inotropes **Positive inotropes = ↑ F contraction Negative ones = ↓ F contraction**		
Cardiac glycosides • Digoxin • Digitoxin	From foxglove (Digitalis) plant **Mechanical** effect • ↑F contraction • Inhibition of **Na^+/K^+ ATPase** **Electrical** effect • Direct effect = ↑ AV conduction • Indirect = stim vagus nerve = ↓HR • Ca^{2+} to SR → release Ca^{2+} to myofilaments = actin/myosin intn • End effect = ↑F contraction • ♥ less dilated = ↓ symp NS • Also ↓ peripheral R Treat toxicity w/ **Digibind** (K^+ Digoxin antibodies)	**Ectopic beats** • Arrhythmia • Raises resting memb pot = ↑ % to get impulse Nausea, vomiting ↓K^+ = **block Na^+/K^+ pump** • **Competitive inhibitor** • ↑K^+ = less effective
β-adrenergic agonists • Dopamine	α1 + α2 = constrict BVs β1 + β2 = dilate BVs Bind β-receptor → **cAMP** → **PKA** → Ca2+ release → contraction **Dopamine**	

• Dobutamine • Prenalterol • Xamoterol	• ↑HR + contractility • ↑ dose = vasoconstriction through α • ↓ dose = ↑ renal blood flow • For shock / acute ♥ failure **β1 agonist** • ↑**CO** w/ little effect on HR - only CO • ↑ AV conduction **Partial β1 agonist** • Prevents NE binding = blocks endogenous catecholamine • ↓ symp NS stim	Worsen atrial **arrhythmias**
Cyclic nucleotide phosphodiesterase inhibition • Bipyridines • Amrinone • Milrinone	↑**cAMP** lvls by inhibiting PDE in BVs ↑**CO** by contractility • Relax smooth muscle = ↓ afterload	Nausea **Thrombocytopenia** • ↓ platelets XS bleeding
Calcium sensitizers • Sulmazole • Pimobendan	↑ affinity of **Troponin C** for Ca^{2+} = ↑ contractility Advantage = rarely get Ca^{2+} overload	
Antihypertensives		
Diuretics • **Loop** diuretics • **Furosemide** • **Thiazide** diuretics • **Hydrochlorothiazide** • **Potassium-sparing** diuretics • **Spironolactone** • **Triamterene**	↓BP + ↓Na^+ → ↓electrolytes in general Most potent • ↑↑↑ excretion Na, Cl, K, Ca, Mg • Inhibition of Na K Cl reabs For ↓ acute edema in CHF Weakly natriuretic = most common • ↑ excretion of Na, Cl, K BP stabilizes at ↓ lvl w/o further major diuretic fx ↓ excretion of Ca^{2+} in hypercalciuria Weakly natriuretic • Potent **anti-kalluretic** = no ↓ K^+ • Inhibits aldosterone mediated reabs of Na → at distal tubule + collecting duct	**Ototoxicity** Hypotension Hypo K^+ + Cl- Arrhythmias **Hypocalcaemia** Hypo K^+ Hypotension Uric acid (**gout**) Ca^{2+} build-up = ppt out • **Kidney stones** **Menstrual irreg** • **Gynecomastia**
ACE inhibitors • **Captopril** • **Enalapril**	↓ Angiotensin II • ↓ aldosterone release ↑**bradykinin** = ↓ BP b/c ↑ dilation	Only in long-term Rash Dry cough

• Lisinopril • Fosinopril	↓peripheral R b/c vasodilation • No reflex ↑ in symp activity / HR • ↓Na^+ serum = ↓ response to inhibit Use • CHF = ↓w by cardiomyocytes • ↓ after load → ↑CO, ↓preload, ↓HR • ↓BP overall only little	↓ taste sensation Severe hypotension Proteinurea
Vasodilators • **Arterialor** • ACE inhibitors • Hydralazine	Relax smooth muscle ↓ arteriolar resistance = ↓ afterload Hydralazine • Moderately effective • For **hypertensive crisis** • Metab by N-acetylation, glucuronidation, hydroxylation	Reflex adrenergic outflow Reflex cardiac stim Na^+ / H_2O retention Genetically slow acetylators = ↑ build up **Lupus-like** syndrome
• Diazoxide	Powerful non-diuretic thiazide For hyper emergency usu	**Hyperglycemia**
• Minoxidil	Powerful oral vasodilator For **refractory hypertension** • Unresponsive to normal therapy Activated by liver metab (sulfate)	**Hypertrichosis** • Main use = hair growth
• Pinacidil	**K^+ channel opening** = more –ve • Need ↑ stim to depol • No smooth muscle constriction	
• **Mixed** • Nitroprusside	For severe hypertension • Relaxes **both** arteriolar + venous capillary beds • Gen nitric oxide	XS vasodilation **Thiocyanate poisoning** • Confusion • Delirium
• Prazosin	Blocks **post-syn α1** receptors (no α2 block) • No stim = dilation	Tolerance b/c of renin sys • Rebound effect of adrenergic-receptor blockers (agonists)
• **Venous** • Nitrates		
β blockers • Propanolol • Atenolol	↓CO = ↓HR + ↓ contractility ↓ renin release in kidneys = ↓Ang II = ↓ constriction → get R • ↓aldosterone = ↓Na^+ + H_2O =	

• Clonidine • **α-methyl dopa**	↓BV α2 agonist • ↓ central adrenergic outflow from brain = ↓ activity of symp NS • ↑ aldosterone = ↑ BP Use • Test for **pheochromocytomas** • If no fx by brain = elsewhere • Does not ↓ renal blood flow / GFR • Good for concomitant renal disease	Sedation Dry nasal mucosa See other β blocker sections
Gastrointestinal drugs		
Antacids • Aluminium hydroxide • Magnesium hydroxide • Calcium carbonate	Act in stomach by ↑GI pH Relieve pain off **dyspepsia** (indigestion) Taken in large doses at ↑# intervals • ↓ compliance • Also ↓ abs of other drugs	$Al(OH)_3$ = constipation $Mg(OH)_2$ = diarrhea $CaCO_3$ = constipation + acid rebound
Mucosal protective (coating) agents • **Sucralfate** • Sucrose octasulfate + aluminum hydroxide • **Bismuth salts** • Bismuth Subsalicylate (Pepto-Bismol) • Misoprostol	Form protective barrier on surface of ulcer • Inhibits **pepsin** • Stim PG syn • If can't tolerate PPIs / H_2 blockers Coats ulcer α-secretory = abs of fluid + electrolytes α-microbial = binds to *E. coli* toxins α-inflam = convert to salicylic acid • Inhibit PG syn via **bismuth oxychloride** / **hydroxide** **Prostaglandin E1 analogue** • Cytoprotective by inhibiting gastric acid secretion • Promote secretn of mucus + bicarb • ↑ blood flow • Block pro-secretory fx of hist • Prevents gastric + duodenal ulcers when taking NSAIDs long-term	Constipation Impair abs of other drugs for 2h Darkened tongue + stools Tinnitus Salicylate allergy • Reye's in children Diarrhea Intestinal cramping Pregnancy = get uterine contractions → abortions

H_2 receptor blockers • **Cimetidine** • Ranitidine • Famotidine	↑intragastric pH above 3 for a few hrs **Competition** to bind to **H2** • Potent inhibitor of both meal-stim + basal acid secretion • ↓V = ↓ [acid] = ↓ pepsin Use • Peptic ulcer disease (**PUD**) • Prevention + treatment of dyspepsia + ♥burn • Gastro esophageal reflux disease (**GERD**)	Gynecomastia in men w/ Cimetidine → b/c weak anti-androgenic Cim = interacts w/ cytochrome P450
Proton pump inhibitors (PPIs) • Omeprazole • Esomeprazole • Lansoprazole • Dexlansoprazole • Pantoprazole • Rabeprazole	Irrev bind to **H^+ / K^+ ATPase pump** • Prodrug activated at ↓pH • Must syn new enz to overcome it Use • Heal all erosive esophagitis (**EE**) • Treat ♥burn associated w/ reflux	Diarrhea Dizziness Headaches

Prokinetics / anti-emetics
 	
• Domperidone
 	
• Metoclopramide
	Dopamine receptor-blocking agent in CNS
	↑ lower esophageal sphincter tone + stomach motility → periphery
	• Stomach-duodenal coord
	• Stim ACh release
	
	↑milk production by blocking D2 in breast-feeding moms → not past BBB
	
	Blocks D2 + 5-HT3 receptors (↑dose)
	• Prevents relaxation of gastric body
	• ↑ phasic contractions of antrum
	• Relaxes proximal duodenum
	• Passes BBB
	
	Use
	• GERD
	• **Diabetic gastroparesis**
	  • Acute = from surgery, trauma
	  • Chronic = **diabetes mellitus**
		Drowsiness
		EPR fx (↑ACh in nigrostriatal pathway)
		↑ prolactin release
		↑ aldosterone release

Laxatives
 	
• **Bulk-forming**
  • Psyllium
  • Fibre
 	
• **Surfactant**
• Docusate sodium
• Docusate calcium
 	
• **Osmotic**
 	
  • Sodium phosphate
 	
  • Magnesium oxide
  • Lactulose
 	
• Stimulant
  • Castor oil
  • Plant extracts of senna
  • Cascara
  • Bisacodyl (synth)
  • Methylnaltrexone
	Stim intestinal peristalsis
	• ↑ movt of material through bowel
	Use
	• Treat constipation
	• Evacuate bowel before surgery
	• Elim drugs / poisons from GI
	
	Abs / retain H_2O in lumen = ↑mass = ↑ GI motility = ↑ peristalsis
	• For **chronic** constipation
	
	Stool softener / emollient
	• More H_2O to fatty intestinal materials = soften feces
	• For **hemorrhoids** = ↓ dry stool
	
	Hyperosmotic = ↑osmotic P b/c salt in lumen draws H_2O out of body
	• Evacuate bowel for surgery / diagnostic exams / OD / poison
	• MgO = Prevent constipation w/ opioid analgesics
	  • **Not** for chronic b/c ↓↓↓ fluid + electrolytes
	
	Work directly on intestinal mucosa
	• Stim peristalsis
	• Alter fluid secretion
	• Lubrification
	• ↓ bioavail of lipid sol **vit DAKE**
	
	Opioid antag = methyl
	• Constipation associated w/ narcotics use
		Elderly → dependence
		
		Abdominal cramping
		Sig electrolyte + fluid depletion

Antidiarrheals • Diphenoxylate • Loperamide (Imodium)	**Opioid agonist** • Prevent rhythmic waves of contraction + relaxation of smooth muscle → activate opioid receptors	Long-term = constipation
Antimicrobials • Hp PAC kit	α-secretory agents to assist in wound healing + ↓ pain	
Acetaminophen toxicity • N-acetylcysteine (**NAC**)	Glutathione substitute = ↑ stores • Enhance glutathiolation of	

	NAPQI • Supply inorganic sulfur = alter metab	